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Hepcludex® (bulevirtide-gmod) Use in Decompensated Cirrhosis

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 decompensated cirrhosis.

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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]

Severe acute exacerbations of HDV and HBV infection may occur after BLV is discontinued, especially in patients with cirrhosis, who may be at increased risk of more severe flares or progression to hepatic decompensation. Monitor hepatic function closely with both clinical and laboratory follow-up, including monitoring HBV DNA and HDV RNA viral load, for ≥6 months in patients who discontinue BLV. Resumption of antiviral therapy may be warranted.

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.

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 Decompensated Cirrhosis

In IMPHROVE-D, a prospective observational study, 70% of participants with chronic HDV infection and advanced chronic liver disease showed a decline in HVPG after 48 weeks of treatment with BLV ± PEG-IFN. Among those with clinically significant portal HTN, 65% achieved an ≥10% reduction in HVPG.[2]

In phase 2 clinical studies (MYR202, MYR203), a phase 2b study (MYR204), and a phase 3 study (MYR301), participants with decompensated cirrhosis were excluded.[3-6]

Real-World Data on BLV Use in Decompensated Cirrhosis

In a retrospective study in Russia that assessed the efficacy and safety of BLV 2 mg in 22 patients with chronic HDV and decompensated cirrhosis, there was a significant decline in median HDV RNA levels (*P*=0.001) and median ALT levels (*P*=0.025) from BL to Week 48, and 80% (12/15) achieved a virologic response by Week 48. No SAEs were reported, and no patients discontinued due to AEs.[7]

In a retrospective study in France that evaluated the use of BLV 2 mg in patients who were awaiting liver transplantation (N=20), 73% (11/15) had a virologic response, and 53% (8/15) had undetectable HDV RNA at Week 48. No SAEs were considered related to BLV treatment.[8]

In a retrospective study in Europe that assessed the efficacy and safety of BLV 2 mg in patients with HDV-related cirrhosis who had a CP class of B and clinical signs of decompensated advanced chronic liver disease (N=19), 74%, 16%, and 11% achieved a virologic response, partial response, and non-response, respectively. ALT normalization was achieved in 74% of patients. No AEs were considered related to BLV treatment.[9]

Clinical Data on BLV Use in Decompensated Cirrhosis

IMPHROVE-D Study[2]

Study design and demographics

A prospective, multicenter, observational study was conducted among participants with chronic HDV infection and clinical signs of advanced chronic liver disease to assess the relationship of treatment response to BLV ± PEG-IFN and changes in portal HTN. HVPG was measured at BL and after 48 weeks of BLV ± PEG-IFN treatment to evaluate changes in portal HTN.

Participants (N=20) had a median (IQR) age of 48 (41.3–57) years, 65% were male, and the median (IQR) BMI was 25.8 (22.3–29) kg/m^2.

Results

The median (IQR) treatment duration was 13 (12–17) months, and 3 participants (15%) received BLV + PEG-INF. Combined, biochemical, and virologic responses were achieved in 60%, 80%, and 70% of participants, respectively. A decline in HVPG was observed in 70% of participants, and 65% of those with clinically significant portal HTN experienced a ≥10% reduction.

Changes from BL in key parameters at Week 48 are reported in Table 1.

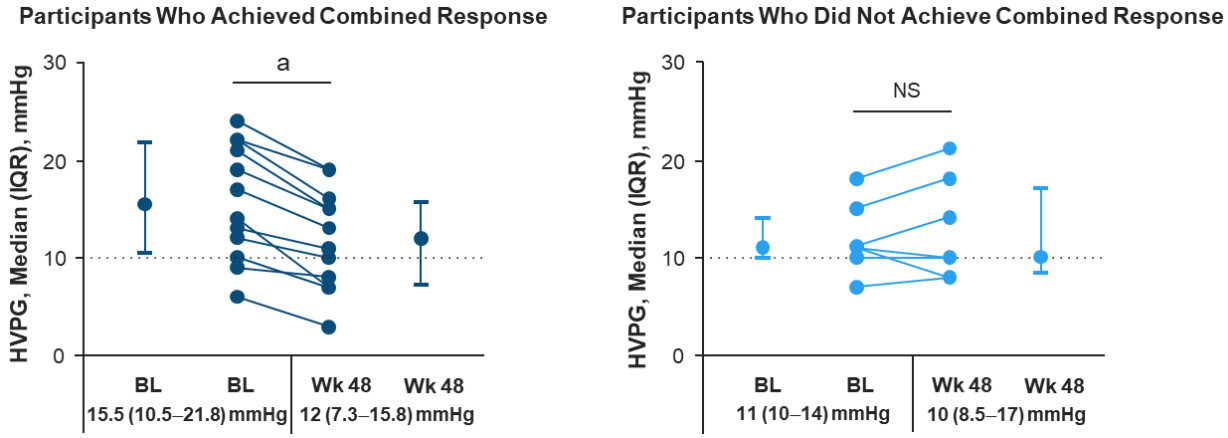
Table 1. IMPHROVE-D: Key Parameters at BL and Week 48[2]

Key Parameters	BL (N=20)	Week 48 (N=20)	*P*-Value
HDV RNA, median (IQR), log_{10} IU/mL	4.45 (3.35–5.57)	1.21 (0.21–2.21)	<0.001
LSM, median (IQR), kPa	24 (13.5–28.5)	13.5 (9–22.7)	<0.001
CP class A/B, n (%)	17 (85)/3 (15)	17 (85)/ 3 (15)	1
MELD score, median (IQR)	10 (9–12)	10 (9–13)	0.524
HVPG, median (IQR), mmHg	12.5 (10–18.8)	10.5 (8–15.8)	0.013
Portal HTN, n (%)	20 (100)	19 (95)	1
Clinically significant portal HTN, n (%)	17 (85)	14 (70)	0.248
Bile acids, median (IQR), mcmol/L	22 (6–46)	36 (20–61)	0.001
Bilirubin, median (IQR), mcmol/L	16 (13–23)	16 (9–28)	0.896
Albumin, median (IQR), g/L	36.9 (33–40)	37.5 (34.8–42)	0.064
Platelets, median (IQR), ×1000/mcl	80 (39–109)	62 (39–125)	1
INR, median (IQR)	1.3 (1.2–1.4)	1.3 (1.2–1.5)	0.9
AST, median (IQR), U/L	70 (47–148)	41 (30–62)	0.001
ALT, median (IQR), U/L	72 (62–117)	33 (23–45)	<0.001

Abbreviation: LSM=liver stiffness measurement.

HVPG declined significantly from BL to Week 48 in participants who achieved any type of treatment response (combined, virologic, or biochemical), with the most notable reduction observed in those with a combined response (Figure 1).

Figure 1. IMPHROVE-D: Changes in HVPG by Combined Treatment Response Status From BL to Week 48[2]



NS=non-significant.
[a]Statistically significant.

Safety data were not reported.

MYR202, MYR203, MYR204, and MYR301

In phase 2 clinical studies (MYR202, MYR203), a phase 2b study (MYR204), and a phase 3 study (MYR301), participants with decompensated cirrhosis (CP Class of B or C or score >6 points) were excluded. Participants with uncomplicated esophageal varices were allowed; however, participants with current bleeding or ligation or a history of bleeding or ligation within the last 2 years were excluded.[3-6]

Real-World Data on BLV Use in Decompensated Cirrhosis

Russian Retrospective Study[7]

Study design and demographics

A retrospective, multicenter study was conducted in Russia to assess the efficacy and safety of BLV in 22 patients with chronic HDV and decompensated cirrhosis. BLV was administered using a low accelerated-dose regimen starting at BLV 2 mg twice weekly (8–12 weeks) that was increased to three times weekly (8–12 weeks), then progressed to daily injections for up to 144 weeks.

Patients had a mean ± age of 50±12.1 years, 36% were male, 59% used nucleos(t)ide analogues for comorbid HBV infection, and 73% had esophageal varices.

Results

From BL to Week 48, there was a significant decline in median HDV RNA from 5.6 $\log_{10}$ c/mL to 3.1 $\log_{10}$ c/mL (*P*=0.001). The rate of virologic response (HDV RNA decline ≥2 $\log_{10}$ c/mL) increased over time, from 8% at Week 12 to 28% at Week 24 and 80% (12/15) at Week 48. Two patients achieved undetectable levels of HDV RNA.

There was a significant decline in median ALT levels from 54 U/L at BL to 35 U/L at Week 48 (*P*=0.025). Normal ALT levels were observed in 32% (7/22) of patients at BL, 42% at Week 12, 78% at Week 24, and 63% (10/16) at Week 48. Changes in liver function parameters are reported in Table 2.

Table 2. Liver Function Parameters at BL, Week 24, and Week 48 (Bogomolov et al)[7]

Parameter		BL (n=22)	Week 24 (n=21)	Week 48 (n=16)
CP class, n (%)	A	0	14 (67)	13 (81)
	B	21 (95)	7 (33)	3 (19)
	C	1 (5)	0	0
CP score, n		8	6	5
Hepatic encephalopathy, n (%)		17 (77)	6 (30)	3 (19)
Ascites, n (%)		17 (77)	4 (20)	3 (19)
Total bilirubin, median (range), mcmol/L		29.8 (11.7–70)	20.8 (9–42.1)	21.1 (9–110.4)
Albumin, median (range), g/L		32.5 (28–43)	34 (29–42)	38.5[a] (14.7–46)
INR, median (range)		1.4 (1.2–1.9)	1.3 (1–1.7)	1.2 (1.1–2.2)

[a]*P*=0.021 compared with BL value.

No SAEs were reported, and there were no discontinuations due to AEs.

French Retrospective Study[8]

Study design and demographics

A multicenter retrospective study in France evaluated the real-world use of BLV in 20 patients who were awaiting liver transplantation. Data were evaluated from patients with HDV who had decompensated cirrhosis or HCC, were treated with BLV 2 mg/day, and were on a waiting list or undergoing evaluation for liver transplantation.

Patients had a mean age of 52.8 years, and 75% were male. At BL, the median (range) MELD score was 9 (6–32), 8 patients had active HCC, 11 had large (Grade 2–3) esophageal varices, and 1 had refractory ascites. The median (range) HDV RNA level was 5.98 (2.23–10) log IU/mL, and 5 patients had detectable HBV DNA.

Results

The rate of virologic response (defined as a decrease from BL in HDV RNA levels by ≥2 log or undetectable HDV RNA) in patients who were treated and remained on the waiting list increased from 41% (7/17) at Week 24 to 73% (11/15) at Week 48; 53% (8/15) of patients had undetectable HDV RNA at Week 48 (Table 3). At liver transplant, 33% (4/12) of patients had a virologic response. From BL to Week 48, HDV RNA levels significantly decreased by a median of 2.56 log IU/mL (95% CI, 0.97–4.91; *P*=0.004).

Table 3. Viral, Clinical, and Biochemical Parameters at BL, Week 24, Week 48, and Liver Transplant (Meszaros et al)[8]

Parameter		BL (n=20)	Week 24 (n=17)	Week 48 (n=15)	Liver Transplant (n=12)
HDV RNA, median (range), log IU/mL		5.98 (2.23–10)	4.53 (0.15–10)	2 (0.1–7.5)	3.11 (0.1–6.37)
HDV RNA decrease by ≥2-log IU/mL, n (%)		-	7 (41.18)	11 (73.33)	4 (33.33)
Undetectable HDV RNA, n (%)		0	3 (19)	8 (53)	3 (38)
Virologic response,[a] n (%)		-	7 (41)	11 (73)	4 (33)
Virologic non-response,[b] n (%)		-	4 (24)	3 (6)	4 (33)
Undetectable HBV DNA, n (%)		15 (75)	14 (82)	14 (93)	11 (92)
CP class, n	A	14	11	12	6
	B	1	3	2	2
	C	5	3	1	4
MELD score, median (range)		9 (6–32)	8 (6–18)	9 (6–16)	12 (6–31)
AST level, median (range), U/L		78 (65.5–125)	60 (25–477)	52 (20–70)	79.5 (26–322)
ALT level, median (range), U/L		91 (60–135.5)	42(14–512)	33.5[c] (8–93)	62 (21–335)
ALT normalization, n (%)		-	6 (35.29)	10 (66.6)	3 (25)

[a]Defined as a decrease from BL in HDV RNA levels by ≥2 log or undetectable HDV RNA.
[b]Defined as a decrease from BL by <1 log.
[c]*P*=0.001 compared with BL value.

There were no reported SAEs that were considered related to BLV therapy.

European Retrospective Study[9]

Study design and demographics

An anonymized, retrospective study using data collected from Austrian, Italian, and German centers was conducted to assess the efficacy and safety of BLV 2 mg once daily in patients with HDV-related cirrhosis who had a CP class of B and clinical signs of decompensated advanced chronic liver disease (N=19). Patients had a mean ± SD age of 51±10 years, and 47% were male. The median (range) MELD score was 12 (9–17), 14 patients had esophageal varices, 2 patients had HCC, and 18 patients had an ALT level >45 U/L.

Results

The median (IQR) observation period was 41 (16–104) weeks, and all patients except 1 received ≥24 weeks of BLV treatment. Fourteen patients (74%) achieved a virologic

response (decline in HDV RNA levels by ≥2 log from BL, undetectable levels, or levels <LLoQ) after a median (IQR) treatment duration of 17 (16–32) weeks. A partial response (decline in HDV RNA >1 log but <2 log) was observed in 3 patients (16%), and 2 patients (11%) had a non-response (decline in HDV RNA <1 log or an increase from BL). Among patients who achieved a virologic response, relapse (an increase in HDV RNA levels by >1 log) was observed in 4 patients; of these patients, 2 had a slight increase in ALT, and 1 experienced a significant ALT flare (ALT >3 × ULN). ALT normalization was observed in 14 patients (74%) after a median (IQR) of 13 (9–16) weeks, and 8 patients (42%) achieved a combined response, with a median (IQR) treatment duration of 19 (16–27) weeks.

Throughout the observation period, median MELD scores remained stable, and improvements in liver function and ascites resulted in an improvement in CP class from B to A in 9 patients (47%).

The following AEs were reported: ascites (n=3, including 2 who had achieved a virologic response), liver transplantation (n=3, resulted in BLV discontinuation), ALT >3 × ULN (n=2, self-limited), acute abdomen requiring surgery with subsequent decompensation due to an incarcerated hernia (n=1), and death secondary to other reasons (n=1); no AEs were considered related to BLV treatment. During BLV treatment, asymptomatic increases in bile acids from BL were reported.

References

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7. Bogomolov P, Bueverov A, Barsukova N, et al. Bulevirtide In Patients With Non-Compensated Liver Cirrhosis Due To Hepatitis D [Poster 1259]. Paper presented at: American Association for the Study of Liver Diseases (AASLD); November 10-14, 2023; Boston, MA.
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9. Dietz-Fricke C, Degasperi E, Jachs M, et al. Safety and efficacy of off-label bulevirtide monotherapy in patients with HDV with decompensated Child-B cirrhosis-A real-world case series. *Hepatology.* 2024;80(3):664-673.

Abbreviations

AE=adverse event
BL=baseline
BLV=bulevirtide-gmod
CP=Child-Pugh
HCC=hepatocellular carcinoma
HTN=hypertension
HVPG=hepatic venous pressure gradient
LLoQ=lower limit of quantitation
MELD=Model for End-Stage Liver Disease
PEG-IFN=pegylated interferon
SAE=serious adverse event
ULN=upper limit of normal

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

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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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