PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY POLICY – 5.01.636

Chronic Hepatitis B and D Antiviral Therapy

Effective Date:	Nov. 1, 2026	RELATED MEDICAL POLICIES:
Last Revised:	Oct. 13, 2026	5.01.606 Hepatitis C Antiviral Therapy
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Hepatitis B is a vaccine-preventable liver infection that is caused by the hepatitis B virus (HBV). Most individuals recover from the infection, but a small percentage goes on to develop chronic hepatitis B (CHB). This risk is higher in younger individuals. In the early stage, the infection may show no symptoms or nonspecific symptoms such as fatigue. Later, the infection can have overlapping symptoms with liver disease as well as extrahepatic manifestations. Hepatitis D virus (HDV) infection is caused by the hepatitis D virus. HDV cannot survive or spread on its own. An individual can only get hepatitis D if they also have hepatitis B, because HDV depends on HBV to reproduce and spread in the body. Chronic hepatitis D infection can cause liver damage to worsen more quickly, leading to scarring of the liver (cirrhosis) and increasing the risk of developing liver cancer. This policy describes the criteria when hepatitis B and D drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity

Baraclude (entecavir)	**Baraclude (entecavir) may be considered medically necessary when all the following criteria are met:**
	• The individual is aged 2 years or older
	AND
	• Has a confirmed diagnosis of chronic hepatitis B virus (HBV) infection
	AND
	• Meets 1 of the following:
	  ○ Is aged 18 years or older with compensated or decompensated liver disease
	  OR
	  ○ Is aged 2 to 17 years with compensated liver disease
	AND
	• Meets 1 of the following:
	  ○ Does not have a co-infection with human immunodeficiency virus (HIV)
	  OR
	  ○ Has a co-infection with HIV and is receiving highly active antiretroviral therapy
	AND
	• Has tried and had inadequate response or intolerance to generic entecavir

Hepcludex (bulevirtide-gmod)	**Hepcludex (bulevirtide-gmod) may be considered medically necessary when all the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a confirmed diagnosis of chronic hepatitis D virus (HDV) infection with a current positive HDV RNA test
	AND
	• Meet 1 of the following:
	  ○ Are without cirrhosis
	  ○ Have compensated cirrhosis (Child-Pugh A)

Vemlidy (tenofovir alafenamide)	**Vemlidy (tenofovir alafenamide) may be considered medically necessary when all the following criteria are met:** • The individual is aged 6 years or older **AND**

Drug	Medical Necessity

	• Has a confirmed diagnosis of chronic hepatitis B virus (HBV) infection
	AND
	• Has compensated liver disease
	AND
	• Meets 1 of the following:
	  ○ Does not have a co-infection with human immunodeficiency virus (HIV)
	  OR
	  ○ Has a co-infection with HIV and is receiving highly active antiretroviral therapy (HAART)
	AND
	• For adults and pediatric individuals who weigh at least 35 kg, the individual has tried and had an inadequate response or intolerance to generic tenofovir disoproxil fumarate

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All reviews for drugs listed in this policy may be approved up to 12 months.**
Re-authorization criteria	**All reviews for drugs listed in this policy may be approved up to 12 months when the medical necessity criteria are met and there is evidence the individual continues to show a positive clinical response to therapy (e.g., a reduction in hepatitis B or D virus DNA levels).**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

Documentation Requirements
• Office visit notes that contain the diagnosis, relevant history, physical evaluation, laboratory tests, and medication history

Coding

Code	Description
HCPCS	
S0145	Injection, PEGylated interferon alfa-2A (Pegasys), 180 mcg per ml (code terminated 11/01/26)

Related Information

Definition of Terms

Hepatitis B surface antigen (HBsAg): is found on the virus surface. All persons with HBsAg are infectious.

Hepatitis B e-antigen (HBeAg): is found in the inner core of the virus. All persons with positive HBeAg are most infectious.

Anti-Hepatitis B e-antigen (anti-HBe): antibodies to HBeAg, an indicator of resolution of acute infection.

HBV DNA: is a partially double-stranded DNA molecule found in the inner core of the virus. All persons with elevated HBV DNA are most infectious.

Chronic hepatitis B (CHB): HBsAg positive for at least 6 months; HBV DNA varies from undetectable to several billion IU/mL; persons can have HBeAg positive (typically associated with higher HBV DNA levels >20,000 IU/mL) and HBeAg negative (typically associated with lower HBV levels); ALT and/or ASL levels may be normal or elevated; liver biopsy results show chronic hepatitis with variable necroinflammation and/or fibrosis.

Immune-tolerant chronic hepatitis B: HBsAg present for at least 6 months; HBeAg positive; HBV DNA levels are very high (typically >1 million IU/mL); normal or minimally elevated ALT and/or AST; liver biopsy or noninvasive test results showing no fibrosis and minimal inflammation.

Immune-Active CHB: HBsAg present for at least 6 months; HBV DNA levels >20,000 IU/mL in HBeAg-positive CHB and >2,000 IU/mL in HBeAg-negative CHB; intermittently or persistently elevated ALT and/or AST levels; liver biopsy or noninvasive test results show CHB with moderate or severe necroinflammation and with or without fibrosis.

Inactive CHB: HBsAg present for at least 6 months; HBeAg negative and anti-HBe positive; HBV DNA levels <2,000 IU/mL; persistently normal ALT and/or AST levels; liver biopsy confirms absence of significant necroinflammation, and biopsy or noninvasive testing show variable levels of fibrosis.

HBeAg seroconversion: loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative.

Viral genotyping

There are 10 genotypes of HBV currently known, labeled A through J, with genotypes A, B, and C being most prevalent in the US Infection or immunization with 1 genotype usually provides immunity to all genotypes.

Benefit Application

Baraclude (entecavir), Hepcludex (bulevirtide-gmod), and Vemlidy (tenofovir alafenamide) are managed through the pharmacy benefit.

Evidence Review

Background

Chronic Hepatitis B

Chronic hepatitis B (CHB) affects approximately 258 million individuals (2022) globally and leads to an estimated 1.1 million deaths annually due to complications of cirrhosis and hepatocellular carcinoma (HCC). Data from the National Health and Nutrition Examination Survey (2017-2020) identified an estimated 660,000 (Confidence Interval (CI): 410,000–1,000,000) individuals with HBV infection but with adjustments for infections among foreign-born individuals immigrating to the United States, the estimated disease burden of HBV infection may be as high as 1.8

million (C.I: 1.3–2.6 million). Importantly, half of those infected are unaware of their diagnosis. Although the greatest incidence was in adults 30 to 39 years of age, infants and young children who were exposed to HBV had a greater chance of developing chronic hepatitis B. Non-Hispanic blacks had more than 2-fold higher rate of infection compared to other racial and ethnic populations in the US.

According to the AASLD 2026 Practice Guideline on treatment of chronic hepatitis B, preferred approved antiviral therapies for CHB treatment in adults and children include peg-interferon alpha-2a, entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide.

Chronic Hepatitis D

Hepatitis D is caused by the HDV, a defective RNA subvirus that cannot replicate independently and requires HBsAg to enter hepatocytes. The susceptible population is individuals with chronic HBV infection (HBsAg-positive) who become superinfected with HDV. Acute HDV-HBV co-infection (simultaneous acquisition of both viruses) is followed by clearance of both viruses in approximately 95% of people, whereas HDV superinfection of a person already chronically infected with HBV results in chronic HDV-HBV infection in more than 90% of cases. In the US, a 2024 meta-analysis estimated approximately 75,005 persons are living with HDV, among an estimated 1.971 million persons with chronic hepatitis B.

Chronic HDV infection is widely regarded as the most severe form of chronic viral hepatitis. HDV co-infection accelerates progression to cirrhosis, increases the incidence of HCC, and increases overall mortality compared with HBV monoinfection alone. At the time of diagnosis, 30% to 70% (with multiple studies converging on a ≥30%-50% range) of individuals with chronic HDV already have established liver cirrhosis. More than 50% of individuals die of liver disease within 10 years of diagnosis, although the natural history is heterogeneous. Recent studies suggest that more than half of individuals may follow a more indolent course, while older age, established cirrhosis, human immunodeficiency virus co-infection, and lack of interferon therapy are the main predictors of a worse clinical outcome. Despite this severity, only approximately 20% to 50% of people infected with HDV have been diagnosed.

Summary of Evidence

Coinfection with Hepatitis C Virus (HCV)

Direct-acting antiviral (DAA) HCV therapy has been reported to increase HBV DNA levels in HBsAg-positive individuals and elevate ALT levels concurrently with HBV reactivation. In HCV/HBV coinfected persons, HBV antiviral therapy should be started concurrently with DAA therapy. Entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide are preferred agents.

Coinfection with Human Immunodeficiency Virus (HIV)

The prevalence of HBV infection among HIV individuals is 5-10% with the highest rate occurring in men who have sex with men and IV drug users. Lamivudine, emtricitabine, and tenofovir are nucleoside analogues with activity against both HIV and HBV. However, due to resistance against lamivudine monotherapy, HIV/HBV-coinfected persons should receive two-drug antiretroviral therapy regimen.

Coinfection with Hepatitis Delta Virus (HDV)

Persons with HIV infection, persons who inject drugs, men who have sex with men, and immigrants from areas of high HDV endemicity with positive HBsAg should be tested for HDV.

Baraclude (entecavir)

Baraclude is a deoxyguanosine nucleoside analogue that inhibits HBV DNA synthesis via its activity against HBV reverse transcriptase.

The efficacy of Baraclude was evaluated in three phase 3 active-controlled trials. Study AI463022 compared Baraclude 0.5 mg once daily to lamivudine 100 mg once daily for 52 weeks in 709 nucleoside-inhibitor-naïve subjects with HBeAg-positive chronic HBV infection and compensated liver disease. Study AI463027 compared Baraclude 0.5mg to lamivudine 100mg once daily for 52 weeks in 638 nucleoside-inhibitor-naïve subjects with HBeAg-negative chronic HBV infection and compensated liver disease. The proportion of subjects who achieved undetectable HBV DNA (<300 copies/mL) was 67% and 90% in Baraclude-treated group in Study AI463022 and Study AIU463027, respectively, compared to 36% and 72% in lamivudine-

treated groups. Study AI463026 evaluated the efficacy of Baraclude in lamivudine-refractory chronic HBV infection and compensated liver disease. Subjects either switched to Baraclude 1 mg once daily (no washout period, n=124) or continued on lamivudine 100 mg (n=116) for 52 weeks. At week 48, 19% of Baraclude-treated group achieved undetectable HBV DNA (<300 copies/mL) versus 1% of lamivudine-treated group.

Study AI463048 compared Baraclude 1 mg once daily (n=100) to adefovir dipivoxil 10 mg once daily (n=91) in adults with HBeAg-positive or HBeAg-negative chronic HBV infection and decompensated liver disease, defined as Child-Turcotte-Pugh score of 7 or higher. At week 48, 57% of Baraclude-treated individuals achieved undetectable HBV DNA while 20% of adefovir-treated individuals.

The efficacy and safety of Baraclude in the pediatric population was evaluated in Study AI463189 which included nucleoside-inhibitor-treatment-naïve subjects 2 to less than 18 years of age with HBeAg-positive chronic HBV infection, compensated liver disease, and elevated ALT. At week 48, 58% of treatment-naïve subjects and 47% of lamivudine-experienced subjects achieved HBV DNA <50 IU/mL. Individuals either received Baraclude 0.015 mg/kg up to 0.5 mg/day (n=120) or placebo (n=60). At week 48, 46% of Baraclude-treated group achieved HBV DNA <50 IU/mL compared to 2% in placebo-treated group.

Hepcludex (bulevirtide-gmod)

The efficacy of Hepcludex 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 multi-center, randomized, open-label, parallel-arm Phase 3 trial, Trial MYR301 (NCT03852719), in which 100 participants received Hepcludex 8.5 mg once daily. The MYR301 protocol specified the Hepcludex dose as 10 mg; however, a dose recovery study later showed that the delivered dose was 8.5 mg. In Trial MYR301, participants with chronic HDV infection without cirrhosis or with compensated cirrhosis were randomized to immediate treatment with Hepcludex 8.5 mg once daily by subcutaneous injection for 144 weeks or to delayed treatment with an observational period of 48 weeks followed by Hepcludex 8.5 mg once daily by subcutaneous injection for 96 weeks. Randomization was stratified by the presence or absence of compensated cirrhosis. The groups were followed for 96 weeks after treatment ended.

Demographic and clinical characteristics at baseline were balanced between treatment groups. The mean age was 41 years; 55% were male, 82% were White, 17% were Asian, and 1% were Black or African American. Forty-eight percent had compensated liver cirrhosis, 98% had HDV genotype 1, and 87% had HBV genotype D. Fifty-seven percent of participants had received

previous interferon therapy and 59% were receiving nucleos(t)ide analog reverse transcriptase inhibitors for chronic hepatitis B. The primary efficacy endpoint was combined response, defined as undetectable HDV RNA or ≥ 2 log10 IU/mL decline from baseline and ALT normalization, at Week 48. At Week 48, the rate of undetectable HDV RNA (defined as less than the lower limit of quantification [LLOQ] [50 IU/mL] with target not detected) was 20% in the Hepcludex group compared with 0% in the Delayed Treatment group. At Weeks 96 and 144, these rates increased to 36% and 50%, respectively, in the Hepcludex group. At Week 96, the Hepcludex group demonstrated a 56% combined response rate, 82% virologic response rate (defined as undetectable HDV RNA or ≥ 2 log10 IU/mL decline from baseline), and 64% ALT normalization rate. At Week 144, these rates were 54%, 76%, and 60%, respectively. Participants in the Delayed Treatment group switched to Hepcludex 8.5 mg once daily at Week 48. At Week 144 (after 96 weeks of treatment), the combined response rate in the Delayed Treatment group was 56%, the rate of undetectable HDV RNA was 52%, virologic response rate was 92%, and ALT normalization rate was 58%. At posttreatment Week 24, 32% and 20% of participants in the Hepcludex group and the Delayed Treatment group, respectively, had combined response, and 26% and 18% of participants, respectively, had undetectable HDV RNA. At posttreatment Week 96, 24% of participants in both the Hepcludex group and the Delayed Treatment group had combined response and 22% and 20% of participants, respectively, had undetectable HDV RNA.

Further supportive data from an additional 50 adult participants with chronic HDV infection without cirrhosis or with compensated cirrhosis receiving Hepcludex 8.5 mg subcutaneously once daily for 96 weeks is available from a randomized, open-label, exploratory Phase 2b trial, Trial MYR204 (NCT03852433). At Week 96, 48% and 22% of participants achieved combined response and undetectable HDV RNA, respectively. At 24 weeks posttreatment, response rates were 26% and 12%, respectively.

Hepcludex has a warning that severe acute exacerbations of HDV and HBV infection may occur after Hepcludex is discontinued, especially in individuals 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 monitoring HBV DNA and HDV RNA viral load, for at least six months in individuals who discontinue Hepcludex. Resumption of antiviral therapy may be warranted. Hypersensitivity reactions, including anaphylaxis, may also occur with Hepcludex. The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with Hepcludex are injection site reactions, headache, abdominal pain, fatigue, and pruritus.

Vemlidy (tenofovir alafenamide)

Vemlidy is a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor. Tenofovir alafenamide is a phosphonamidite prodrug of tenofovir, which is then converted to an active metabolite that incorporates into viral DNA reverse transcriptase, inhibiting HBV replication.

The efficacy of Vemlidy in the treatment of adults with CHB and compensated liver disease is based on 48-week data from 2 randomized, double-blind, active-controlled trials including both treatment-naïve and treatment-experienced adults. In trial 108, HBeAg-negative individuals either received Vemlidy 25 mg (n=285) once daily or tenofovir disoproxil fumarate (TDF) 300mg (n=140) once daily. In trial 110, HBeAg-positive individuals either received Vemlidy 25mg once daily (n=581) or TDF 300mg (n=292) once daily. The efficacy endpoint in both trials was the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at week 48. In trial 108, 92% of Vemlidy-treated adults and 93% of TDF-treated adults achieved HBV DNA <29 IU/mL. The corresponding proportions in trial 110 were 63% and 67% in the Vemlidy-treated group and TDF-treated group, respectively.

The efficacy of switching from TDF to Vemlidy in virologically suppressed adults with CHB infection was evaluated in a 48-week, randomized, double-blind, active-controlled trial requiring subjects to have been taking TDF 300 mg once daily for at least 12 months with HBV DNA <20 IU/mL at screening. Individuals were then randomized to receive Vemlidy 25 mg once daily (n=243) or TDF 300mg once daily (n=245). The primary endpoint was the proportion of adults with plasma HBV DNA levels of ≥20 IU/mL at week 48. Both groups had <1% who achieved the primary endpoint.

Trial 4035 evaluated the efficacy and safety of switching from TDF and/or other antivirals to Vemlidy in an open-label study of adults with virological suppression and moderate to severe renal impairment (Cohort 1, n=78) or end-stage renal disease (ESRD) on hemodialysis (Cohort 2, n=15). At week 24, 98% of subjects achieved HBV DNA <20 IU/mL. There were no significant differences in mean change from baseline in ALT values and mean change in HBsAg level from baseline between these groups.

Trial 1092 was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of Vemlidy in subjects 12 to 18 years of age weighing at least 35 kg with CHB infection. Individuals either received Vemlidy (n=47) or placebo (n=23) once daily. At week 24, 21% of Vemlidy-treated group achieved HBV DNA <20 IU/mL versus 0% in placebo-treated group. ALT normalization (according to AASLD criteria) was achieved in 44% of Vemlidy-treated group and 0% in placebo-treated group.

The safety of Vemlidy was assessed based on pooled data of 1298 individuals from Trial 108 and Trial 110 who continued treatment through week 120. Week 97 analysis showed that the most common adverse reactions reported in at least 10% of subjects was headache, similarly in both Vemlidy- and TDF-treated groups. Other adverse reactions reported in at least 5% of subjects included abdominal pain, cough, back pain, fatigue, nausea, arthralgia, diarrhea, and dyspepsia.

Practice Guidelines

Practice Guideline on Treatment of Chronic Hepatitis B

The American Association for the Study of Liver Diseases (AASLD) integration of AASLD 2018 and 2025 Guidelines addressed 6 questions covering prevention (maternal to infant transmission and horizontal transmission), surveillance for liver cancer (among hepatitis B surface antigen positive (HBsAg) persons co-infected with hepatitis C virus, hepatitis D virus and/or human immunodeficiency viruses and after HBsAg loss) and treatment (HBsAg positive persons in immune-tolerant or indeterminate phases as well as withdrawal of antiviral therapy), providing evidence-based recommendations on these topics. There are multiple topics well covered in the previous 2018 guidance and for which recommendations have not changed. The 2018 update in available on the Internet at **https://www.aasld.org/practice-guidelines/chronic-hepatitis-b** and included (1) the use of tenofovir alafenamide; (2) guidance on screening, counseling, and prevention; (3) specialized virological and serological tests; (4) monitoring of untreated individuals; and (5) treatment of hepatitis B in special populations, including persons with viral coinfections, acute hepatitis B, recipients of immunosuppressive therapy, and transplant recipients.

References

1. Baraclude (entecavir). Prescribing information. Bristol-Myers Squibb Company. Princeton, NJ. Revised November 2019.
2. Hepcludex (bulevirtide-gmod). Prescribing Information. Gilead Sciences, Inc.; Foster City, CA. Revised May 2026.
3. Vemlidy (tenofovir aladenamide). Prescribing information. Gilead Sciences, Inc. Foster City, CA. Revised March 2024.
4. Wright TL: Introduction to chronic hepatitis B infection. Am J Gastroenterol 2006; 101 Suppl 1:S1-S6.
5. Abara WE, Qaseem A, Schillie S, et al: Hepatitis B vaccination, screening, and linkage to care: best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017; 167(11):794-804.
6. Wright TL: Introduction to chronic hepatitis B infection. Am J Gastroenterol 2006; 101 Suppl 1:S1-S6.

7. Schillie S , Vellozzi C , Reingold A , et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018; 67(1):1-31.

8. Haber BA, Block JM, Jonas MM, et al: Recommendations for screening, monitoring, and referral of pediatric chronic hepatitis B. Pediatrics 2009; 124(5):e1007-e1013.

9. Centers for Disease Control and Prevention: Surveillance for acute viral Hepatitis - United States, 2007. MMWR Morb Mortal Wkly Rep 2009; 58(SS-3):1-27.

10. Koziel MJ & Peters MG: Viral hepatitis in HIV infection. N Engl J Med 2007; 356(14):1445-1454.

11. Terrault, Norah A.*; Lok, Anna S.F.; McMahon, Brian J.; Chang, Kyong-Mi; Hwang, Jessica P.; Jonas, Maureen M.; Brown, Robert S. Jr.; Bzowej, Natalie H.; Wong, John B.. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67(4):p 1560-1599, April 2018. | DOI: 10.1002/hep.29800

12. Janssen HL, van Zonneveld M, Senturk H, et al; HBV 99-01 Study Group. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomized trial. Lancet. 2005; 365(9454):123-129.

13. Chan HL, Leung NW, Hui Ay et al. A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. Ann Intern Med. 2005:142(4):240-250.

14. Lau GK, Piratvisuth T, Luo KX, et al; Peginterferon Alfa-2a HbeAg-Positive Chronic Hepatitis B Study Group. Peginterferon alfa-2a, lamivudine, and the combination for HbeAg-positive chronic hepatitis B. N Engl J Med. 2005; 352(26):2682-2695.

15. Marcellin P, Lau GK, Bonino F, et al; Peginterferon Alfa-2a HbeAg-Negative Chronic Hepatitis B Study Group. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HbeAg-negative chronic hepatitis B. N Engl J Med. 2004; 351(12):1206-1217.

16. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45(2):507-539.

17. Marcellin P, Brunetto M, Bonino F et al. In patients with HbeAg-negative chronic hepatitis B HbsAg serum levels early during treatment with peginterferon alfa-2° predict HbsAg clearance 4 years post-treatment [abstract]. The 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD). Boston, MA. November 2-6, 2007.

18. Wedemeyer H, et al. Peginterferon plus Adefovir versus Either Drug Alone for Hepatitis Delta. N Engl J Med 2011;364:322-331.

19. Ianotto JC, Chauveau A, Boyer-Perrard F, et al. Benefits and pitfalls of pegylated interferon-α2a therapy in patients with myeloproliferative neoplasm-associated myelofibrosis: a French Intergroup of Myeloproliferative neoplasms (FIM) study. Haematologica 2018 Mar;103(3):438-446.

20. Mosca M, Hermange G, Tisserand A, et al. Inferring the dynamics of mutated hematopoietic stem and progenitor cells induced by IFNα in myeloproliferative neoplasms. Blood 2021 Dec 2;138(22):2231-2243.

21. Mascarenhas J, Kosiorek HE, Prchal JT, et al. A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia. *Blood* (2022) 139 (19): 2931–2941.

22. Yacoub A, Mascrenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood* (2019) 134 (18): 1498–1509.

23. Tremblay D, et al. Diagnosis and Treatment of Polycythemia Vera: A Review. JAMA 2025 Jan 14;333(2):153-160.

24. Ghany MG, Pan CQ, Lok AS, et al. AASLD ISDA Practice Guideline on treatment of chronic hepatitis B. *Hepatology* 83(4):p 974-997, April 2026. **https://journals.lww.com/hep/pages/currenttoc.aspx**. Accessed March 23, 2026.

25. Negro F, Lok AS. Hepatitis D: A review. JAMA. 2023;330(24):2376-2387.

26. Rizzetto M. Hepatitis D virus: introduction and epidemiology. Cold Spring Harb Perspect Med. 2015;5(7):a021576.

27. Marlowe EM, Swanson BE, Realegeno SE, et al. Epidemiological burden of hepatitis delta virus in the United States. J Viral Hepat. 2025;32(6):e70029.

28. Vlachogiannakos J, Papatheodoridis GV. New epidemiology of hepatitis delta. Liver Int. 2020;40(Suppl 1):48-53.

History

Date	Comments
11/01/23	New policy, approved October 10, 2023, effective for dates of service on or after November 1, 2023. Add to Prescription Drug section. Added coverage criteria for Baraclude, Epivir-HBV, Hepsera, and Vemlidy for the treatment of chronic hepatitis B. Moved Pegasys (peginterferon alfa-2a) policy criteria for the treatment of chronic hepatitis B from 5.01.606 Hepatitis C Antiviral Therapy to 5.01.636 Chronic Hepatitis B Antiviral Therapy.
06/01/24	Annual Review, approved May 14, 2024. Removed Hepsera (adefovir dipivoxil) as it was withdrawn from the market. Updated Vemlidy (tenofovir alafenamide) age requirement from 12 years and older to 6 years and older and added generic tenofovir disoproxil fumarate trial first requirement.
07/01/24	Interim Review, approved June 11, 2024. Added coverage criteria for Viread (tenofovir disoproxil fumarate).
03/01/25	Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
11/01/25	Interim Review, approved October 14, 2025. Updated Pegasys (peginterferon alfa-2a) coverage criteria to include treatment of certain individuals with myelofibrosis. Added HCPC code S0145 for Pegasys.
01/01/26	Interim Review, approved December 22, 2025. Removed criteria for Viread (tenofovir disoproxil fumarate).
05/01/26	Annual Review, approved April 14, 2026. Updated criteria for Pegasys (peginterferon alfa-2a) adding the following indications: for treatment of polycythemia vera, as first- or second-line treatment of essential thrombocytopenia, and treatment of hepatitis D virus. Updated criteria for Pegasys (peginterferon alfa-2a) for treatment of myelofibrosis clarifying for individuals with a *JAK2* V617F mutation. Removed coverage criteria for Epivir-HBV (lamivudine) as product has been discontinued. Removed reference to non-formulary exception reviews.
11/01/26	Interim Review, approved October 13, 2026. Updated policy title from Chronic Hepatitis B Antiviral Therapy to Chronic Hepatitis B and D Antiviral Therapy. Added coverage criteria for Hepcludex (bulevirtide-gmod) for the treatment of chronic hepatitis delta virus. Moved coverage criteria for Pegasys (peginterferon alfa-2a) from policy 5.01.636 Chronic Hepatitis B and D Antiviral Therapy to policy 5.01.664 Peginterferon alfa-2a. Termed HCPCS code S0145.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.