Medical Drug Clinical Criteria

Subject:	Hepcludex (bulevirtide-gmod)		
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Overview

This document addresses the use of Hepcludex (bulevirtide-gmod), a sodium taurocholate co-transporting polypeptide (NTCP)-directed HDV attachment inhibitor, for the treatment of chronic hepatitis delta (D) virus (HDV) infection in adults with cirrhosis or with compensated cirrhosis. Hepcludex blocks the entry of HBV and HDV into hepatocytes by binding to and inactivating sodium taurocholate co-transporting polypeptide (NTCP), a bile salt liver transporter serving as essential HBV/HDV entry receptor.

Hepatitis D, also known as “delta hepatitis,” is a liver infection caused by the hepatitis D virus (HDV). Hepatitis D is a satellite virus that only occurs in people who are also infected with the hepatitis B virus (HBV). Prevention of hepatitis B with hepatitis B vaccine also protects against future hepatitis D infection. HDV is a small, single stranded, circular ribonucleic acid (RNA) virus, which acquires the envelope proteins from HBV infected cells to assemble and disseminate. The combination of HDV and HBV infection is considered the most severe form of chronic viral hepatitis due to more rapid progression towards liver-related death and hepatocellular carcinoma. The mechanisms by which HDV accelerates progression and more severe disease are not clear. Initial assessment for HDV includes testing for anti-HDV total immunoglobulin antibodies. If anti-HDV total antibodies are detected, quantitative testing with polymerase chain reaction (PCR) should follow. The PCR test looks for evidence of active HDV infection, specifically HDV RNA, which provides evidence of active HDV replication if present. Pegasys (peginterferon alfa-2a), interferon-based therapies, have been used off-label. However, relapse is common after discontinuation of therapy.

The 2018 American Association for the Study of Liver Diseases (AASLD) HBV guidance recommend 12 months of peginterferon alfa-2a (Pegasys) for patients with elevated HDV RNA and ALT. The guideline predates the approval of Hepcludex. The 2023 European Association for the Study of the Liver (EASL) recommends considering Hepcludex, Pegasys, or, in select individuals, a combination of these two agents for chronic HDV with compensated liver disease.

Hepcludex was FDA-approved under accelerated approval based on participants who achieved a decrease in HDV RNA and alanine aminotransferase (ALT) normalization. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). In a moderate quality trial, Hepcludex achieved a combined response at week 48 more often than delayed treatment/control, defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline plus ALT normalization (48% vs 2%; NNT=3) (Wedemeyer 2023). In a low quality, open-label safety extension, relapse rates after discontinuation of Hepcludex were common (Asselah 2024).

The optimal duration of treatment with Hepcludex is unknown. Labeling states treatment should be continued as long as it is associated with a response to treatment.

Hepcludex carries a boxed warning due to the risk of severe acute exacerbations of HDV and HBV infection that may occur after Hepcludex is discontinued, especially in patients with cirrhosis, who may be at increased risk of more severe flares or progression to hepatic decompensation.

Clinical Criteria

When a drug is being reviewed for coverage under a member’s medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Hepcludex (bulevirtide-gmod)

Initial requests for Hepcludex (bulevirtide-gmod) may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of chronic hepatitis delta (D) virus (HDV) infection; **AND**
III. Individual does not have cirrhosis, or has compensated cirrhosis; **AND**
IV. Documentation is provided that chronic HDV infection is verified by presence of positive serum anti-hepatitis delta virus (HDV) antibody **or** HDV RNA; **AND**
V. Individual has elevated alanine transaminase (ALT) level of greater than 1 times the upper limit of normal (ULN).

Continuation requests for Hepcludex (bulevirtide-gmod) may be approved if the following criteria are met:

I. Documentation is provided that individual has a decrease in HDV RNA; **AND**
II. Individual has a normalization in alanine transaminase (ALT) levels.

Approval Duration
Initial and continuation requests: 1 year

Quantity Limits

Hepcludex (bulevirtide-gmod) Quantity Limits

Drug	Limit
Hepcludex (bulevirtide-gmod) 8.5 mg vial	1 vial per day

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

C9399	Unclassified drugs or biologicals [when specified as Hepcludex (bulevirtide-gmod)]
J3590	Unclassified biologics [when specified as Hepcludex (bulevirtide-gmod)]

ICD-10 Diagnosis

B18.0	Chronic viral hepatitis B with delta-agent

Document History

New: 06/08/2026
Document History:
- 06/08/2026 – Annual Review: Add new clinical criteria document for new agent Hepcludex. Coding Reviewed: Added HCPCS NOC C9399, J3590 and ICD-10-CM B18.0.

References

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Federal and state laws or requirements, contract language, and Plan utilization management programs or policies may take precedence over the application of this clinical criteria.

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