

Bulevirtide-gmod (HEPCLUDEX) in Chronic Hepatitis D Virus (HDV) Infection

National Drug Monograph

September 2026

VA Pharmacy Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION¹

Description / MOA	Bulevirtide-gmod is a sodium taurocholate co-transporting polypeptide (NTCP)-directed HDV attachment inhibitor. It is a synthetic 47-amino acid lipopeptide that inhibits HDV infection by binding to the NTCP receptor on the plasma membrane of hepatocytes, thereby blocking HDV attachment and entry.
Indication Under Review	Treatment of chronic HDV infection in adults without cirrhosis or with compensated cirrhosis. <u>Indication is approved under accelerated approval based on a decrease in HDV RNA and alanine aminotransferase (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).</u>
Dosage Regimen	8.5mg once daily administered by subcutaneous injection Treatment should be continued as long as it is associated with a response; optimal duration is currently unknown.
Dosage Forms Under Review	For injection: 8.5mg lyophilized powder or cake in a single-dose vial for reconstitution <ul style="list-style-type: none">This is a specialty distribution medication.
Pretreatment Procedures	Manage and treat the underlying hepatitis B virus (HBV) infection in all patients, as clinically appropriate.

EFFICACY CONSIDERATIONS

Trial	MYR 301^{2,3}
Design	Phase 3, multicenter, randomized, open-label, parallel-arm trial
Population	N= 150. Eligible patients were 18 to 65 years old with chronic HDV and ALT level >1x to <10x ULN. <u>Definition of chronic HDV:</u> Positive serum anti-HDV antibody or HDV RNA detected by PCR at least 6 months before screening plus HDV RNA detected by PCR at screening. <u>Key Exclusions:</u> Decompensated cirrhosis (Child-Pugh Class B or C), HCV or HIV coinfection, CrCl <60 mL/min, active or suspected malignancy, history of hepatic carcinoma, NYHA Class III-IV heart failure, receipt of interferon therapy within 6 months before screening, platelets <60,000 cells/mm ³ , pregnancy/actively lactating <u>Demographics:</u> 57% male, 83% White, mean age: 42 years, 47% cirrhosis, 99% HDV genotype 1, 84% HBV genotype D, 56% previously received interferon therapy, 60% were receiving concomitant nucleos(t)ide analogs, mean HDV RNA level: 5.0 log ₁₀ IU/mL
Intervention	Bulevirtide 2mg per day or 10mg per day for 144 weeks
Comparator	No treatment for 48 weeks, followed by bulevirtide 10mg per day for 96 weeks
Results	<ul style="list-style-type: none">Combined Response: Virologic Response + Biochemical Response<ul style="list-style-type: none">Virologic Response: Undetectable HDV RNA (<50 IU/mL with target not detected) or decrease ≥2 log₁₀ IU/mL from baselineBiochemical Response: Normalization of ALT level (≤34 U/L for women and ≤49 U/L for men)

Primary and Key Secondary Endpoints

Outcome	Bulevirtide 2mg (n/N)		Bulevirtide 10mg ^c (n/N)		Delayed Treatment	p-value
	Week 48	→ Week 96	Week 48	→ Week 96	Week 48 → Week 96	
Combined Response ^a	45% (22/49)	→ 55% (27/49)	48% (24/50)	→ 56% (28/50)	2% (1/51) → 39% (20/51)	<0.001
Virologic Response ^b	71% (35/49)	→ 76% (37/49)	76% (38/50)	→ 82% (41/50)	4% (2/51) → 90% (46/51)	N/A
Undetectable HDV RNA ^b	12% (6/49)	→ 20% (10/49)	20% (10/50)	→ 36% (18/50)	0% (0/51) → 24% (12/51)	N/A
ALT Normalization ^b	51% (25/49)	→ 63% (31/49)	56% (28/50)	→ 64% (32/50)	12% (6/51) → 43% (22/51)	N/A

^a Primary endpoint ^b Secondary endpoint

^c The MYR 301 protocol specified bulevirtide dose as 10 mg; however, a dose recovery study later showed that delivered dose was 8.5 mg.

SAFETY CONSIDERATIONS^{1,2,3}

Boxed Warnings	Posttreatment Severe Acute Exacerbation of Hepatitis D and B: Severe exacerbations may occur after treatment is discontinued, especially in patients with cirrhosis. Monitor hepatic function closely with both clinical and laboratory follow-up, including HBV DNA and HDV RNA viral loads, for at least 6 months in patients who discontinue treatment. Resumption of antiviral therapy may be warranted.
Contraindications	None
Other Warnings	Hypersensitivity Reactions Including Anaphylaxis: If signs of symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue bulevirtide-gmod and initiate appropriate treatment. Bile Salt Elevations: Bulevirtide-gmod inhibits NTCP-mediated bile acid transport, leading to asymptomatic, dose-dependent increases in total serum bile salt levels that resolve upon discontinuation.

Top AEs	Eosinophilia (33%), injection site reactions (30%), headache (20%), abdominal pain (18%), fatigue (14%), pruritus (14%)
Drug Interactions	<p>Low potential for drug-drug interactions via CYP enzymes or transporters at clinically relevant concentrations</p> <ul style="list-style-type: none"> No CYP enzyme or transporter mediated inhibition/induction by bulevirtide-gmod is anticipated. Due to peptide catabolism of bulevirtide-gmod, potential of other drugs to impact its pharmacokinetics – via CYP enzymes or transporters – is low.
Pregnancy	<p>Insufficient data in humans</p> <p>Animal studies showed no adverse effects on embryofetal development when bulevirtide-gmod administered at exposures significantly higher than the recommended human dose.</p>
Lactation	<p>Insufficient data in humans</p> <p>In animal studies, bulevirtide-gmod was not measured in the plasma of nursing animals. Due to its high protein binding, liver tropism, and high specificity for NTCP, bulevirtide-gmod is not likely to be secreted in milk.</p>
Renal Impairment	<p>No dosage adjustment recommended in patients with creatinine clearance (CrCl) ≥ 15 mL/min.</p> <p>Bulevirtide-gmod has not been studied in patients with end-stage renal disease (CrCl < 15 mL/min).</p>
Hepatic Impairment	<p>No dosage adjustment recommended in patients with mild hepatic impairment (Child-Pugh Class A).</p> <p>Bulevirtide-gmod has not been studied in patients with moderate (Class B) or severe (Class C) impairment.</p>
Antiviral Resistance	<p>HBV or HDV viruses resistant to bulevirtide-gmod in cell culture have not been identified to date. In clinical trials, no baseline polymorphisms or post-baseline substitutions in the bulevirtide-gmod regions of HBsAg or were associated with virologic non-response or breakthrough.</p> <p>Cross-resistance between bulevirtide-gmod and nucleos(t)ide analog reverse transcriptase inhibitors approved for chronic HBV infection is not expected given their different mechanisms of action.</p>

THERAPEUTIC ALTERNATIVES

DRUG	VANF	CFU	Dosing	Clinical Guidance
Bulevirtide-gmod, inj	No	Yes	8.5mg SC daily	FDA-approved treatment for chronic HDV; unknown treatment duration
Peginterferon alfa-2a, inj	Yes	No	180mcg SC weekly	Off-label use for HDV; treatment duration of 48 weeks

POTENTIAL PLACE IN THERAPY⁴⁻¹¹

- Treatment for chronic HDV has historically relied on off-label use of pegylated interferon-alfa (pegIFN- α), a regimen associated with significant adverse effects and poor tolerability. Among patients who completed therapy, undetectable HDV RNA at 24 weeks after treatment cessation was achieved in only approximately 30%, and relapse rates following discontinuation remained high even among those who attained sustained virologic response or received prolonged courses exceeding 48 weeks.
- Bulevirtide-gmod, a first-in-class NTCP entry inhibitor, is the only FDA-approved therapy for chronic HDV infection in patients without cirrhosis or with compensated cirrhosis. In the pivotal MYR301 trial, bulevirtide was generally well tolerated and demonstrated durable virological and biochemical responses – 48% of patients receiving bulevirtide 10mg achieved a combined response at Week 48, increasing to 56% at Week 96 and sustained through Week 144. Notably, patients with suboptimal early virologic response at week 24 still derived meaningful benefit from continued therapy – 71% (10/14) achieved virologic response by week 96, underscoring the importance of treatment persistence.
- Combination therapy with bulevirtide and pegIFN- α may be considered in selected patients. In the MYR204 study, 46% of patients receiving bulevirtide 10mg plus pegIFN- α achieved undetectable HDV RNA at 24 weeks post-treatment, compared with 12% in the bulevirtide monotherapy arm and 17% in the pegIFN- α monotherapy group. However, the patient populations most likely to benefit from combination therapy, as well as the optimal sequencing of the individual agents, remain to be clearly defined.
- The optimal duration of bulevirtide-gmod therapy has not been established. Current regulatory and clinical guidance recommend continuation of treatment for as long as clinical benefit is evident, as assessed by ongoing virologic response. In patients who discontinue treatment, there is potential for acute exacerbation of HBV and HDV infection, particularly in those with cirrhosis. Resumption of antiviral treatment may be warranted in these cases.
- Concurrent chronic HBV infection should be appropriately managed with nucleos(t)ide analogs, as clinically indicated. These agents have no direct activity against HDV and do not preclude the use of bulevirtide-gmod.
- Patients with Child-Pugh Class B or C cirrhosis are generally not candidates for bulevirtide-gmod therapy. Referral for liver transplantation evaluation can be considered in this population.

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