

PHARMACY POLICY – 5.01.606

Hepatitis C Antiviral Therapy

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RELATED MEDICAL POLICIES:

None

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[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

Introduction

Hepatitis C is caused by a virus that infects the liver. Sometimes the virus clears up on its own within a few months. This is called acute hepatitis C. In other cases, the infection lasts a long time. This is known as chronic hepatitis C. A person might be unaware of chronic hepatitis C because in the early stages the infection usually shows no symptoms or very mild symptoms. The drugs used to treat hepatitis C vary, but most of the newer antiviral drugs require a genetic test. This is because hepatitis C has different genetic types and certain drugs target specific genetic types. Other factors determining which drug may be recommended is whether other drugs were tried first and the status of a person's current medical condition. This policy describes the criteria when hepatitis C 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

Prioritizing Patients for Treatment for Chronic Hepatitis C

New direct-acting antiviral agents (DAA) are revolutionizing treatment for Hepatitis C. Clinical trials for these regimens have demonstrated sustained viral response rates (SVR) of greater than 90% except in the most complicated patients.

Combined AASLD and IDSA guidelines for the treatment of chronic hepatitis C are available on the Internet at <http://www.hcvguidelines.org>. Due to the rapidly advancing clinical evidence, these guidelines are updated frequently, thus for the most up-to-date information please refer to <http://www.hcvguidelines.org>.

Treatment for chronic active hepatitis C may be considered medically necessary, as outlined in the most recent AASLD guidelines (see <http://www.hcvguidelines.org>), except as noted under the "Preferred Therapies" table below:

Preferred Therapies

Mavyret™ (glecaprevir/pibrentasvir), Epclusa® (sofosbuvir/velpatasvir) and Harvoni® (ledipasvir/sofosbuvir) are preferred over all other direct-acting antiviral agents (DAA) for treatment of patients without cirrhosis or with compensated cirrhosis (Child-Pugh A).

Treatment experienced patients may be treated with Vosevi® (sofosbuvir / velpatasvir / voxilaprevir) according to the current AASLD and IDSA guideline recommendations, taking into consideration known resistance-associated substitutions (RASs).

Exceptions:

- The use of other regimens is considered not medically necessary, since equally or more effective alternative treatments are available at lower cost, **unless** analysis of RASs indicates that none of the above preferred combinations will likely be effective. In such cases, treatment according to the guidelines may be considered medically necessary.
- Patients with more advanced cirrhosis (Child-Pugh B or C) should be treated according to current guideline recommendations (ideally in a liver transplant center).
- Treatment with other regimens for patients with special circumstances not meeting the above criteria will be evaluated on an individual case basis.



Drug	Current Guidelines
Pegylated interferons and ribavirin <ul style="list-style-type: none"> • Pegasys® (peginterferon alfa-2a) • PEGIntron® (peginterferon alfa-2b) • Ribavirin 	Pegylated interferons and ribavirin no longer require prior authorization. Use in accordance with current guidelines is recommended.

Drug	Length of Therapy
Mavyret™ (glecaprevir/pibrentasvir)	<ul style="list-style-type: none"> • Mavyret™ (glecaprevir/pibrentasvir) was approved by the FDA for an 8-week course of therapy in treatment naïve patients with genotype 1, 2, 3, 4, 5, or 6 without cirrhosis based on the results from the clinical trials conducted by the manufacturer. Treatment naïve adult and pediatric patients weighing at least 45 kg with compensated cirrhosis (Child-Pugh A) should be treated for 12 weeks. • FDA approved a 12-week course of treatment for treatment-experienced genotype 1 adult and pediatric patients weighing at least 45 kg, with or without cirrhosis, having had earlier DAA regimens with an NS3/4A PI without prior treatment with an NS5A inhibitor. • FDA approved a 16-week course of treatment for treatment-experienced genotype 1 adult and pediatric patients weighing at least 45 kg, with or without cirrhosis, having had earlier DAA regimens with an NS5A without prior treatment with an NS3/4A PI inhibitor. • Genotype 3 adult and pediatric patients weighing at least 45 kg, with or without cirrhosis, and with prior treatment with pegylated interferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an NS3/4A PI or NS5A inhibitor should receive 16 weeks. • Genotype 1, 2, 4, 5, or 6 adult and pediatric patients weighing at least 45 kg with no cirrhosis and with prior treatment with pegylated interferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an NS3/4A PI or NS5A inhibitor



Drug	Length of Therapy
	<p>should receive 8 weeks.</p> <ul style="list-style-type: none"> Genotype 1, 2, 4, 5, or 6 adult and pediatric patients weighing at least 45 kg with cirrhosis and with prior treatment with pegylated interferon, ribavirin, and/or sofosbuvir but no prior treatment experience with an NS3/4A PI or NS5A inhibitor should receive 12 weeks.
<p>Epclusa® (sofosbuvir/velpatasvir)</p>	<ul style="list-style-type: none"> Epclusa® (sofosbuvir/velpatasvir) was approved by the FDA for a 12-week course of therapy in treatment of adult patients of all genotypes without cirrhosis or with compensated cirrhosis. Adult patients with decompensated cirrhosis may be treated with Epclusa in combination with ribavirin.
<p>Harvoni® (ledipasvir/sofosbuvir)</p>	<ul style="list-style-type: none"> Harvoni® (ledipasvir/sofosbuvir) was approved by the FDA for the treatment of chronic hepatitis C virus in: <ul style="list-style-type: none"> Adults with genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis Adults with genotype 1 infection with decompensated cirrhosis, in combination with ribavirin Adults with genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin Pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis.
<p>Vosevi™ (sofosbuvir, velpatasvir, and voxilaprevir)</p>	<ul style="list-style-type: none"> Vosevi™ (sofosbuvir, velpatasvir, and voxilaprevir) is FDA approved for treatment of adult patients without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have: <ul style="list-style-type: none"> Genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor. Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. <p>Note: Vosevi is contraindicated in severe renal failure.</p>
<p>Deviations from AASLD guidelines</p>	<p>All other deviations from the length of therapy recommended by the AASLD guidelines are considered investigational.</p>



Documentation Requirements

The patient'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, genotyping of hepatitis C virus, and medication history

Coding

N/A

Related Information

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 a patient-specific DAA regimen in circumstances where it is recommended by the current guidelines.

Hepatitis C

Approximately 4 million Americans have been infected with hepatitis C virus (HCV), of whom 74% have chronic infection. Most patients 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 hepatitis C virus. 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 implication 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.

Various direct-acting oral agents (DAAs) have been approved. Direct acting agents are administered orally, tend to have fewer side effects and achieve higher SVR rates with shorter courses of therapy. The most recently approved products have pangenotypic coverage. They are Mavyret (glecaprevir/pibrentasvir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir) and Epclusa (sofosbuvir/velpatasvir).

Benefit Application

This policy is managed through the Pharmacy benefit.

Evidence Review

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 HCV pharmacotherapy. An SVR is the clearance of HCV 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 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.

Adherence-Chronic Hepatitis C

Adherence is important to chronic HCV treatment success. The currently recommended all-DAA regimens are orally administered with convenient dosing regimens and have much fewer side effects, compared to the older regimens. Sustained viral response is achieved in over 95% of patients in most subpopulations in clinical trials. Real world retrospective analyses confirm fairly similar SVR rates outside of controlled trial settings.

Non-adherence is the principal reason for failure with these highly effective treatments; therefore, patients should be screened for poor adherence risks. All patients should be strongly encouraged to follow the directions from their prescriber. Those having difficulty with side effects should discuss these concerns with their prescriber or pharmacist.

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/>.

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 patients or for those awaiting transplantation will be approved in accordance with current guideline recommendations. See <http://www.hcvguidelines.org/>.



Extended Treatment Intervals

Extended treatment is not normally advised with today's highly efficient regimens. Patients failing to achieve SVR should be evaluated for retreatment with a guideline-appropriate regimen, rather than extending current treatment.

Unique Populations

Providers treating patients in these groups, eg, HIV- and/or HBV-coinfected individuals or those with other serious infections, patients with decompensated cirrhosis, patients with end stage renal disease, or children should consult the guidelines for the most current recommendations. Treatment for such cases is reviewed on an individual basis.

Sofosbuvir/Velpatasvir Combination Product (Epclusa®)

Four Phase-3 ASTRAL clinical trials demonstrated that a 12-week, fixed-dose, single-tablet regimen of sofosbuvir and velpatasvir (SOF/VEL 400/100 mg) achieved high sustained virologic responses (cures) for all hepatitis C genotypes. The primary efficacy endpoint for each of the four ASTRAL trials was a sustained virologic response (SVR), which was defined as an HCV RNA level of less than 15 IU/mL (undetectable) at 12 weeks after the end of treatment (SVR12). Viral loads <15 IU/mL are considered undetectable. Secondary endpoints included safety/tolerability, resistance, and additional efficacy outcomes.

ASTRAL-1 enrolled patients with HCV genotypes 1, 2, 4, 5, and 6. Patients received either SOF/VEL or placebo for 12 weeks. SOF/VEL taken once daily for 12 consecutive weeks produced cure rates of approximately 99% across all genotypes. Among the patients enrolled in this trial, 121 participants had cirrhosis, and at the end of study, 120 of those participants (99%) achieved SVR12. Also, 99% of the patients with baseline NS5A resistance-associated variants (RAVs) had an SVR.

ASTRAL-2 assigned patients with genotype 2 to either sofosbuvir + velpatasvir (SOF/VEL) for 12 weeks or sofosbuvir + ribavirin (SOF+RBV) for 12 weeks. 86% of patients had previously been treated for HCV (treatment experienced). Treatment with SOF/VEL was superior to the SOF+RBV regimen. SVR was achieved in 99% of patients in the SOF/VEL group, compared with an SVR of



94% in the SOF+RBV group. There were no cases of treatment failure despite the presence of baseline NS5A resistance-associated variants (RAVs).

ASTRAL-3 assigned patients with genotype 3 to either SOF/VEL for 12 weeks or SOF+RBV for 24 weeks. Cirrhosis was present in 30% of patients, and 74% of patients had previous HCV treatment. The SVR12 rates were 95% with SOF/VEL and 80% with SOF+RBV. Of 43 study participants with baseline NS5A RAVs, 88% achieved SVR compared to 97% SVR in participants without resistance mutations. Note that all participants who had cirrhosis did not have symptoms associated with severe scarring of the liver, so cure rates were relatively high (99%). The combination of SOF/VEL led to higher SVR12 rates than 24 weeks of SOF/RBV and was very well tolerated. SOF/VEL for 12 weeks yielded high rates of SVR12 without the need for RBV.

ASTRAL-4 only enrolled patients with decompensated cirrhosis, a more difficult group to cure. Patients had genotypes 1, 2, 3, 4, and 6, and the majority of study participants (75%) had HCV genotype 1. Patients were assigned to one of three treatment groups: SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, or SOF/VEL for 24 weeks. The highest SVR rate was 94% in the SOF/VEL + RBV group vs 83% and 86% in the SOF/VEL 12 week and SOF/VEL 24 week groups, respectively. Overall, 8 out of 72 patients with baseline NS5A RAVs experienced virologic failure (89% achieved SVR).

Glecaprevir/Pibrentasvir Combination Product (Mavyret™)

Glecaprevir/pibrentasvir (GLE/PIB) is a fixed dose, oral, pangenotypic combination NS3/4A protease inhibitor and NS5A inhibitor indicated for the treatment of chronic HCV in GT 1-6 without cirrhosis or with compensated cirrhosis (Child-Pugh A) and HCV GT 1 previously treated with NS5A inhibitors or NS3/4A protease inhibitors but not both. Mavyret was approved for an 8-week treatment regimen in patients with treatment-naïve (GT 1-6) or experienced (GT 1, 2, 4, 5, 6; PEG-IFN, RBV, and/or SOF) chronic HCV. Additionally, Mavyret was approved for a 12-week regimen in patients with GT 1-6 and compensated cirrhosis; GT 1 and prior NS3/4A protease inhibitor experience + cirrhosis; and GT 1, 2, 4, 5, 6 and prior PEG-IFN, RBV, and/or SOF experience with compensated cirrhosis. Mavyret was approved for a 16-week regimen in GT 1 patients with prior NS5A inhibitor experience + cirrhosis; and GT 3 patients with prior PEG-IFN, RBV and/or SOF experience + cirrhosis.

The regimen GLE/PIB has been studied in eight fair-quality, unpublished, phase 3 trials. Most trials were open-label with the exception of a single double-blind trial. A non-comparative trial design was used in three trials, four trials compared GLE/PIB to a historical SVR12 rate, and one trial included an active comparator. The GLE/PIB phase-3 trials showed good efficacy in a wide



range of populations including HCV GT 1-6, compensated cirrhosis (excluding GT 3), human immunodeficiency virus (HIV) coinfection, chronic kidney disease (CKD), and transplant patients (liver or renal). Overall, GLE/PIB was highly effective with an SVR12 ranging from 97% to 100% in the majority of trials. Exceptions were an SVR12 of 93% in patients with HIV coinfection and compensated cirrhosis in GT 1-6, SVR12 of 95% in treatment-naïve GT 3 patients, and SVR12 of 89%-92% in patients with prior DAA treatment. Trial limitations with GLE/PIB included very little exposure to certain subgroups such as treatment-experienced or cirrhotic GT 3 or DAA-experienced patients. Additionally, an 8-week regimen was assessed in three phase 3 trials among noncirrhotic patients with GT 1 (treatment experienced or naïve), GT 3 (nonrandomized arm, treatment naïve only), and HIV coinfection (GT 1-6) with SVR12 of 99%, 95%, and 100%, respectively. Each of these trials met their respective goals for noninferiority for the 8-week regimen. Of note, data for use of an 8-week regimen among other populations came from phase 2 trials and was limited by a very low exposure among GT 4-6 patients and an SVR12 of 93% with GT 4 patients.

Sofosbuvir/Velpatasvir/Voxilaprevir Combination Product (Vosevi™)

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is a fixed dose, single-tablet, pangenotypic combination NS5B polymerase inhibitor, NS5A inhibitor, and NS3/4A protease inhibitor approved in July 2017 for the treatment of chronic hepatitis C virus (HCV) + compensated cirrhosis (Child-Pugh A) in patients with 1) genotype (GT) 1-6 and prior NS5A inhibitor treatment and 2) for GT 1a and GT 3 with prior sofosbuvir (SOF) exposure without NS5A treatment. Vosevi was assessed in four published, fair quality, phase 3 trials (POLARIS 1-4). The majority of the trials were multicenter (MC), randomized, open-label (OL) trials which compared SOF-VEL-VOX to a prespecified performance standard. The POLARIS-1 and -4 trials assessed the efficacy of SOF-VEL-VOX (Vosevi) and SOF-VEL (Epclusa) for 12 weeks in comparison to a performance goal (sustained viral response [SVR] 85%). Polaris-1 included patients with HCV GT 1-6 + compensated cirrhosis who had failed NS5A inhibitors while the POLARIS-4 trial included patients with GT 1-3 + compensated cirrhosis who failed pegylated-interferon (PEG-IFN) + ribavirin (RBV) + protease inhibitor (PI) or any direct-acting antiviral (DAA) other than NS5A inhibitors.

SOF-VEL-VOX met criteria for superiority compared to the performance goal with SVR12 of 96% and 98%, respectively, in both trials. Of note, SVR12 decreased to 93% in patients with cirrhosis who failed NS5A treatment. Relapse following treatment occurred in <2% of SOF-VEL-VOX patients with both trials. Of note, no difference in SVR12 was found between treatment groups (SOF-VEL-VOX and SOF-VEL) in patients with GT 1b and 2 HCV in the POLARIS-4 trial.



Consequently, Vosevi is indicated in GT 1a and 3 patients only in this population. The POLARIS-2 and -3 trials assessed the efficacy of SOF-VEL-VOX for 8 or 12 weeks in DAA-naïve patients with HCV GT 1-6 + cirrhosis. The 8-week regimen did not meet the prespecified performance goal in the POLARIS-2 trial (GT 1, 2, 4, 5, 6) with overall SVR12 of 95%. Vosevi did not receive approval for an 8-week regimen.

Ledipasvir/Sofosbuvir Combination Product (Harvoni®)

In the 3 Phase III clinical trials (the ION trials), the SVR rates of sofosbuvir/ledipasvir were found to be efficacious in treatment naïve patients at 8 weeks (SVR rate 94%, 95% CI 90 to 97 in patients without cirrhosis), 12 weeks (SVR rate 99%, 95% CI 96 to 100), and 24 weeks (SVR rate 98%, 95% CI 95 to 99). However in the patients who received 8 week treatment, a 10% relapse rate was seen in patients who had a baseline HCV RNA load \geq 6 million IU/mL leading to the FDA only recommending considering 8 week treatment in treatment naïve patients whose viral load is $<$ 6 million IU/mL. Treatment with sofosbuvir/ledipasvir was also found to be efficacious in treating patients who are treatment experienced (treatment experienced = patients who tried and failed pegIFN and ribavirin \pm a NS3/4a protease inhibitor) at 12 weeks and 24 weeks; SVR rates 94% (95% CI 87-97) and 99% (95% CI 95-100), respectively. In all of the studies, the addition of ribavirin added no significant increase in efficacy while generally increasing the AEs experienced in each patient group.

In regards to cirrhosis, treatment naïve patients who were cirrhotic at baseline achieved similar response rates as those who had no cirrhosis at 12 and 24 weeks of sofosbuvir/ledipasvir treatment. Cirrhotic patients were not part of the 8 week trial for treatment naïve patients. The only distinguishing factor of predicting treatment response in treatment experienced patients was cirrhosis. Patients with baseline cirrhosis and treated with 12 weeks of sofosbuvir/ledipasvir had an SVR rate of 92% (95% CI 84 to 97) compared to an SVR rate of 98% (95% CI 96 to 99) for patients without cirrhosis.

There are currently studies underway to evaluate sofosbuvir/ledipasvir in different HCV genotypes 1-6 and in patients who have advanced liver disease and in patients who have undergone liver transplant. There is also a study not yet in the recruiting phase designed to test the efficacy of sofosbuvir/ledipasvir in patients co-infected with HIV. Currently there are no guidelines for the off-label use of sofosbuvir/ledipasvir in the above populations. Sofosbuvir is considered pan-genotypic in combination with ribavirin and pegIFN in all HCV genotypes 1-6.

There are no trials currently which compare the use of sofosbuvir/ledipasvir to current recommended sofosbuvir, ribavirin, and pegIFN. However, as stated in the studies, the typical



SVR rate seen with standard therapy range around 60-70% for HCV genotype 1. In all sofosbuvir/ledipasvir studies, the SVR rates were >97% for the use of the product for the duration FDA has approved in each patient group.

Sofosbuvir/ledipasvir was generally safe over varying treatment lengths with the shorter the length of treatment resulting in fewer AE. More AE were seen in treatment arms of the studies that included ribavirin. No patients discontinued treatment early due to AE in ION-2 (440 patients). 10 patients (out of 865) in ION-1 discontinued treatment early due to AE, 4 from the sofosbuvir/ledipasvir 24 week arm and 6 from the sofosbuvir/ledipasvir + ribavirin 24 week arm. There was no early discontinuation in either 12 week arm. In ION-3 (647 patients), 3 patients discontinued sofosbuvir/ledipasvir due to AE; 1 in the 8 week arm (due to road accident), 2 in the 12 week arm of sofosbuvir/ledipasvir (1 due to arthralgia and 1 due to lung cancer). Out of a total of 1952 patients exposed to sofosbuvir/ledipasvir 13 patients (<1%) discontinued treatment early due to AE. This is much lower than the standard discontinuation rate of interferon based therapy. Mild to moderate AE were common across all trials (67 to 92% of patients reported at least one AE). The most common AE were fatigue, headache, nausea, diarrhea, and insomnia.

Daclatasvir (Daklinza®)

Daclatasvir is an inhibitor of HCV NS5A protein, and is thus direct-acting antiviral agent against HCV. It binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly.

The efficacy and safety of DAKLINZA in combination with sofosbuvir were evaluated in the Phase III ALLY-3 (AI444-218) clinical trial. ALLY-3 was an open-label trial that included 152 subjects with chronic HCV genotype 3 infection and compensated liver disease who were treatment-naive (n=101) or treatment-experienced (n=51). Most treatment-experienced subjects had failed prior treatment with peginterferon/ribavirin, but 7 subjects had been treated previously with a sofosbuvir regimen and 2 subjects with a regimen containing an investigational cyclophilin inhibitor. Previous exposure to NS5A inhibitors was prohibited. Subjects received DAKLINZA 60 mg plus sofosbuvir 400 mg once daily for 12 weeks and were monitored for 24 weeks post treatment. HCV RNA values were measured during the clinical trial using the COBAS® TaqMan® HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL. Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA below the LLOQ at post-treatment week 12 (SVR12). The 152 treated subjects in ALLY-3 had a median age of 55 years (range, 24-73); 59% of the subjects were male; 90% were white, 5% were Asian, and 4% were black. Most subjects (76%) had



baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 21% of the subjects had compensated cirrhosis, and 40% had the IL28B rs12979860 CC genotype. SVR and outcomes in subjects without SVR in ALLY-3 are shown by patient population in Table 8. For SVR outcomes related to the baseline NS5A Y93H polymorphism, see Microbiology (12.4). SVR rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level.

Treatment Outcomes in ALLY-3: Daklinza in Combination with Sofosbuvir in Subjects with HCV Genotype 3 Infection

Treatment Outcomes	Treatment-Naïve	Treatment Outcomes	Treatment-Naïve
SVR			
ALL	90% (91/101)	86% (44/51)	89% (135/152)
No cirrhosis	98% (80/82)	92% (35/38)	96% (115/120)
With cirrhosis	58% (11/19)	69% (9/13)	63% (20/32)
Outcomes for subjects without SVR			
On-treatment virologic failure	1% (1/101)	0	0.7% (1/152)
Relapse	9% (9/100)	14% (7/51)	11% (16/151)

Elbasvir and Grazoprevir (Zepatier®)

Zepatier® combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir inhibited the proteolytic activity of the recombinant HCV genotype 1a, 1b, and 4a NS3/4A protease enzymes with IC50 values of 7 pM, 4 pM, and 62 pM, respectively.

The efficacy of Zepatier® was assessed in 2 placebo-controlled trials and 4 uncontrolled Phase 2 and 3 clinical trials in 1401 subjects with genotype (GT) 1, 4, or 6 chronic hepatitis C virus



infection with compensated liver disease (with or without cirrhosis). An overview of the 6 trials (n=1373) contributing to the assessment of efficacy in genotype 1 or 4 is provided in Table 12. C-EDGE TN, C-EDGE COINFECTION, C-SCAPE, and C-EDGE TE also included subjects with genotype 6 HCV infection (n=28). Because Zepatier is not indicated for genotype 6 infection, results in patients with genotype 6 infection are not included in clinical studies.

Trials Conducted with Zepatier®

Trial	Population	Study Groups and Duration (Number of Subjects Treated)
C-EDGE TN (double-blind)	GT1,4 TN with or without cirrhosis	<ul style="list-style-type: none"> ZEPATIER® for 12 weeks (N=306) Placebo for 12 weeks (N=102)
C-EDGE COINFECTION (open-label)	GT 1, 4 TN with or without cirrhosis HCV/HIV-1 co-infection	<ul style="list-style-type: none"> ZEPATIER® for 12 weeks (N=217)
C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Severe renal impairment including hemodialysis	<ul style="list-style-type: none"> EBR* + GZR* for 12 weeks (N=122) Placebo for 12 weeks (N=113)
C-SCAPE (open-label)	GT 4 TN without cirrhosis	<ul style="list-style-type: none"> EBR* + GZR* for 12 weeks (N=10) EBR* + GZR* + RBV for 12 weeks (N=10)
C-EDGE TE (open-label)	GT 1, 4 TE with or without cirrhosis HCV/HIV-1 co-infection	<ul style="list-style-type: none"> ZEPATIER® for 12 or 16 weeks (N=105, and 101, respectively) ZEPATIER® + RBV for 12 or 16 weeks (N=104 and 104, respectively)
C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen† with or without cirrhosis	<ul style="list-style-type: none"> EBR* + GZR* + RBV for 12 weeks (N=79)

GT = Genotype

TN = Treatment-Naïve

TE = Treatment-Experienced (failed prior treatment with interferon [IFN] or peginterferon alfa [PegIFN] with or without ribavirin [RBV] or were intolerant to prior therapy).

*EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR + GZR = co-administered as single agents.

† Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with PegIFN + RBV.



Zepatier® was administered once daily by mouth in these trials. For subjects who received ribavirin (RBV), the RBV dosage was weight-based (less than 66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, greater than 105 kg = 1400 mg per day) administered by mouth in two divided doses with food.

Sustained virologic response (SVR) was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12). Serum HCV RNA values were measured during these clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with an LLOQ of 15 HCV RNA IU per mL, with the exception of C-SCAPE where the assay had an LLOQ of 25 HCV RNA IU per mL.

2007 Update

When Hepatitis C patients receive a liver transplant, allograft infection is universal, and recurrent hepatitis C progresses at an accelerated rate. Preemptive antiviral therapy after transplantation has been disappointing. However, treatment of established histological disease with a combination of pegylated interferon and ribavirin is associated with sustained virologic response (SVR) in roughly 25% of cases. A recent meta-analysis reported a pooled SVR rate of 27% (range 23-31%). Stable and improved fibrosis scores can be expected in most patients who achieve SVR. While these rates are not impressive, pegylated interferon plus ribavirin remains the best available treatment and represents the current standard of care. Further research in this area is clearly needed.

2008 Update

A literature search of the MEDLINE database did not identify any additional published studies that would prompt reconsideration of the policy statement, which remains unchanged.

2009 Update

A literature search of the MEDLINE database from May 2008 to March 2009 and the 2008 AASLD annual meeting proceedings did not identify any additional published studies that would result in major reconsideration of the policy statement, excepting results from the EPIC3 (Evaluation of PegIntron in Control of Hepatitis C Cirrhosis) study. EPIC3 is a multinational, open-label trial



assessing the efficacy and safety of peginterferon alfa-2b 1.5 mcg/kg/wk in combination with weight-based ribavirin for 48 weeks in the retreatment of chronic hepatitis C patients with fibrosis (METAVIR F2-F4) unresponsive to or relapsing after standard or pegylated interferon-alfa/ribavirin combination treatment. Overall, SVR rates were 7%, 6%, and 18% in Peg-2b, Peg-2a, and standard interferon combination therapy nonresponders and 32%, 34%, and 43% in Peg-2b, Peg-2a, and standard interferon combination therapy relapsers. Undetectable HCV-RNA at week 12 was the most important predictor of SVR in this population. Overall, 56% achieved SVR if HCV-RNA was undetectable vs. 5% achieved SVR if only a ≥ 2 log decrease in HCV-RNA was observed at week 12).

2010 Update

A literature search did not identify any additional published studies that would require reconsideration of the policy statement. The Policy Guidelines dealing with slow responders and also requests for more than 2 courses of retreatment per year were added based on expert consultation.

2011 Update

A literature search did not identify any additional published studies that would require reconsideration of the policy statement.

2012 Update

Added criteria for Hepatitis C protease inhibitors telaprevir and boceprevir, based on a review of the primary literature.

2014 Update

Two new antiviral agents were approved in late 2013. These agents are rapidly changing the standard of care for treating Hepatitis C.



2015 Update

One additional prioritization criteria was added to the list. A brief description of NASH and NAFLD has been added to the discussion section. Two new antiviral agents (Technivie® and Daklinza®) were approved at the end of July 2015.

2015 Update (August)

A new direct acting antiviral agent combination product was approved in December 2014. This product, Viekira Pak®, consists of three active ingredients, paritaprevir (boosted by ritonavir), ombitasvir and dasabuvir.

2016 Update

One new agent (Zepatier®), and its related criteria and clinical summary were added to the medical policy.

Restructuring of the policy and guidelines to reflect AASLD/IDSA recommendations.

2016 Update (December)

Step therapy criteria requiring the use of Harvoni before Epclusa can be approved (only when clinically appropriate) has been added to the EXCEPTIONS' section of the policy.

2017 Update (August)

Step therapy criteria requiring the use of Mavyret first line wherever 8- or 12-week courses of therapy are adequate. Other patients may be treated with Epclusa or other agents, according to AASLD/IDSA guidelines and case-based assessment of medical necessity. Vosevi added as salvage therapy in treatment experienced patients with resistance to other regimens.



2017 Update (September)

Step therapy criteria updated requiring the use of Mavyret, Epclusa or Harvoni first line wherever one or more of these is indicated.

2018 Update (November)

Reviewed AASLD/IDSA guidelines update of May 24, 2018, which is the reference for these criteria. No changes were made to the guidelines that would affect these medical necessity criteria.

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History

Date	Comments
11/11/05	Add to Prescription Drug Section - New policy, held for notification—originally scheduled to publish 4/1/06; due to system logistics publication moved to 5/1/06. P&T reviewed 1/27/06 minor changes incorporated.
06/16/06	Update Scope and Disclaimer - No other changes.
11/14/06	Replace Policy - Policy reviewed by Pharmacy and Therapeutics Committee on September 26, 2006; recommended for adoption with no changes to policy statement.
01/09/06	Replace Policy - Policy updated with references and addition of medically necessary policy statement for treatment of liver transplant patients. Policy reviewed by P&T 11/28/06.
02/12/08	Replace Policy - Policy updated with literature search; no change to the policy statement. Reviewed by Pharmacy and Therapeutics Committee on January 22, 2008; recommended for adoption with no changes to policy statement.
05/12/09	Replace Policy - Policy updated with literature search. Policy statements re-written for clarification. References added.
07/29/09	Update Benefit Application - No other changes.
05/11/10	Replace Policy - Policy statement revised to indicate initiation of greater than 2 courses of retreatment with pegylated interferon plus ribavirin per year for relapse or non-response must be reviewed and approved by a Medical Director on a case-by-case basis; and slow responder patients with a ≥ 2 log decrease in hepatitis C viral load after 12 weeks of therapy, an additional 12 weeks of combination treatment may be reauthorized. Patients in this subpopulation who have undetectable HCV-RNA after 24 weeks of therapy may be reauthorized for up to an additional 48 weeks of treatment with a pegylated interferon plus ribavirin (for up to a 72-week course of therapy). Reviewed and recommended by P&T in March 2010.
05/10/11	Replace Policy - Policy updated with literature review; no change in policy statement.



Date	Comments
10/24/11	Coding update: HCPCS S0146 removed; S0148 added.
06/12/12	Replace policy. Updated to include Hepatitis C protease inhibitor criteria. Deleting review requirement for interferons in Hepatitis B, as this use is very infrequent.
10/11/12	Minor Update – Medco is now Express Scripts.
07/08/13	Minor Update – Clarification was added to the policy that it is managed through the member’s pharmacy benefit; this is now listed in the header and within the coding section.
12/09/13	Replace policy. Policy updated with review; no change in policy statement. CPT codes removed from the policy; this policy is managed through the pharmacy benefit.
04/14/14	Annual review. Policy updated with Sovaldi® (sofosbuvir) as medically necessary as combination therapy for the listed FDA-approved indications of chronic hepatitis C for off-label indications when all criteria are met; it is investigational for all other indications. Olysio® (simeprevir) is added as medically necessary as combination therapy for the FDA-approved indication for chronic hepatitis C genotype 1; all other uses are considered investigational. ICD-9 diagnosis codes removed from policy; they are not utilized in adjudication.
09/08/14	Interim review. Policy section updated with new direct-acting antiviral agents (DAA) as medically necessary treatment regimens for chronic hepatitis C when criteria are met; guidelines for prioritization of patients and expanded treatment information for genotypes 3-5 added (previously only genotypes 1 and 2 were addressed). This update reflects combined AASLD and IDSA guidelines for the treatment of chronic hepatitis C.
11/10/14	Interim review. Policy updated with literature search and information on FDA-approval of the new ledipasvir/sofosbuvir product (Harvoni®) to treat all genotype 1 patients on October 10, 2014. Additionally, the FDA recently approved the combination use of simeprevir (Olysio®) and sofosbuvir (Sovaldi®) to treat Hepatitis C; however, there is no evidence of improved patient outcomes versus use of Harvoni®, and this therapy regimen is considered not medically necessary.
12/22/14	Interim update. Clarifying wording added to the not medically necessary policy statement regarding combination therapy of simeprevir (Olysio®) and sofosbuvir (Sovaldi®): “since an equally or more effective alternative, ledipasvir/sofosbuvir (Harvoni®), is available at a much lower cost.” Regimen tables updated to align with policy statements: SOF (Sovaldi®) / SMV (Olysio®) ± RBV removed as a regimen to treat either treatment naïve or treatment resistant patients with Genotype 1; this regimen has been replaced with Harvoni®.
01/30/15	Annual review. Policy updated with addition of exceptions to specific treatment regimen guidelines relative to of Viekira Pak® within the Policy section. References 59-64 added.
04/14/15	Interim Review. Policy updated for treatment naïve patients with addition of Harvoni® for genotype 4 and 6; addition of Viekira Pak® for genotype 1 and 4; addition of Sovaldi® /Olysio® for genotype 1. Policy updated for treatment experienced patients



Date	Comments
	with addition of Harvoni® for genotype 4 and 6; addition of Viekira Pak® for genotype 4; Sovaldi®/Olysio® for genotype 1; addition of Sovaldi®/RBV for genotype 4. Multiple regimens for each genotype in the “alternative therapy” column have been removed as those are no longer recommended by the AASLD/IDSA guidelines. All data used have been taken from the AASLD/IDSA guidelines. Medical necessity criterion for proteinuria levels delineated to >2 grams urinary protein/24hours related to cryoglobulinemia. “Exceptions” section updated with the application to genotypes 1 and 4 only; genotype 6 removed. HCPCS codes J9213, J9214, S0145 and S0148 removed; these are not reviewed.
08/11/15	Interim Update: Added one more prioritization criteria to the list, as well as a brief description of NASH and NAFLD to the discussion section, Added two new agents: Technivie® and Daklinza®.
09/08/15	Interim update. Policy section addition to address re-treatment criteria after all DAA regimen.
11/10/15	Interim Update. Added type I diabetes as a prioritization criteria to the section “Prioritizing Patients for Treatment for Chronic Hepatitis C.”
12/08/15	Interim update. Medical necessity prioritization criteria removed. Charts for initial and retreatment revised to remain consistent with AASLD guidelines and for clarity; intent is unchanged.
01/08/16	Clarified that Viekira Pak is approved for genotype 1 in Exceptions explanation.
03/08/16	Interim update. Addition of one new agent Zepatier®, and its related criteria and clinical summary.
05/01/16	Annual Review, approved April 12, 2016. Revision of the policy language; removal of the drug tables.
06/14/16	Interim Update. Clarification of the Harvoni step requirement, and removal of outdated information.
06/30/16	Interim Update: Inclusion of the criteria for a brand new agent named Epclusa (sofosbuvir/velpatasvir). Currently has the same status as Harvoni. Status is subject to change.
07/08/16	Minor formatting updates for clarity.
09/01/16	Interim Update, approved August 9, 2016. Inclusion of an updated version of Viekira Pak® (Viekira® XR).
01/01/17	Interim Review, approved December 13, 2016. Step therapy criteria requiring the use of Harvoni before Epclusa can be approved has been added to the Exceptions section of the policy.
04/21/17	Policy moved into new format; no change to policy statements.
09/15/17	Annual Review, approved September 12, 2017, effective September 15, 2017. Policy updated to reflect new criteria for preferred DAA agents, adding Mavyret and Vosevi



Date	Comments
	as preferred agents replacing Harvoni and Eplusa where indicated. Update reflecting current guideline recommendations.
09/25/17	Interim Review, approved September 22, 2017, effective September 25, 2017. Modified step therapy criteria. Harvoni re-incorporated into policy as a preferred treatment agent; length of therapy information included.
12/01/18	Annual Review, approved November 21, 2018. Reviewed changes to AASLD/IDSA guidelines. No changes required. Remove HCPCS code J8499.
08/01/19	Interim Review, approved July 25, 2019. Updated criteria for Mavyret. Documented Eplusa and Vosevi are FDA-approved for adult patients.

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). ©2019 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.



Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
 - Qualified sign language interpreters
 - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
 - Qualified interpreters
 - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀናት ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፈላጊ እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታወቅ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):

يحتوي هذا الإشعار على معلومات هامة. قد يحتوي هذا الإشعار على معلومات مهمة بخصوص طلبك أو التغطية التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينه للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisni kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):

Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):

Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hns ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyto wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):

この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):

ແຈ້ງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈໍາເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວີ້ ຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកកាមរយ: Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កំណត់ថ្លៃជាតំបន់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអន្តរជាតិរបស់អ្នក ឬប្រាក់ដុល្លារចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងដុល្លារនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਜਦ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਕੱਠ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیر بران TTY تماس با شماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Prezenta notificare conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).