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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 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 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 subcutaneous 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 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.[8]

In a retrospective study in France that evaluated the use of BLV 2 mg in patients who were awaiting liver transplantation (N=20), among 7 patients with decompensated cirrhosis, 3 achieved a virologic response and 5 achieved a biochemical response at Week 48; 3 patients were removed from the transplant list. Among patients with decompensated cirrhosis, pruritus and fatigue were reported by 1 patient each.[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-IFN. 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.

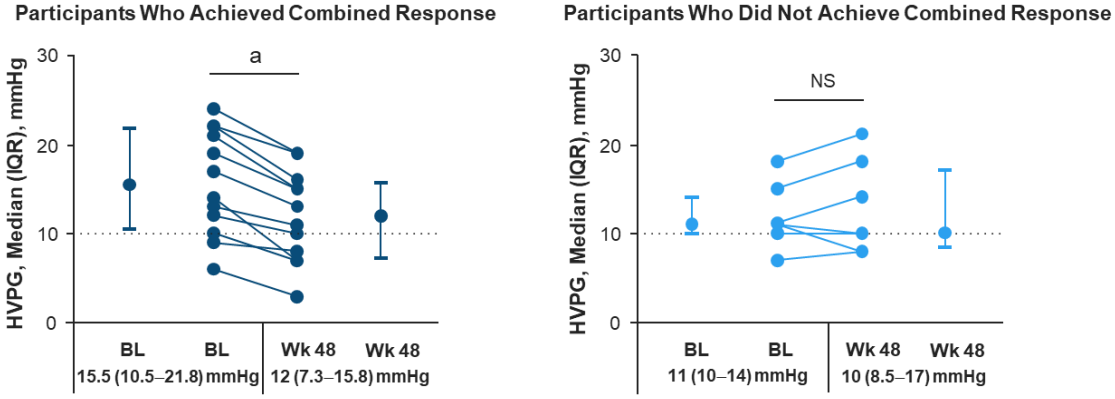
Table 1. IMPHROVE-D: Key Parameters at BL and Week 48[2]

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]



Abbreviation: NS=nonsignificant.
[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 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 ± SD age of 50±12.1 years, 36% were male, 59% used NUCs 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.

European Retrospective Study[8]

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 below the lower limit of quantitation) 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.

French Retrospective Study[9]

Study design and demographics

A multicenter retrospective study in France evaluated the real-world outcomes among patients who were awaiting liver transplantation and were either treated with BLV (BLV cohort, n=20) or not treated with BLV (control cohort, n=21). Data from the BLV cohort were evaluated for consecutive patients who had HDV and cirrhosis, were treated with BLV 2 mg/day, and were on a waiting list or undergoing evaluation for liver transplantation. Indications for liver transplantation evaluation included decompensated cirrhosis (ie, overt ascites, encephalopathy, or variceal bleeding), a minimum MELD score of 15 (some exceptions were permitted), and unresectable HCC, if AFP score was ≤2 (French AFP model).

The primary study outcome was virologic response (undetectable HDV RNA or a ≥2-log decrease vs BL) at Week 48. Secondary outcomes included virologic non-response (<1 log decrease in HDV RNA vs BL), biochemical response (ALT normalization vs BL), combined response (virologic and biochemical response), proportion of patients requiring liver transplantation, rate of liver-related events (decompensation, new HCC, or HCC progression) during BLV treatment or while on the waiting list, safety, and a comparison of outcomes between BLV-treated and untreated patients.

Results

BLV cohort: efficacy and safety among decompensated patients

Of the 7 patients with decompensated cirrhosis within the BLV cohort, at Week 48, virologic response was achieved in 3 patients (42.8%; 2 with CP Class C and 1 with Class B) and biochemical response was achieved in 5 patients (71.4%; 4 with CP Class C and 1 with CP Class B); 3 patients (42.9%; 2 with CP Class C and 1 with Class B) were removed from the transplant list. Overall, 2 AEs were considered related to BLV therapy. Outcomes in patients with decompensated cirrhosis who received BLV are summarized in Table 3.

Table 3. Patient Disease Characteristics, BLV Treatment Details and Outcomes, and BLV-Related Safety in Decompensated Patients (Meszaros et al)[9]

Pt Info	Disease Characteristics		Treatment Info	Treatment Outcomes	Last Status; Safety
	BL	Wk 48			
67 y/o M	CP: C12 MELD: 24 Ascites: G 2 Encephalopathy: G 2 HCC: None	CP: – MELD: – HCC: –	Follow-up period: 28 wk BLV duration: 7 wk	VR: No BR: No	LT: At Wk 7 for decompensation (MELD, 25) Last status: Died 5 mo post LT BLV-related AEs: None
35 y/o M	CP: C10 MELD: 12 Ascites: G 2 Encephalopathy: G 2 HCC: No	CP: A5 MELD: 13 HCC: No	Follow-up period: 72 wk BLV duration: 72 wk	VR: Wk 24; relapse at Wk 48 BR: Wk 24	LT: Delisted Last status: Alive; BR at Wk 72 on BLV; no VR BLV-related AEs: Pruritus at Wk 24
46 y/o, F	CP: C11 MELD: 16 Ascites: G 3 Encephalopathy: G 2 HCC: No	CP: B8 MELD: 16 HCC: BCLC A	Follow-up period: 95 wk BLV duration: 48 wk	VR: Wk 24, no relapse BR: Wk 24	LT: At Wk 48 for HCC BCLC A Last status: Alive BLV-related AEs: None
42 y/o, M	CP: C10 MELD: 31 Ascites: G 2 Encephalopathy: G 2 HCC: No	CP: A5 MELD: 13 HCC: No	Follow-up period: 53 wk BLV duration: 53 wk	VR: No BR: Wk 48, maintained through Wk 53	LT: Delisted Last status: Alive BLV-related AEs: None
47 y/o, M	CP: C12 MELD: 32 Ascites: G 2 Encephalopathy: G 2 HCC: No	CP: A5 MELD: 10 HCC: No	Follow-up period: 162 wk BLV duration: 142 wk	VR: Wk 48; relapse at Wk 142 BR: Wk 48	LT: At Wk 142 for decompensation (MELD, 29) Last status: Alive BLV-related AEs: None
40 y/o, F	CP: B7 MELD: 10 Ascites: Refractory Encephalopathy: G 2 HCC: No	CP: A6 MELD: 9 HCC: No	Follow-up period: 100 wk BLV duration: 98 wk	VR: Wk 48, relapsed at Wk 98 BR: Wk 48; maintained through last follow-up	LT: Delisted Last status: Alive BLV-related AEs: Fatigue
51 y/o, M	CP: B7 MELD: 11 Ascites: G 2 Encephalopathy: No HCC: BCLC B	CP: A6 MELD: – HCC: –	Follow-up period: 126 wk BLV duration: 34 wk	VR: Wk 34, no relapse BR: Wk 24	LT: At Wk 34 for HCC BCLC A Last status: Alive BLV-related AEs: None

Abbreviations: BCLC=Barcelona Clinic Liver Cancer stage; BR=biochemical response; F=female; G=grade; info=information; LT=liver transplantation; M=male; pt=patient; VR=virologic response.

Untreated cohort transplant and post-transplant outcomes vs BLV cohort

Twenty of the 21 patients underwent liver transplantation, with a mean (range) waiting time of 17.2 (1–32) weeks. No patients in the untreated cohort died post-transplant; 1 patient died while on the waiting list. The transplant-free survival rate (95% CI) at Month 3 was significantly longer in the BLV cohort than in the untreated cohort: 76.9% (44.2–91.9%) vs 36.7% (16.9–56.8%), respectively (P=0.00714). In a multivariate Cox regression analysis, MELD score at BL was a significant predictor of transplant-free survival (hazard ratio, 1.11; 95% CI: 1.04–1.18; P<0.001).

All patients had undetectable HDV and HBV RNA levels and were negative for hepatitis B surface antigen post-transplant. Concomitant NUC treatment by agent was as follows: entecavir, 53.1%; tenofovir disproxil fumarate, 43.6%; and lamivudine, 3.1%.

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Abbreviations

AE=adverse event
AFP=α-fetoprotein
BL=baseline
BLV=bulevirtide-gmod
CP=Child-Pugh
HCC=hepatocellular carcinoma
HTN=hypertension
HVPG=hepatic venous pressure gradient
IMPHROVE-D= Improvement of Portal Hypertension During Viral Suppression in Patients with Hepatitis Delta
MELD=Model for End-Stage Liver Disease
NUC=nucleos(t)ide analog
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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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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