PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis D Virus – Hepcludex Prior Authorization Policy
- Hepcludex® (bulevirtide-gmod subcutaneous injection – Gilead)

REVIEW DATE: 05/26/2026

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Hepcludex, a sodium taurocholate co-transporting polypeptide (NTCP)-directed HDV attachment inhibitor, is indicated for the treatment of **chronic hepatitis delta virus (HDV)** infection in adults without cirrhosis or with compensated cirrhosis.[1] This indication was approved under accelerated approval based on patients 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 confirmatory trial(s).

Hepcludex should be continued as long as it is associated with a response to treatment.[1] The optimal treatment duration is unknown.

In all patients, manage the underlying hepatitis B virus (HBV) infection as clinically appropriate.[1]

Disease Overview

HDV is the most severe form of viral hepatitis and occurs only in the setting of HBV infection.[2,3] HDV is a small, defective RNA virus that requires hepatitis B virus surface antigen (HBsAg) for entry into hepatocytes and for assembly and secretion of new virions.[3] Transmission of the virus occurs via parenteral, percutaneous, and sexual exposure. HDV enters hepatocytes via the NTCP receptor and replicates using host enzymes. Compared with HBV monoinfection, co-infection with HDV and chronic HBV is associated with a significantly greater risk of disease progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma (two- to six-times higher), and liver-related mortality (two- to three-times higher).[2,3] It is estimated that 30% to 70% of patients have cirrhosis at the time of HDV diagnosis. The primary goal of treatment for HDV is to prevent cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related mortality through suppression of HDV replication and reduction of hepatic inflammation and fibrosis.[3] While the optimal endpoint of treatment for HDV would be clearance of HBsAg, this is rarely achieved. Therefore, the regulatory-accepted combined response is defined as ≥2 $\log_{10}$ decline in HDV RNA (or undetectable) plus ALT normalization.

Clinical Efficacy

The efficacy of Hepcludex in adults with chronic HDV infection without cirrhosis or with compensated cirrhosis is based on data from a multicenter, open-label, parallel-arm, randomized Phase III trial called MYR 301 (n = 151).[1,4-6] The mean patient age was 42 years, 47% of patients had compensated cirrhosis, 60% of patients received concomitant nucleos(t)ide analog therapy for chronic HBV (those who did not were ineligible based on guideline recommendations for the management of HBV), and 56% of patients previously received interferon therapy. Patients received up to 144 weeks of active treatment and were followed for 96 weeks after treatment ended. Through Week 144 with Hepcludex treatment, there was continued on-treatment improvement in HDV RNA and ALT levels (Table 1). Upon discontinuation, responses substantially diminished over time (Table 1).

Table 1. MYR 301: Summary of Key Efficacy Endpoints at Weeks 48, 96, and 144 and Follow-Up.[1,4-6]

	Hepcludex® (bulevirtide-gmod SC injection)		**Control** (n = 51)**
	10 mg$^{\beta}$ (n = 50)	**2 mg (n = 49)**	
Combined response*			
Week 48	48%	45%	2%
Week 96	56%	55%	39%
Week 144 (EOT)	54%	57%	56%
48-week follow-up	20%	22%	18%
96-week follow-up	24%	24%	24%
Virologic response†			
Week 48	76%	71%	4%
Week 96	82%	76%	90%
Week 144 (EOT)	76%	73%	92%
48-week follow-up	40%	29%	28%

96-week follow-up	30%	33%	32%
ALT normalization			
Week 48	56%	51%	12%
Week 96	64%	63%	~40%
Week 144 (EOT)	60%	59%	58%
48-week follow-up	28%	27%	24%
96-week follow-up	32%	24%	28%
Undetectable HDV RNA			
Week 48	20%	12%	n = 0
Week 96	36%	20%	24%
Week 144 (EOT)	50%	29%	52%
48-week follow-up	24%	16%	16%
96-week follow-up	22%	20%	20%

SC – Subcutaneous; ** Reflects 48 weeks of treatment with Hepcludex (Week 48 to Week 96); β The MYR 301 protocol specified the Hepcludex dose as 10 mg; however, a dose recovery study later showed that the delivered dose was 8.5 mg; * Undetectable hepatitis D virus (HDV) RNA level or a level that decreased by ≥ 2 $\log_{10}$ IU/mL from baseline (virologic response) and normalization of alanine aminotransferase (ALT) [biochemical response]; EOT – End of treatment; † Undetectable HDV RNA or ≥ 2 $\log_{10}$ decline from baseline; ALT – Alanine aminotransferase; HDV – Hepatitis D virus.

Guidelines

Hepcludex has been addressed in the European Association for the Study of the Liver Clinical Practice Guidelines on HDV (2023).[7] Antiviral therapy is recommended for all patients with chronic HDV, including consideration of pegylated interferon alfa and Hepcludex, though the optimal duration for Hepcludex is unknown and relapse after short courses is common. The American Gastroenterological Association Clinical Practice Update (2025) highlights Hepcludex as an emerging therapy; pegylated interferon alfa remains the only treatment (off-label use), though response rates are modest and relapse is common.[2]

Safety

Hepcludex has a Boxed Warning regarding post-treatment severe acute exacerbation of HDV and HBV.[1] Severe acute exacerbations of HDV and HBV 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. Safety and efficacy have not been studied in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Hepcludex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hepcludex as well as the monitoring required for adverse events and long-term efficacy, approval requires Hepcludex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Hepcludex® (bulevirtide-gmod subcutaneous injection – Gilead) is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Chronic Hepatitis D Virus.** Approve for 1 year if the patient meets the following (A or B):
   - **A)** Initial Therapy: Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient does not have cirrhosis; OR
       - **b)** Patient has compensated cirrhosis (Child-Pugh Class A); AND
     - **iii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has underlying chronic hepatitis B virus infection; AND
       - **b)** According to the prescriber, chronic hepatitis B virus infection is being managed according to standard of care; AND
     - **iv.** The medication will be prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist, or liver transplant physician; OR
   - **B)** Patient is Currently Receiving Hepcludex. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** Patient does not have cirrhosis; OR
       - **b)** Patient has compensated cirrhosis (Child-Pugh Class A); AND
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has underlying chronic hepatitis B virus infection; AND
       - **b)** According to the prescriber, chronic hepatitis B virus infection is being managed according to standard of care; AND
     - **iii.** According to the prescriber, patient has evidence of clinical benefit; AND Note: Examples of clinical benefit are a ≥ 2 $\log_{10}$ decline in hepatitis D virus (HDV) RNA from baseline, undetectable HDV RNA, normalization of alanine aminotransferase level.
     - **iv.** The medication will be prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist, or liver transplant physician.

CONDITIONS NOT COVERED

Hepcludex® (bulevirtide-gmod subcutaneous injection – Gilead) is(are) considered not medically necessary for ANY other use(s). Criteria will be updated as new published data are available.

REFERENCES

1. Hepcludex® subcutaneous injeciton [prescribing information]. Foster City, CA: Gilead; May 2026.
2. Kushner T, Cohen SM, Ahn J, and Wong RJ. American Gastroenterological Association clinical practice update on management of hepatitis delta: commentary. *Gastroenterol*. 2025;169:1063-1069.
3. Negro F and Lock AS. Hepatitis D. A review. *JAMA*. 2023;330(24):2376-2387.
4. Wedemeyer H, Aleman S, Brunetta MR, et al; for the MYR 301 Study Group. A Phase 3, randomized trial of bulevirtide in chronic hepatitis D. *N Engl J Med.* 2023;389:22-32.
5. Wedemeyer H, Aleman S, Brunetta M, et al. Bulevirtide monotherapy in patients with chronic HDV: efficacy and safety results through week 96 from a Phase III randomized trial. *J Hepatol*. 2024;81(4):621-629.
6. Wedemeyer H, Aleman S, Blank A, et al. 144 Weeks of bulevirtide monotherapy for chronic hepatitis D; Final and posttreatment results from a Phase III randomized trial. *J Hepatol*. 2026 April 9 [Online ahead of print].
7. European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis delta virus. *J Hepatol.* 2023;79:433-460.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	05/26/2026