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PHARMACY POLICY – 5.01.664

Peginterferon alfa-2a

Effective Date:	Nov. 1, 2026	RELATED MEDICAL POLICIES:
Last Revised:	Oct. 13, 2026	None
Replaces:	N/A	

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Introduction

Peginterferon alfa-2a belongs to a group of medications known as alpha interferons. Alpha interferons are natural proteins made by the body's cells that help fight infections, slow the growth of abnormal cells, and regulate the immune system. When interferons attach to cells, they send signals that activate the body's defenses. These signals can help slow the growth of cells, improve the immune system's ability to recognize and destroy infected or abnormal cells, and enhance the activity of immune cells that help remove harmful viruses and potentially cancerous cells from the body. This policy describes when peginterferon alfa-2a 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
Pegasys (peginterferon alfa-2a) SC	**Pegasys (peginterferon alfa-2a) may be considered medically necessary for the treatment of chronic hepatitis B virus (HBV) infection in:** • Individuals aged 18 years or older with hepatitis B e-antigen (HBeAg) positive and HBeAg-negative chronic HBV infection who have compensated liver disease and evidence of viral replication and liver inflammation **OR** • Non-cirrhotic pediatric individuals aged 3 years or older with HBeAg-positive chronic hepatitis B (CHB) and evidence of viral replication and elevations in serum alanine aminotransferase (ALT) **Pegasys (peginterferon alfa-2a) may be considered medically necessary for the treatment of chronic hepatitis C virus when used in accordance with current guidelines.** **Pegasys (peginterferon alfa-2a) may be considered medically necessary for the treatment of chronic hepatitis D virus (HDV) in:** • Individuals with compensated liver disease **AND** • Pegasys (peginterferon alfa-2a) is used as a single agent for 48 weeks **Pegasys (peginterferon alfa-2a) may be considered medically necessary as first- or second-line treatment of individuals with essential thrombocytopenia.** **Pegasys (peginterferon alfa-2a) may be considered medically necessary for the treatment of individuals aged 18 years or older with myelofibrosis with a *JAK2* V617F mutation.** **Pegasys (peginterferon alfa-2a) may be considered medically necessary for the treatment of polycythemia vera.**

Drug	Investigational
Brand (generic)	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of Pegasys (peginterferon alfa-2a) for conditions not outlined in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in this policy may be approved up to 12 months.**
Re-authorization criteria	**All drugs listed in this policy may be approved up to 12 months when the medical necessity criteria are met and there is evidence that the individual continues to show a positive clinical response to therapy.**

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

Coding

N/A

Related Information

Consideration of Age

Pegasys is FDA labeled for the treatment of chronic hepatitis C (CHC) in adult and pediatric individuals aged 5 age or greater, and for the treatment of chronic hepatitis B (CHB) in adult and pediatric individuals aged 3 or greater.

Benefit Application

Pegasys (peginterferon alfa-2a) is managed through the pharmacy benefit.

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.

Evidence Review

Background

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.

Hepatitis C

Approximately 4 million Americans have been infected with hepatitis C virus (HCV), of whom 74% have chronic infection. Most individuals are diagnosed based on elevated liver transaminases and the presence of hepatitis C virus ribonucleic acid (HCV RNA). Hepatitis C is a major cause of liver-related morbidity and mortality. Although the disease typically progresses

without symptoms for several decades, 20% to 30% of infected individuals develop cirrhosis within 10 to 20 years and 5% to 10% develop end stage liver disease. After development of cirrhosis, the annual risk of development of hepatocellular carcinoma is 1% to 4%. Chronic hepatitis C is also the most common indication for liver transplantation in the United States.

There are 6 known genotypes and over 50 subtypes of HCV. These genotypes vary by as much as 34% in their genetic sequencing and subtypes are known to differ by 20% to 23%. This genetic heterogeneity has known implications for therapeutic management and its effectiveness. Genotypes 1 and 4 are associated with less chance of achieving a sustained virologic response (SVR) or the clearance of HCV RNA by qualitative analysis 24 weeks after therapy cessation. Although SVR is a surrogate endpoint which has not yet been correlated with improved survival, it is the current standard measure of response to therapy.

Viral Genotyping

Genotyping of hepatitis C virus is considered medically necessary when used according to current guideline recommendations.

Resistance Mutations (Resistance-Associated Substitutions, or RASs)

Genetic testing for resistance mutations is commercially available and is considered medically necessary to guide the selection of an individual-specific direct-acting antiviral agents (DAA) regimen in circumstances where it is recommended by the current guidelines.

Sustained Virologic Response-Chronic Hepatitis C

Although sustained virologic response (SVR) is a surrogate endpoint, it has recently been correlated with improved survival, and it is the current gold standard measure of response to chronic hepatitis C virus (HCV) pharmacotherapy. An SVR is the clearance of HCV ribonucleic acid (RNA) by qualitative analysis 24 weeks after therapy cessation. Pretreatment factors associated with achievement of SVR include lower body mass indexes (body weight <75 kg), milder histology on liver biopsy (Metavir fibrosis stage 0 or 1), genotype 2 or 3, and lower initial viral titers (HCV RNA level <2 million copies/mL or 800,000 IU/mL). During treatment, factors associated with achievement of an SVR include rapid or early virologic response, therapy adherence, and lack of human immunodeficiency virus (HIV) co-infection. Achievement of an

SVR has been associated with resolution of liver injury, reduction in hepatic fibrosis, a low likelihood of relapse, and survival.

Early Virologic Response-Chronic Hepatitis C

Early virologic response (EVR) is defined as clearance of HCV-RNA during the first 12 weeks of therapy. A partial response is defined as a minimum 2-log decrease in hepatitis C viral load after 12 weeks of therapy.

Relapse and Non-Response-Chronic Hepatitis C

Relapse is defined as initial achievement of an SVR that is not sustained over time. Non-response is defined as never achieving an SVR. Guidelines for retreatment of this population are evolving rapidly. See **http://www.hcvguidelines.org/**. Accessed October 5, 2026.

Transplantation-Chronic Hepatitis C

Hepatitis C frequently recurs in the transplant setting. Guidelines for retreatment of this population are evolving rapidly. Treatment for post-transplant individuals or for those awaiting transplantation will be approved in accordance with current guideline recommendations. See **http://www.hcvguidelines.org**. Accessed October 5, 2026.

Pegasys (peginterferon alfa-2a)

The biological activity of Pegasys is derived from its recombinant human interferon α-2a moiety. Peginterferon α-2a binds to the human type 1 interferon receptor leading to receptor dimerization. Receptor dimerization activates multiple intracellular signal transduction pathways initially mediated by the JAK/STAT pathway. Given the diversity of cell types that respond to interferon α-2a, and the multiplicity of potential intracellular responses to interferon receptor activation, peginterferon α-2a is expected to have pleiotropic biological effects in the body. Pegasys has activity against both hepatitis B and C viruses.

The safety and effectiveness of Pegasys in combination with ribavirin for the treatment of hepatitis C virus infection were assessed in two randomized controlled clinical trials. All

individuals were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. Approximately 20% of individuals in both studies had compensated cirrhosis (Child Pugh class A). Individuals coinfected with HIV were excluded from these studies.

In Study 1, individuals were randomized to receive either Pegasys 180 mcg subcutaneous once weekly with an oral placebo, Pegasys 180 mcg once weekly with ribavirin 1000 mg by mouth (body weight less than 75 kg) or 1200 mg by mouth (body weight greater than or equal to 75 kg) or Rebetron (interferon alfa-2b 3 MIU subcutaneous three times a week plus ribavirin 1000 mg or 1200 mg by mouth). All individuals received 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. Ribavirin or placebo treatment assignment was blinded. Sustained virological response was defined as undetectable (less than 50 IU/mL) HCV RNA on or after study week 68. Pegasys in combination with ribavirin resulted in a higher SVR compared to Pegasys alone or interferon alfa-2b and ribavirin. In all treatment arms, individuals with viral genotype 1, regardless of viral load, had a lower response rate.

In Study 4, individuals with CHC/HIV were randomized to receive either Pegasys 180 mcg subcutaneous once weekly plus an oral placebo, Pegasys 180 mcg once weekly plus ribavirin 800 mg by mouth daily or interferon alfa-2a, 3 MIU subcutaneous three times a week plus ribavirin 800 mg by mouth daily. All individuals received 48 weeks of therapy and sustained virologic response (SVR) was assessed at 24 weeks of treatment-free follow-up. Ribavirin or placebo treatment assignment was blinded in the Pegasys treatment arms. All individuals were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis C, and were previously untreated with interferon. Individuals also had CD4+ cell count greater than or equal to 200 cells/mm3 or CD4+ cell count greater than or equal to 100 cells/mm3 but less than 200 cells/mm3 and HIV-1 RNA less than 5,000 cells/mm3, and stable status of HIV. Approximately 15% of individuals in the study had cirrhosis. Treatment response rates are lower in CHC/HIV individuals with poor prognostic factors (including HCV genotype 1, HCV RNA greater than 800,000 IU/mL, and cirrhosis) receiving pegylated interferon alpha therapy. Geographic region is not a prognostic factor for response. However, poor prognostic factors occur more frequently in the US population than in the non-US population. Of the individuals who did not demonstrate either undetectable HCV RNA or at least a 2 log10 reduction from baseline in HCV RNA titer by 12 weeks of Pegasys and ribavirin combination therapy, 2% (2/85) achieved an SVR. In CHC individuals with HIV coinfection who received 48 weeks of Pegasys alone or in combination with ribavirin treatment, mean and median HIV RNA titers did not increase above baseline during treatment or 24 weeks post-treatment.

The safety and effectiveness of Pegasys for the treatment of hepatitis C virus infection were assessed in three randomized, open-label, active-controlled clinical studies. All individuals were

adults, had compensated liver disease, detectable hepatitis C virus (HCV), liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. All individuals received therapy by subcutaneous injection for 48 weeks, and were followed for an additional 24 weeks to assess the durability of response. In studies 5 and 6, approximately 20% of individuals had cirrhosis or bridging fibrosis. Study 7 enrolled individuals with a histological diagnosis of cirrhosis (78%) or bridging fibrosis (22%). In all three studies, treatment with Pegasys 180 mcg resulted in significantly more individuals who experienced a sustained response (defined as undetectable HCV RNA [less than 50 IU/mL] using the Cobas Amplicor HCV Test, version 2 and normalization of ALT on or after study week 68) compared to treatment with Roferon-A.

The efficacy of Pegasys was evaluated in Study 8 (HBeAg-positive) and Study 9 (HBeAg-negative) individuals with CHB and compensated liver disease. In Study 8, individuals were randomized to receive Pegasys 180mcg SC once weekly (n=271) or lamivudine 100mg once daily (n=272). At week 48, 32% of Pegasys-treated group achieved HBV DNA <100,000 copies/mL compared to 62% of lamivudine-treated group. In Study 9, individuals were randomized to receive Pegasys 180mcg SQ once weekly (n=177) or lamivudine once daily (n=181). At week 48, 43% of Pegasys-treated group achieved HBV DNA <20,000 copies/mL compared to 85% of lamivudine-treated group.

Study 10 evaluated the efficacy of Pegasys in pediatric individuals aged 3 to less than 18 years with HBeAg-positive CHB in the immune-active phase and no cirrhosis. Individuals were randomized to receive Pegasys (n=101) or no treatment (n=50). At week 48, Pegasys-treated group had 34% achieve HBV DNA <20,000 IU/mL and 29% achieve HBV DNA <20,000 IU/mL, compared to 4% and 2% of the untreated group, respectively.

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History

Date	Comments
11/01/26	New policy, approved October 13, 2026. 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. Moved coverage criteria for Pegasys (peginterferon alfa-2a) from policy 5.01.606 Hepatitis C Antiviral Therapy to policy 5.01.664 Peginterferon alfa-2a.

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.

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