GILEAD | Medical Information

Hepcludex® (bulevirtide-gmod) Use in Renal Impairment

This document is in response to your request for information regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) for the treatment of chronic HDV infection in patients with renal impairment.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hdv/hepcludex/hepcludex_pi.

Summary

Product Labeling[1]

BLV is indicated for the treatment of chronic HDV infection in adults without cirrhosis or with compensated cirrhosis.

This indication is approved under accelerated approval based on a decrease in HDV RNA and ALT normalization. An improvement in disease-related clinical outcomes has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The recommended dosage in adults is BLV 8.5 mg once daily administered by SUBQ injection.

No dosage adjustment of BLV is recommended in patients with mild, moderate, or severe renal impairment (CrCl ≥15 mL/min). BLV has not been studied in patients with end-stage renal disease (CrCl <15 mL/min).

In a phase 1, open-label study in participants without HDV infection, the steady state PK of BLV were similar among participants with normal renal function and participants with severe renal impairment (CrCl 15 to <30 mL/min), and no clinically relevant differences in total bile acid elevations were observed between the two groups. The PK of BLV have not been evaluated in participants with end-stage renal disease (CrCl <15 mL/min), including those on dialysis. As BLV is >99% protein bound, dialysis is not expected to alter exposures of BLV.

The efficacy of BLV once daily in the treatment of adults with chronic HDV infection without cirrhosis or with compensated cirrhosis is based on data through Week 144 from a multicenter, randomized, open-label, parallel-arm phase 3 trial, Trial MYR301 (NCT03852719), in which 100 participants received BLV 8.5 mg once daily. The MYR301 protocol specified the BLV dose as 10 mg; however, a dose recovery study later showed that the delivered dose was 8.5 mg.

Clinical Data on BLV Use in Renal Impairment

In a phase 3 study (MYR301) and phase 2/2b clinical studies (MYR204, MYR203, and MYR202), participants with renal impairment were excluded.[2-5]

In a phase 1 PK/PD and safety study, BLV 10 mg was administered SUBQ daily for 6 days to participants with severe renal impairment without HDV/HBV and healthy matched controls. PK exposures were similar between groups. Transient, reversible elevations in total bile acid levels were observed in both groups, though the increases were approximately 27% to 30% lower in the severe renal impairment group than in the healthy matched control group. The incidence of TEAEs was similar between study groups, and TEAEs were generally mild; most AEs were Grade 1 or 2 in severity.[6]

Clinical Data on BLV Use in Renal Impairment

Phase 3 and Phase 2 Clinical Studies

In a phase 3 study (MYR301) and phase 2/2b clinical studies (MYR204, MYR203, and MYR202), participants with renal impairment were excluded (Table 1).[2-5]

Table 1. Studies MYR301, MYR204, MYR203, and MYR202: Renal-Related Exclusion Criteria[2-5]

Study	Renal-Related Exclusion Criteria
MYR301	$CrCl_{CG}$ <60 mL/min
MYR204	$CrCl_{CG}$ <60 mL/min; history of autoimmune disorders, including interstitial nephritis and systemic lupus erythematosus
MYR203	SCr >1.5 × ULN; history of or current severe renal insufficiency or a significant renal function disorder; history of immunologically mediated disorders, including lupus erythematosus
MYR202	$CrCl_{CG}$ <60 mL/min

Abbreviations: CG=CrCl calculated using Cockcroft Gault equation.

PK/PD Study of BLV 10 mg in Severe Renal Impairment[6]

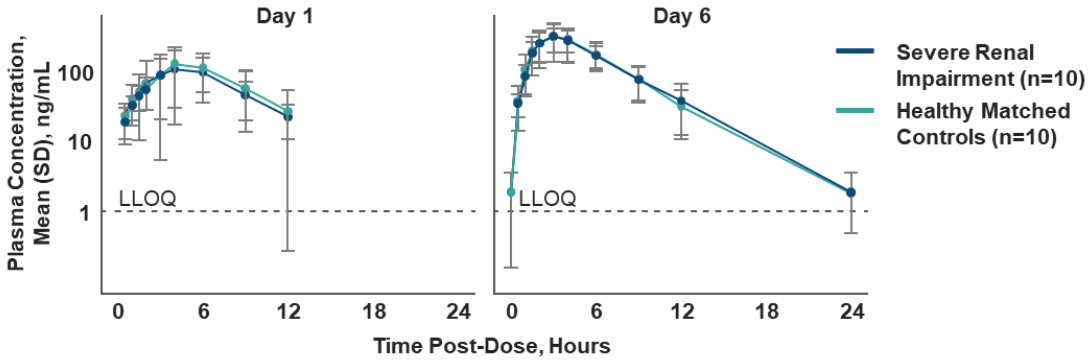
Study design and demographics

An open-label, multicenter, multiple-dose phase 1 study compared PK/PD and safety outcomes with BLV in participants with severe renal impairment (eGFR ≥15 to ≤29 mL/min/1.73 m^2; those currently or anticipating requiring dialysis in the next 90 days were excluded) and without HDV/HBV vs those with normal renal function (eGFR ≥90 mL/min/1.73 m^2). Each treatment group included 10 participants, and healthy volunteers were matched for age (±10 years), sex, and BMI (±20%). All participants received BLV 10 mg SUBQ daily for 6 days. Intensive PK/PD sampling of BLV and total bile acid levels occurred on Days 1 and 6, and sampling of trough BLV and bile acid levels occurred on Days 2, 3, 4, 5, 7, and 8.

PK results

From Day 1 to Day 6, both groups had a 2-fold accumulation in PK exposures, while CL/F and Vz/F decreased accordingly (Figure 1). The median $T_{1/2}$ was similar between groups (Table 2).

Figure 1. PK/PD Study: PK Concentrations[6]



Abbreviation: LLOQ=lower limit of quantitation.

Table 2. PK/PD Study: BLV PK Parameters at Day 1 and Day 6[6]

Mean (CV%)	Severe Renal Impairment (n=10)						
	$AUC_{0–12h}$, ng·h/mL	$AUC_{0–24h}$, ng·h/mL	C_{max}, ng/mL	CL/F, L/h	$T_{1/2}$, h[a]	T_{max}, h[b]	Vz/F, L
Day 1	741 (61.5)	843 (56.9)	121 (71.4)	16.8 (69.2)	2.86 (2.45, 4.54)	4 (3–6)	158 (178)
Day 6	1750 (34.4)	1880 (34.1)	311 (35.3)	5.8 (29.1)	2.79 (2.27, 2.99)	3 (2–4.03)	24.4 (43.8)
Mean (CV%)	**Healthy Matched Controls (n=10)**						
	$AUC_{0–12h}$, ng·h/mL	$AUC_{0–24h}$, ng·h/mL	C_{max}, ng/mL	CL/F, L/h	$T_{1/2}$, h[a]	T_{max}, h[b]	Vz/F, L
Day 1	828 (49.8)	876 (52.2)	146 (57.5)	19.1 (95.9)	3.03 (2.67, 3.76)	4 (1.5–9)	128 (133)
Day 6	1670 (33.6)	1810 (30.9)	307 (50.8)	6.1 (36.5)	2.75 (2.46, 2.97)	3 (3–6)	25 (56.7)

Abbreviation: Q=quartile.
[a]Median (Q1, Q3). [b]Median (range).

GLSM ratios of PK parameters were similar between the severe renal impairment and healthy matched control groups (Table 3).

Table 3. PK/PD Study: GLSM Ratios of PK Parameters[6]

GLSM Ratio (90% CI)	$AUC_{0–12h}$, ng·h/mL	AUC_T, ng·h/mL	C_{max}, ng/mL
Day 1	0.89 (0.51–1.57)	1 (0.56–1.79)	0.78 (0.43–1.42)
Day 6	1.05 (0.81–1.37)	1.04 (0.81–1.33)	1.08 (0.78–1.51)

Abbreviation: AUC_T= area under the concentration-time curve over the dosing interval.

PD results

Similar elevations in total bile acid levels were noted between groups; NetAUC and C_{max} GLSM ratios were approximately 27% to 30% lower in the severe renal impairment group than in the healthy matched control group (Table 4 and Table 5). Increases in total bile acid levels were transient and reversible in both groups within 24 to 48 hours postdose.

Table 4. PK/PD Study: PD Parameters of Total Bile Acid Levels[6]

Total Bile Acid Level, GM (GCV%)	Severe Renal Impairment (n=10)		
	$AUC_{0–24h}$, mcM·h	NetAUC, mcM·h	C_{max}, mcM
Day 1	1110 (71.5)[a]	1070 (71)[a]	93 (80.4)[a]
Day 6	1850 (63.9)	1800 (64.1)	145 (66.5)

Total Bile Acid Level, GM (GCV%)	Matched Healthy Control (n=10)		
	AUC_{0-24h}, mcM·h	NetAUC, mcM·h	C_{max}, mcM
Day 1	1300 (58.6)	1250 (62.1)	107 (61.6)
Day 6	2630 (27.6)	2580 (27.1)	200 (28.1)

Abbreviations: GCV=geometric coefficient of variation; GM=geometric mean.
[a]n=11.

Table 5. PK/PD Study: GLSM Ratios of PD Parameters of Total Bile Acid Levels[6]

GLSM Ratio (90% CI)	NetAUC, mcM·h	C_{max}, ng/mL
Day 1	0.86 (0.54–1.36)	0.87 (0.53–1.41)
Day 6	0.7 (0.49–0.99)	0.73 (0.5–1.05)

Safety

The incidence of TEAEs were similar between study groups, TEAEs were generally mild, and most AEs were Grade 1 or 2 in severity. No BLV-related Grade ≥3 TEAEs, serious AEs, or AEs that led to BLV discontinuation occurred.

References

1. Enclosed. Gilead Sciences Inc. HEPCLUDEX® (bulevirtide) injection, for subcutaneous use. US Prescribing Information. Foster City, CA.
2. Wedemeyer H, Aleman S, Brunetto MR, et al. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D.[Protocol]. *N Engl J Med.* 2023;389(1):22-32.
3. Asselah T, Chulanov V, Lampertico P, et al. Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D [Supplementary Appendix]. *N Engl J Med.* 2024;391(2):133-143.
4. Lampertico P, Bogomolov PO, Chulanov V, et al. Phase 2 Randomised Study of Bulevirtide as Monotherapy or Combined With Peg-IFNalpha-2a as Treatment for Chronic Hepatitis Delta [Supplement]. *Liver Int.* 2025;45(2):e70008.
5. Wedemeyer H, Schoneweis K, Bogomolov P, et al. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial. *Lancet Infect Dis.* 2022.
6. Wang Y, Mercier R-C, Nieves W, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide 10 mg Once Daily for 6 Days in Participants With Severe Renal Impairment and in Matched Control Participants With Normal Renal Function. [Poster #WED-313]. Paper presented at: European Association for the Study of the Liver; May 7–10, 2025; Amsterdam, the Netherlands.

Abbreviations

AE=adverse event
AUC_{0-12h}=area under the concentration-time curve from time 0 to 12 hours after administration
AUC_{0-24h}=area under the concentration-time curve from time 0 to 24 hours after administration
BLV=bulevirtide-gmod
CL/F=apparent clearance
C_{max}=maximum plasma concentration
CP=Child-Pugh
CPT=Child-Pugh-Turcotte
CV%=coefficient of variation percentage
GLSM=geometric least-squares mean
NetAUC=AUC_{0-24h} of total bile acids after baseline adjustment
PD=pharmacodynamic(s)
PK=pharmacokinetic(s)
SUBQ=subcutaneous(ly)
$T_{1/2}$=terminal elimination half-life
TEAE=treatment-emergent adverse event
T_{max}=time to reach maximum plasma concentration
Vz/F=volume of distribution

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Hepcludex US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hdv/hepcludex/hepcludex_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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