Hepcludex® (bulevirtide-gmod) Use in Hepatic 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 hepatic impairment.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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 hepatic impairment (CP Class A). The safety and efficacy of BLV have not been studied in patients with moderate (CP Class B) or severe (CP Class C) hepatic impairment.

In a phase 1, open-label study in participants without HDV infection, the steady-state PK of BLV were approximately 27% lower in participants with moderate hepatic impairment (CP Class B) than participants with normal hepatic function. The steady-state PK of BLV were similar among participants with severe hepatic impairment (CP Class C) and participants with normal hepatic function.

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 Hepatic Impairment

In a phase 3 study (MYR301) and phase 2/2b clinical studies (MYR204, MYR203, and MYR202), participants with decompensated cirrhosis and other types of hepatic impairment were excluded.[2-9]

In a phase 1 PK/PD and safety study, BLV 10 mg was administered SUBQ daily for 6 days to participants with moderate hepatic impairment without HDV/HBV and healthy matched controls. PK exposures were reduced approximately 22% to 46% in patients with moderate hepatic impairment relative to healthy matched controls. Transient and reversible increases in total bile acid levels were noted in both groups; however, total bile acid levels on Day 6 were approximately 80% higher in the moderate hepatic impairment group than in the healthy matched controls. The incidence and severity of TEAEs were similar between study groups and were generally mild.[10]

Clinical Data on BLV Use in Hepatic 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 decompensated cirrhosis and other types of hepatic impairment were excluded (Table 1).[2-9]

Table 1. Studies MYR301, MYR204, MYR203, and MYR202: Hepatic-Related Exclusion Criteria[2-9]

Study	Hepatic-Related Exclusion Criteria
MYR301	CPT Class B/C (score >6); ALT level ≥10 × ULN; current or previous decompensated cirrhosis (including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, and esophageal varices hemorrhage); complicated esophageal varices, including current or history of bleeding/ligation; HCV co-infection; TB level ≥34.2 mcmol/L[a]; serum albumin level ≤2.8 mg/dL; history of hepatic carcinoma; ≥1 primary or secondary cause of liver disease other than HBV (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, α-1 antitrypsin deficiency, Wilson's disease, other congenital/metabolic conditions affecting the liver, or CHF or other severe cardiopulmonary disease); current alcohol abuse or abuse within 6 months of enrollment
MYR204	CPT Class B/C (score >6); ALT level ≥10 × ULN; current or previous decompensated cirrhosis (including coagulopathy, hepatic encephalopathy, and esophageal varices hemorrhage); complicated esophageal varices, including current bleeding/ligation or history of bleeding/ligation in past 2 years; HCV co-infection; TB level ≥34.2 mcmol/L[a]; serum albumin ≤2.8 mg/dL; history of hepatic carcinoma; ≥1 primary or secondary cause of liver disease other than HBV (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, α-1 antitrypsin deficiency, Wilson's disease, other congenital/metabolic conditions affecting the liver, or CHF or other severe cardiopulmonary disease); current alcohol abuse or abuse within 6 months of enrollment
MYR203	CPT score ≥6; HCV co-infection; ALT level ≥10 × ULN; TB level >34.2 mcmol/L[a]; current or history of decompensated liver disease (including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, and esophageal varices hemorrhage); HCC; medication- or alcohol-induced liver impairment or other chronic liver disease (eg, autoimmune hepatitis, hemochromatosis, thalassemia, alcoholic hepatitis, toxic hepatitis); decompensated severe cardiovascular disease (including unstable/poorly controlled status in the previous 6 months); current alcohol abuse or abuse within 6 months of enrollment

Study	Hepatic-Related Exclusion Criteria
MYR202	CP Class B/C (score >6 points); HCV co-infection; TB ≥2 mg/dL[a], ALT ≥10 × ULN; current or previous decompensated liver disease (including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, and esophageal varices hemorrhage); hepatic carcinoma; current alcohol abuse or abuse within 6 months of enrollment

Abbreviations: CHF=congestive heart failure; HCC=hepatocellular carcinoma; TB=total bilirubin; ULN=upper limit of normal.
[a]Participants with elevated TB levels associated with Gilbert's syndrome were not excluded.

PK/PD Study of BLV 10 mg in Moderate Hepatic Impairment[10]

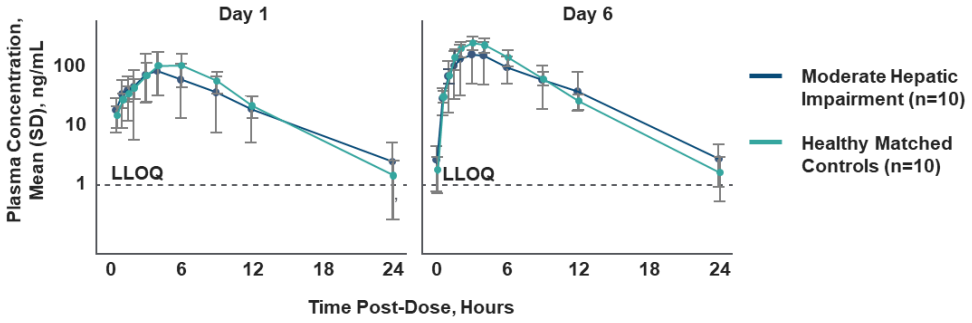
Study design and demographics

An open-label, multicenter, parallel-group, multiple-dose phase 1 study compared PK/PD and safety outcomes with BLV in participants with moderate hepatic impairment (CPT Class B) and without HDV/HBV vs participants with normal hepatic function. 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 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 and Table 2). CL/F and Vz/F were higher among those in the moderate hepatic impairment group than in the healthy matched control group on both days; however, the median $T_{1/2}$ was similar between groups (Table 2).

Figure 1. PK/PD Study: PK Concentrations[10]



Abbreviation: LLOQ=lower limit of quantitation.

Table 2. PK/PD Study: BLV PK Parameters at Day 1 and Day 6[10]

Mean (CV%)	Moderate Hepatic Impairment (n=10)						
	$AUC_{0–24h}$, ng·h/mL	AUC_{inf}, 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	671.4 (64.7)	696.4 (60)	99.2 (95.1)	22.8 (79.6)	3.9 (2.6, 6.3)	4 (1–9)	217.2 (125)
Day 6	1266.4 (61.3)	1283.5 (60.1)	175 (64.7)	9.6 (40.3)	3.4 (2.6, 4.7)	3 (3–6)	53 (64.2)

Mean (CV%)	Healthy Matched Controls (n=10)						
	$AUC_{0–24h}$, ng·h/mL	AUC_{inf}, 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	853 (39.6)	859.4 (39.2)	126.8 (51.8)	14.2 (57.7)	2.8 (2.6, 3.2)	5 (2–9)	66 (93.4)
Day 6	1561.1 (22.2)	1568.8 (22)	260.6 (24.6)	6.7 (24.2)	2.8 (2.4, 3.1)	3 (2–4)	28.5 (46.7)

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

GLSM ratios of PK parameters were 22% to 46% lower in the moderate hepatic impairment group than in the healthy matched control group (Table 3).

Table 3. PK/PD Study: GLSM Ratios of PK Parameters[10]

GLSM Ratio (90% CI)	$AUC_{0–24h}$, ng·h/mL	AUC_{inf}, ng·h/mL	C_{max}, ng/mL
Day 1	0.67 (0.4–1.12)	0.78 (0.49–1.26)	0.54 (0.26–1.12)
Day 6	0.73 (0.54–0.99)	0.74 (0.55–1)	0.58 (0.41–0.83)

PD results

Similar elevations in total bile acid levels were noted between groups at Day 1, though by Day 6, NetAUC and C_{max} GLSM ratios were approximately 80% higher in the moderate hepatic impairment group than in the healthy matched control group (Table 4 and Table 5). Increases in total bile acid levels were reversible in both groups within 24 to 48 hours post dose.

Table 4. PK/PD Study: PD Parameters of Total Bile Acid Levels[10]

Total Bile Acid Level, GM (GCV%)	Moderate Hepatic Impairment		
	$AUC_{0–24h}$, mcM·h	NetAUC, mcM·h	C_{max}, mcM
Day 1	1780.1 (99.2)	1470.5 (109.6)	137.5 (109.3)
Day 6	4323.6 (39.2)	4017.7 (33)	321.3 (39.6)
Total Bile Acid Level, GM (GCV%)	**Matched Healthy Control**		
	$AUC_{0–24h}$, mcM·h	NetAUC, mcM·h	C_{max}, mcM
Day 1	1652.3 (22.4)	1595 (22.1)	139.2 (29.7)
Day 6	2281.1 (22.6)	2215.4 (24)	176.6 (20.4)

Abbreviations: GCV=geometric coefficient of variation; GM=geometric mean.

Table 5. PK/PD Study: GLSM Ratios of PD Parameters of Total Bile Acid Levels[10]

GLSM Ratio (90% CI)	NetAUC, mcM·h	C_{max}, mcM
Day 1	0.92 (0.56–1.52)	0.99 (0.59–1.65)
Day 6	1.81 (1.46–2.26)	1.82 (1.44–2.31)

Safety

The incidence and severity of TEAEs were similar between study groups, and TEAEs were generally mild. No 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. *N Engl J Med.* 2023;389(1):22-32.

3. 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.
4. Asselah T, Chulanov V, Lampertico P, et al. Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D. *N Engl J Med.* 2024;391(2):133-143.
5. Asselah T, Chulanov V, Lampertico P, et al. Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D [Protocol]. *N Engl J Med.* 2024;391(2):133-143.
6. 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. *Liver Int.* 2025;45(2):e70008.
7. 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.
8. 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.
9. 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 [Supplementary appendix]. *Lancet Infect Dis.* 2022.
10. Kumar P, Nieves W, Pan D, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide 10 mg Once Daily for 6 Days in Participants With Moderate Hepatic Impairment and in Matched Control Participants With Normal Hepatic Function. [Poster #WED-312]. Paper presented at: European Association for the Study of the Liver; May 7–10, 2025; Amsterdam, the Netherlands.

Abbreviations

AE=adverse event
$AUC_{0–24h}$=area under the concentration-time curve from Time 0 to 24 hours after administration
AUC_{inf}=area under the concentration-time curve from Time 0 to infinity
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

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact gilead.privacy@gilead.com.