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Hepcludex® (bulevirtide-gmod) Treatment Interruption/Adherence

This document is in response to your request for information regarding Hepcludex® (bulevirtide-gmod [BLV]) and the effect of adherence and treatment interruption on efficacy outcomes.

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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 at least 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.

BLV should be continued as long as it is associated with a response to treatment. The optimal treatment duration is unknown.

In all patients, manage the underlying HBV infection as clinically appropriate.

If a dose is missed, that dose should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and resume the original schedule.

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 Adherence and Effects of Treatment Interruption on Efficacy

In an analysis of MYR301, mean adherence rates in the BLV 2 mg and 10 mg groups at Week 96 were 98.1% and 94.6%, respectively. Virologic and biochemical response rates increased in both groups through Week 96. ISRs occurred more frequently in the BLV 10 mg group, which received two injections daily, than the BLV 2 mg group, which received one injection daily.[2]

Real-World Data on BLV Adherence and Effects of Treatment Interruption on Effectiveness

In a multicenter study in Italy that assessed BLV adherence rates and factors influencing adherence (N=273), adherence rates increased with a longer duration of BLV treatment and stabilized at approximately 80% after the first 6 months of treatment. At >12 months of BLV treatment, 77% of patients were considered highly adherent to treatment.[3]

A study using data from HERACLIS-HDV, a real-world cohort study, assessed rates of adherence to BLV 2 mg and the effect of adherence on virologic and biochemical outcomes. Participants with poor adherence (<90%) had lower rates of virologic response than participants with good adherence (≥90%) at Year 1 (40% vs 77%, respectively; *P*=0.108) and Year 2 (60% vs 97%; *P*=0.033).[4]

An observational, real-world study assessed the feasibility and efficacy of 12 months of BLV in participants with HBV/HDV-related cirrhosis and clinically significant portal hypertension. One participant reported variable adherence, including complete withdrawal of BLV for 1 to 2 months, followed by 50% adherence, and full adherence beginning at Month 6. HDV RNA levels rose during the period of nonadherence, then decreased after resumption of full adherence. No participants in the study experienced major complications or drug-related SAEs.[5]

In a study that evaluated outcomes in participants who discontinued BLV after long-term HDV RNA suppression, BLV was subsequently reintroduced in 3 participants after 13, 14, and 43 weeks of BLV discontinuation due to having detectable HDV RNA and either normal or elevated ALT levels. HDV RNA suppression was achieved in all 3 participants following retreatment.[6]

Clinical Data on BLV Adherence and Effects of Treatment Interruption on Efficacy

Study MYR301[2]

Study design and demographics

Study MYR301 was a randomized, open-label, phase 3 study that evaluated the efficacy and safety of SUBQ BLV 2 mg (n=49) or 10 mg (n=50) once daily for 144 weeks or delayed treatment for 48 weeks followed by SUBQ BLV 10 mg (n=51) for 96 weeks. Adherence in the BLV 2 mg and BLV 10 mg groups was assessed at each visit using patient diaries and study drug accountability, defined as the number of dispensed BLV vials vs the number of used/unused returned vials; overall adherence was calculated as the ratio of cumulative BLV dose actually administered to the total planned dose at each assessed time point. Baseline demographics in the BLV 2 mg and 10 mg groups were as follows: male, 61% and 60%, respectively; cirrhosis, 47% and 48%; HDV genotype 1, 100% and 96%; and mean ± SD liver stiffness, 14±8.2 and 14.8±9.3 kPa.

Results

In total, 96% of participants (47/49) in the BLV 2 mg group and 94% (47/50) in the BLV 10 mg group completed 96 weeks of treatment. Mean adherence rates ranged from 94.6% to 99.9% at all assessed time points and were higher in the BLV 2 mg group than in the BLV 10 mg group (Table 1).

Table 1. MYR301: Adherence Rates in the BLV 2 mg and BLV 10 mg Groups at Weeks 24, 48, and 96[2]

Parameter, Mean ± SD		BLV 2 mg (n=49)	BLV 10 mg (n=50)
Week 24	Total cumulative dose of BLV given, mg	335.6 ±5.5	1621.7 ±236.4
	Missed BLV injections	0.4±0.9	1±2.6
	Rate of adherence to BLV, %	99.9±1.6	96.5±14.1
Week 48	Total cumulative dose of BLV given, mg	669±7.3	3195.3±618.5
	Missed BLV injections	0.9±2.3	5±26.9
	Rate of adherence to BLV	99.6±1.1	95.1±18.4
Week 96	Total cumulative dose of BLV given, mg	1318±117.8	6357.5±1420.7
	Missed BLV injections	4.4±19	6.1±27.3
	Rate of adherence to BLV, %	98.1±8.8	94.6±21.1

Note: Participants in the BLV 2 mg required one injection of 2 mg; participants in the BLV 10 mg group required two injections of 5 mg.

Rates of virologic response (ie, undetectable HDV RNA levels or a decrease of ≥2 $\log_{10}$ IU/mL from baseline) and biochemical response increased through 96 weeks of treatment in both groups (Table 2).

Table 2. MYR301: Key Efficacy Outcomes at Week 48 and Week 96[2]

Outcome, n (%)	BLV 2 mg (n=49)		BLV 10 mg (n=50)	
	Week 48	Week 96	Week 48	Week 96
Combined response	22 (45)	27 (55)	24 (48)	28 (56)
Virologic response	36 (73)	37 (76)	38 (76)	41 (82)
Undetectable HDV RNA	6 (12)	10 (20)	10 (20)	18 (36)
ALT normalization	25 (51)	31 (63)	28 (56)	32 (64)

Overall, AEs occurred at similar rates across both treatment groups, although ISRs occurred more frequently in the BLV 10 mg group (n=15 [30%] at both Week 48 and Week 96), which received two injections daily, than in the BLV 2 mg group (Week 48, n=9 [18%]; Week 96, n=10 [20%]), which received one injection daily.

Real-World Data on BLV Adherence and Effects of Treatment Interruption on Effectiveness

Behavioral Study in Italy[3]

Study design and demographics

A cross-sectional, multicenter study in Italy consecutively enrolled patients during regularly scheduled visits between May and November 2025 to investigate BLV adherence rates and factors influencing adherence (N=273). The COM-B framework was applied using a 34-item questionnaire to explore behavioral drivers of adherence and unmet needs. At baseline,

66% of patients were age >50 years, 55% were Italian, and 84% had been receiving BLV treatment for >12 months.

Results

Adherence was assessed using an analysis of responses to three questions; 76% of patients were highly adherent, 18% were adherent, 5% were moderately adherent, and 1% were occasionally adherent. Overall, 17% of patients acknowledged occasional missed doses, with reports of "oversight" in 49% of cases. Adherence rates increased with a longer duration of BLV treatment, and the proportion of patients who were highly adherent increased from 63% at <3 months of BLV treatment to 64% at 3 to 6 months, 73% at 6 to 12 months, and to 77% at >12 months. Adherence stabilized at approximately 80% after the first 6 months of BLV treatment, and treatment effectiveness was reported as a key motivational factor to maintain adherence. Twenty percent of patients considered discontinuing BLV treatment, and the most common reason (34%) patients considered BLV discontinuation was that they believed their HDV was under control.

HERACLIS-HDV Cohort Study[4]

Study design and demographics

A study using data from HERACLIS-HDV, a retrospective-prospective cohort study, assessed rates of adherence to BLV 2 mg once daily, predictors of adherence, and the effect of adherence on virologic and biochemical response rates in participants with HCV (N=76). Baseline demographics were as follows: mean ± SD age, 50±12 years; male, 49%; cirrhosis, 59%; mean ± SD liver stiffness, 15.9±9.5 kPa, and injection drug use, 7%.

Results

Mean ± SD adherence was 98±6% at Year 1, 93±13% at Year 2, and 91±17% at Year 3 ($P \leq 0.01$). BLV discontinuations, defined as no executed BLV prescription for >3 months at the end of follow-up, were reported in 5 participants (7%) each in Year 1 and Year 2 and in 3 participants (6%) in Year 3; none discontinued due to AEs. Of the participants who discontinued BLV, 7 (54%) had cirrhosis, and 5 (38%) died (due to liver disease, n=4 [31%]; decompensated cirrhosis, n=3 [23%]; cholangiocarcinoma, n=1 [8%], and lung cancer, n=1 [8%]). Seven of the participants who discontinued BLV had achieved a virologic response (undetectable HDV RNA or ≥2-log decline from baseline), and 5 had achieved a biochemical response (normal ALT ≤40 IU/mL) at ≥6 months. No participant characteristic was associated with good (≥90%) or poor (<90%) adherence to BLV.

Overall rates of virologic response and biochemical response were 73% and 71%, respectively, at Year 1 and 93% and 74% at Year 2. Participants with poor adherence had lower virologic and biochemical response rates (Table 3).

Table 3. Effect of Adherence on Virologic and Biochemical Responses (Lakiotaki et al)[4]

Response, %		BLV 2 mg		
		Poor Adherence (<90%)	Good Adherence (≥90%)	*P*-Value
Year 1	Virologic response[a]	40	77	0.108
	Complete virologic response[b]	40	61	0.392

Response, %		BLV 2 mg		
		Poor Adherence (<90%)	Good Adherence (≥90%)	*P*-Value
Year 2	Virologic response[a]	60	97	0.033
	Complete virologic response[b]	40	87	0.04
	Biochemical response[c]	40	78	0.103

[a]Defined as undetectable HDV RNA or ≥2-log decline from baseline. [b]Defined as undetectable HDV RNA. [c]Defined as normal ALT (≤40 IU/mL).

Variable Adherence in a Real-World Study[5]

Study design and demographics

An observational, prospective, single-center study was conducted to assess the preliminary feasibility and efficacy of BLV in participants with HBV/HDV-related cirrhosis and clinically significant portal hypertension, and who were enrolled in a compassionate use program at INMI Spallanzani in Rome, Italy (N=13). The median (IQR) age was 42 (48–62) years, 54% of participants (7/13) were male, 38% (5/13) had HIV, and 15% (2/13) had concomitant cancer and HIV. FibroScan liver stiffness scores ranged from 9.5 kPa to 54 kPa. Clinical assessment, including for adherence, was conducted after Months 1, 2, 3, 4, 6, 9, and 12. The median (IQR) treatment duration of BLV was 11 (8.8–11.8) months. All participants had been receiving long-term nucleos(t)ide analog therapy for chronic HBV.

Initial BLV injection was performed at the outpatient clinic, and a brief training of the injection instruction manual was provided. Afterward, participants were instructed to self-administer BLV injections subcutaneously at home. During the clinical assessment periods, adherence was monitored via participant self-reports. Adherence was also indirectly confirmed through serum bile acid increases >2 × baseline levels during BLV treatment.

Results

One participant with HIV and hepatocellular carcinoma reported discontinuation of BLV between Months 3 and 4, 50% adherence until Month 6, and full adherence thereafter. HDV DNA and bile acid levels for this participant are presented in Table 4.

Table 4. On-Treatment HDV RNA and Bile Acid Levels in Participant With Variable Adherence (Visco et al)[5]

Parameter	Baseline	T1	T2	T3	T4	T6	T9	T12
HDV RNA, IU/mL	684,500	290,682	26,744	6930	47,025	27,041	13,707	950
Bile acid level, mcmol/L	4	25	13	20	12	32	9	15

Abbreviation: T1–T12=on-treatment Months 1–12.

Four additional participants experienced HDV RNA rebound between Months 6 and 9. One of those participants also had concomitant bile acid normalization, which was an indirect measure of nonadherence. Overall, no participants experienced systemic itching, although 2 participants reported injection site pruritus. Additionally, there were no major complications, and no participants experienced decompensation or drug-related SAEs.

BLV Reintroduction After Discontinuation[6]

A study reported the outcomes of 7 participants who had participated in a prospective BLV registry in Austria and had discontinued BLV after a period of long-term HDV RNA

suppression (undetectable HDV RNA). HDV RNA was detected in 3 participants, and BLV was subsequently reintroduced.

Participant 1 was a 68-year-old female with compensated cirrhosis who had received BLV treatment for 141 weeks and had achieved HDV RNA suppression for 39 weeks prior to discontinuing BLV. At Week 43 after BLV cessation, HDV RNA was detectable. ALT levels increased at Week 62. BLV 2 mg once daily was reintroduced at Week 65, resulting in normalization of ALT and decreasing HDV RNA levels. At retreatment Week 46, HDV RNA was undetectable. Retreatment with BLV was well tolerated, and the participant was also asymptomatic during the treatment-free period.

Participant 2 was a 53-year-old male with compensated cirrhosis and subclinical portal hypertension, had received BLV treatment for 60 weeks, and had achieved HDV RNA suppression for 12 weeks prior to discontinuing BLV. At Week 13 after BLV cessation, HDV RNA was detectable. BLV was immediately reintroduced despite ALT levels remaining normal. HDV RNA suppression was inconsistent during the following 60 weeks of retreatment, with repeated HDV RNA detectability following intervals (8–12 weeks) of undetectability. Transient noncompliance could not be ruled out, and PEG-IFN 180 mcg once weekly was added to the participant's regimen. After 12 weeks, HDV RNA became undetectable, and ALT levels rose as an expected consequence of the PEG-IFN.

Participant 3 was a 40-year-old female with fibrosis stage F1, had received BLV treatment for 27 weeks, and had achieved HDV RNA suppression for 24 weeks prior to discontinuing BLV. At Week 4 after BLV cessation, HDV RNA was detectable, and ALT was slightly elevated (61 U/L). While HDV RNA remained at the lower limit of detection (100 copies/mL), by Week 14 ALT levels had risen to 160 U/mL. BLV was then reintroduced, resulting in ALT normalization in the following weeks. HDV RNA suppression was also achieved after 17 weeks of BLV retreatment.

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5. Visco Comandini U, De Santis E, De Maria F, et al. "Real world" efficacy of bulevirtide in HBV/HDV-related cirrhosis including people living with HIV: Results from the compassionate use programme at INMI Spallanzani in Rome, Italy. *HIV Med.* 2023;24(10):1075-1082.
6. Jachs M, Panzer M, Hartl L, et al. Long-term follow-up of patients discontinuing bulevirtide treatment upon long-term HDV-RNA suppression. *JHEP Rep.* 2023;5(8):100751.

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Abbreviations

AE=adverse event
BLV=bulevirtide-gmod
COM-B=capability, opportunity, motivation-behavior
INMI=National Institute for Infectious Diseases
ISR=injection site reaction
PEG-IFN=pegylated interferon
SAE=serious adverse event
SUBQ=subcutaneous

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:

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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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