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Policy Number: C30954-A

Hepcludex (bulevirtide-gmod)

PRODUCTS AFFECTED

Hepcludex (bulevirtide-gmod)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Chronic Hepatitis D Infection

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. This clinical policy will be reviewed along with state and federal requirements, the benefit being administered, and formulary preferencing. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available. The Pharmacy and Therapeutics Committee has determined that biosimilars may be preferred.

A. CHRONIC HEPATITIS D INFECTION:
   1. Documented diagnosis of hepatitis D virus (HDV) infection confirmed by positive anti-HDV antibody test and detectable HDV RNA (HDV viral load) within the past 6 months [DOCUMENTATION REQUIRED]

AND

2. Documentation of positive hepatitis B surface antigen (e.g., HBsAg)
   AND
3. Documentation of elevated alanine transaminase (ALT) laboratory values within the past 12 months (see Appendix 1)
   AND
4. Documentation of treatment plan for concurrent hepatitis B virus (HBV) management (e.g., entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide) or treatment not clinically indicated per current AASLD guidance (see Appendix 2)
   AND
5. Member has no evidence of cirrhosis
   AND
6. Member had no evidence of previous (within the last 2 years) or current decompensated liver disease (including ascites, hepatic encephalopathy, variceal bleeding, or Child-Pugh class B or C)

CONTINUATION OF THERAPY:

A. CHRONIC HEPATITIS D INFECTION:
   1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
      AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
      AND
   3. Documentation of positive clinical response as demonstrated by ANY of the following [DOCUMENTATION REQUIRED]:
      a. Undetectable HDV RNA
      b. ≥ 2 log10 IU/mL decline from baseline
      c. Normalization of alanine transaminase (ALT) laboratory values (see Appendix 1)
      d. Improvement in other markers of liver disease

      AND
   4. Member has no evidence of cirrhosis or decompensated liver disease (including ascites, hepatic encephalopathy, variceal bleeding, or Child-Pugh class B or C)

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified gastroenterologist, hepatologist, or infectious disease specialist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:

8.5 mg once daily

PLACE OF ADMINISTRATION:

The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Hepatitis D Agents

FDA-APPROVED USES:
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 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).

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX 1:
Alanine aminotransferase (ALT) is a hepatocellular enzyme and a sensitive marker of liver injury. ALT is predominantly localized within hepatocytes; therefore, hepatocellular damage or inflammation results in the release of ALT into the circulation, leading to elevated serum concentrations.

For the purposes of clinical assessment, ALT values may be interpreted as follows:

- Normal ALT
  Females: ≤19 U/L
  Males: ≤30 U/L

- Elevated ALT
  ≥ 2 times ULN

Elevated ALT levels should be interpreted in the context of the patient's overall clinical presentation, underlying liver disease, and other laboratory findings, as persistent elevations may indicate ongoing hepatic inflammation, hepatocellular injury, or disease progression. For patients with chronic hepatitis delta virus (HDV) infection, ALT is commonly used to assess disease activity and monitor response to treatment.

APPENDIX 2:
The AASLD 2025 guidelines recommend antiviral therapy with entecavir, tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) for chronic hepatitis B, guided by disease phase, viral load, ALT levels, fibrosis stage, and patient-specific factors.

Disease Phases and Treatment Indications
Chronic hepatitis B is classified into five phases: immune-tolerant, HBeAg-positive immune active, HBeAg-negative immune active, inactive carrier, and HBsAg-negative immune clearance. Treatment is generally indicated for:

- Immune-active phase:
  Elevated ALT (≥2× ULN) and high HBV DNA (HBeAg-positive >20,000 IU/mL; HBeAg-negative >2,000 IU/mL)
- Immune-tolerant phase:
  Consider treatment in patients >40 years, or with significant fibrosis (F2 or higher) or inflammation (grade ≥2)
- Indeterminate (“grey zone”) phase:
  Individualized risk assessment guides therapy initiation
- Special populations:
  Pregnant individuals with HBV DNA >200,000 IU/mL, patients with coinfections (HCV, HDV, HIV), and those with cirrhosis or immunocompromised states require tailored management

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Hepatitis D virus (HDV) is a liver infection caused by the hepatitis delta virus, which requires co-infection with hepatitis B virus (HBV) to replicate. Infection may be acute or progress to chronic disease. Chronic HDV is defined by the persistence of HDV antibodies for more than 6 months with detectable HDV RNA or hepatitis D antigen (HDAg).

HDV infection occurs either as a coinfection with HBV or as a superinfection in individuals with existing chronic HBV. In the United States, HDV is relatively uncommon and is most often reported among persons who inject drugs and individuals from regions with high endemicity (e.g., Eastern/Southern Europe, the Mediterranean, the Middle East, West and Central Africa, East Asia, and the Amazon Basin). Although prevalence data are limited, an estimated 1% to 4% of adults with chronic HBV are coinfected with HDV.

HDV is transmitted through percutaneous or mucosal exposure to infected blood or body fluids. Risk factors largely mirror those for HBV infection. Populations at highest risk include persons who inject drugs, individuals with multiple sexual partners, men who have sex with men (MSM), and those with coexisting HIV or hepatitis C virus (HCV) infection. Individuals from regions with high HDV endemicity are also at increased risk.

Additional at-risk groups include household contacts of infected individuals, people with occupational exposure to blood or body fluids, and patients receiving hemodialysis. In the United States, HDV prevalence is notably higher among persons who inject drugs, with some studies reporting coinfection rates of up to 50% among those with HBV.

The clinical course of HDV infection is variable. In immunocompetent adults with HBV/HDV coinfection, more than 95% clear both viruses. In contrast, HDV progresses to chronic infection in approximately 90% of individuals with superinfection. Chronic HDV infection is associated with a more aggressive disease course than HBV monoinfection, with accelerated progression to advanced fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and hepatic decompensation.

The American Association for the Study of Liver Diseases (AASLD) recommends screening in patients with chronic HBV who are at high risk for HDV, including those with HIV infection, injection drug users, MSM, those at risk for sexually transmitted diseases, and immigrants from areas of high HDV endemicity. In addition, patients who are hepatitis B surface antigen (HBsAg)-positive with low or undetectable HBV DNA but high alanine aminotransferase (ALT) levels should be considered for HDV testing.

Patients with confirmed chronic HDV infection should be evaluated for treatment. Current AASLD guidelines recommend pegylated interferon (peg-IFN) alfa-2a or alfa-2b for 48 weeks in patients with detectable HDV RNA and elevated ALT levels. Treatment response rates are limited, with approximately 29% of patients achieving undetectable HDV RNA 24 weeks after therapy completion, and long-term sustained response observed in about 12% of patients. Nucleoside or nucleotide analogues (NAs) (e.g., entecavir, tenofovir) are not effective against HDV and do not improve HDV-specific treatment outcomes; however, they are indicated for concomitant treatment in patients with elevated HBV DNA levels. In patients with fulminant hepatitis or advanced liver disease, liver transplantation may be considered.

Hepcludex (bulevirtide-gmod) is a viral entry inhibitor that binds to sodium taurocholate co-transporting polypeptide (NTCP) surface receptors, preventing entry of HDV and HBV into hepatocytes.

Clinical Trials

MYR301 (NCT03852719) was a multicenter, randomized, open-label, parallel-group Phase 3 study evaluating the efficacy and safety of Hepcludex in adults with chronic HDV infection, either without cirrhosis or with compensated cirrhosis. A total of 100 participants received Hepcludex 8.5 mg administered subcutaneously once daily. Although the protocol-specified dose was 10 mg, a subsequent dose recovery

study demonstrated that the actual delivered dose was 8.5 mg.

Participants were randomized to either immediate treatment (Hepcludex 8.5 mg daily for 144 weeks) or delayed treatment (observation for 48 weeks followed by Hepcludex 8.5 mg daily for 96 weeks).

Randomization was stratified by the presence or absence of compensated cirrhosis, and participants were followed for an additional 96 weeks after treatment completion.

The primary efficacy endpoint was combined response at Week 48, defined as: Undetectable HDV RNA or ≥2 log10 IU/mL reduction from baseline in HDV RNA and normalization of alanine aminotransferase (ALT).

At Week 48, the rate of undetectable HDV RNA (defined as less than the lower limit of quantification [50 IU/mL with target not detected) was 20% in the group immediately treated with Hepcludex versus 0% in the delayed-treatment group. The rate of undetectable HDV RNA in the group immediately treated with Hepcludex continued to increase at Weeks 96 and 144 to 36% and 50%, respectively.

Efficacy outcomes within the two treatment groups were measured at end of therapy (144 weeks for the immediate-treatment group and 96 weeks for the delayed-treatment group) and at various timepoints after the end of therapy. While additional patients were noted to achieve efficacy endpoints between Week 48 of treatment and end of therapy, response rates deteriorated following drug discontinuation.

MYR204 (NCT03852433) was a randomized, open-label, exploratory Phase 2b study that provided additional efficacy data for Hepcludex in 50 adults with chronic HDV infection without cirrhosis or with compensated cirrhosis.

Participants received Hepcludex 8.5 mg subcutaneously once daily for 96 weeks. At Week 96, 48% achieved a combined response (virologic response plus ALT normalization) and 22% achieved undetectable HDV RNA.

At 24 weeks post-treatment, combined response rate declined to 26% and undetectable HDV RNA was maintained at 12%.

The Phase 3 MYR301 trial and supportive Phase 2b MYR204 study demonstrate that Hepcludex provides clinically meaningful antiviral and biochemical improvements in adults with chronic HDV infection, including patients with compensated cirrhosis. Long-term treatment was associated with substantial rates of combined response and HDV RNA suppression, while post-treatment declines in response suggest ongoing therapy may be necessary to maintain disease control in a proportion of patients. These findings support Hepcludex as an effective treatment option for chronic HDV infection, a disease with historically limited therapeutic options.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Hepcludex (bulevirtide-gmod) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Hepcludex include: no labeled contraindications.

Exclusions/Discontinuation:
Hypersensitivity reactions have been reported with Hepcludex (bulevirtide-gmod). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Hepcludex and initiate appropriate treatment.
There are insufficient human data on the use of Hepcludex during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Hepcludex was not studied in pregnant women.

OTHER SPECIAL CONSIDERATIONS:
Hepcludex (bulevirtide-gmod) has a Black Box Warning for posttreatment severe acute exacerbation of Hepatitis D and B. Severe acute exacerbations of hepatitis D and hepatitis B 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. Monitor hepatic function closely with both clinical and laboratory follow-up, including hepatitis B virus (HBV) DNA and hepatitis delta virus (HDV) RNA viral load, for at least six months in patients who discontinue Hepcludex. Resumption of antiviral therapy may be warranted.

Hepcludex requires reconstitution prior to administration by subcutaneous injection.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Hepcludex SOLR 8.5MG single-dose vial

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SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q3 2026