BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Treatment of Hepatitis C with a simeprevir (Olysio) Based Regimen

Policy # 00396
Original Effective Date: 01/15/2014
Current Effective Date: 01/15/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Treatment of Hepatitis C with Triple Therapy (Ribavirin Plus Pegylated Interferon Alfa Plus Telaprevir [Incivek] or Boceprevir [Victrelis]) is addressed separately in medical policy 00373.

Note: Treatment of Hepatitis C with Dual Therapy (Ribavirin Plus Pegylated Interferon Alfa) is addressed separately in medical policy 00374.

Note: Pegylated Interferons (Pegasys, PegIntron) for Other (Non-Hepatitis C) Uses is addressed separately in medical policy 00375.

Note: Treatment of Hepatitis C with a sofosbuvir (Sovaldi) Based Regimen is addressed separately in medical policy 00397.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a simeprevir (Olysio) based regimen (including pegylated interferon alfa + ribavirin) for the treatment of individuals with chronic hepatitis C virus (HCV) genotype 1 to be **eligible for coverage.**

Patient Selection Criteria
Based on review of available data, the Company may consider the use of a simeprevir (Olysio) based regimen (including pegylated interferon alfa + ribavirin) when ALL of the following criteria are met:

- Patient has diagnosis of chronic hepatitis C virus (HCV) genotype 1 infection; and
- Patient with chronic hepatitis C virus (HCV) genotype 1a does NOT have an NS3 Q80K polymorphism as detected by laboratory testing; and
- Patient has compensated liver disease (including those with cirrhosis); and
- Patient must NOT have previously undergone therapy with a treatment regimen that includes chronic hepatitis C virus (HCV) NS3/4A protease inhibitors (e.g. telaprevir, boceprevir, simeprevir); and
- Patient must use Olysio in combination with ribavirin plus pegylated interferon alfa.

Note: An initial authorization will be granted and a re-authorization will be granted based on hepatitis C virus ribonucleic acid (HCV RNA) levels submitted (per the table below):

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Simeprevir (Olysio) Based Regimen:	**At Treatment Week:**	**Submit:**
Treatment Naïve OR Prior Relapser Patients (Including Cirrhosis)	4 (1st Re-auth)	HCV RNA levels from treatment week 4
	12 (2nd Re-auth)	HCV RNA levels from treatment week 12
Prior Partial OR Null-Responder Patients (Including Cirrhosis)	4 (1st Re-auth)	HCV RNA levels from treatment week 4
	24 (2nd Re-auth)	HCV RNA levels from treatment weeks 12 and 24

Note: Due to time frames for hepatitis C virus ribonucleic acid (HCV RNA) level turnaround times, there is a window of extended approval time to allow for labs to result and be submitted.

Note: Subsequent treatment lengths will be determined based on the tables below:

Olysio based regimen:

Patient-Type	**Length of Therapy** (O = Olysio, P = Pegylated interferon alpha, R = Ribavirin)	**Approvals (See Stopping Rules Chart For Levels)**
Treatment Naïve OR Prior Relapser Patients (Including those in this category with cirrhosis)	24 weeks (12 weeks of O/P/R + 12 weeks of P/R)	Initial Auth Time: Approve through treatment week 4 1st Re-auth Time (based on 4 week levels): Approve through treatment week 12 2nd Re-auth Time (based on 4 and 12 week levels): Approve through treatment week 24
Prior Non-Responder Patients (Including Partial OR Null Responders) (Including those in this category with cirrhosis)	48 weeks (12 weeks of O/P/R+ 36 weeks of P/R)	Initial Auth Time: Approve through treatment week 4 1st Re-auth Time (based on 4 week levels): Approve through treatment week 24 2nd Re-auth Time (based on 4, 12, and 24 week levels): Approve through treatment week 48

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Note: In order to continue treatment with an Olysio based regimen, the patient's hepatitis C virus ribonucleic acid (HCV RNA) levels must NOT be greater than or equal to 25 IU/mL as reflected in the below chart at the defined re-authorization periods.

Treatment Stopping Rules for Olysio:

HCV RNA	Action
Treatment Week 4: greater than or equal to 25 IU/mL	Discontinue Olysio, pegylated interferon alfa, and ribavirin.
Treatment Week 12: greater than or equal to 25 IU/mL	Discontinue pegylated interferon alfa and ribavirin (treatment with Olysio is complete at week 12).
Treatment Week 24: greater than or equal to 25 IU/mL	Discontinue pegylated interferon alfa and ribavirin.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of a simeprevir (Olysio) based regimen (including pegylated interferon alfa + ribavirin) for the treatment of individuals with chronic hepatitis C virus (HCV) genotype 1 when patient selection criteria are not met to be **investigational.***

Based on review of available data, the Company considers the use of a simeprevir (Olysio) based regimen (including pegylated interferon alfa + ribavirin) for indications not approved by the U.S. Food and Drug Administration (FDA) to be **investigational.***

Background/Overview

Olysio is a HCV NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Olysio's efficacy has been established in combination with pegylated interferon alfa and ribavirin in genotype 1 infected patients with compensated liver disease (including cirrhosis). Olysio must not be used as monotherapy. It is recommended that patients with HCV genotype 1a infections with the Q80K mutation be given an alternative therapy.

Hepatitis C
Hepatitis C is the most common blood borne pathogen. In the US, there are approximately 3.2 million people chronically infected with hepatitis C. Hepatitis C, a single-stranded RNA virus, is genetically complex with several recognized genotypes. Genotypes 1, 2, and 3 are the most frequently encountered genotypes worldwide. Type 1a is most frequently found in Northern Europe and North America, while 1b is most common in Japan and Southern and Eastern Europe.

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Up until the last few years, Interferon alfa has been considered the only effective treatment of hepatitis C. A total of 40% of patients will show an initial response to interferon alfa, but most patients relapse soon after stopping treatment. Ribavirin (Rebetron®)‡†, a synthetic nucleoside analogue with antiviral activity, has also been investigated as a treatment of hepatitis C. In the past few years, pegylated interferon alfa (Pegasys and Pegintron) and ribavirin have become the standard treatment in patients with non-genotype 1 infections. The addition of the pegylated moiety improved the pharmacokinetic profile of the drug as well as doubled sustained virologic response (SVR) rates. The recent approval of hepatitis C protease inhibitors such as Victrelis and Incivek have improved the arsenal of treatment options for those patients with hepatitis C genotype 1. These new protease inhibitors are used in combination with pegylated interferon alfa and ribavirin for a variety of timeframes depending on the patient's hepatitis C treatment status. The latest addition to the protease inhibitor family of medications is simeprevir (Olysio). Drugs and treatment regimens used for CHC will be part of an ever evolving landscape over the next few years.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration
Pegasys (peginterferon alfa-2a) was approved by the FDA in 2002. It carries indications for both Hepatitis C and Hepatitis B Virus. Peg-Intron (peginterferon alfa-2b) was approved by the FDA in 2001. It carries an indication for the treatment of hepatitis C. Olysio was approved in November of 2013 and is indicated for the treatment of CHC genotype 1 infections in select patient populations as part of a combination antiviral treatment regimen. Rash and photosensitivity reactions have been noted to occur while undergoing treatment with Olysio.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Treatment Naïve Adult Subjects with HCV Genotype 1 Infections
The efficacy of Olysio in treatment-naïve patients with HCV genotype 1 infection was demonstrated in two randomized, double-blind, placebo-controlled, 2-arm, multicenter, Phase 3 trials (QUEST 1 and QUEST 2). The design of both trials was similar. All subjects received 12 weeks of once daily treatment with 150 mg Olysio or placebo, plus pegylated interferon alfa-2a (QUEST 1 and QUEST 2) or pegylated interferon alfa-2b (QUEST 2) and ribavirin, followed by 12 or 36 weeks of therapy with pegylated inferferon alfa and ribavirin in accordance with the on-treatment protocol-defined RGT criteria. Subjects in the control groups received 48 weeks of pegylated interferon alfa-2a or -2b and ribavirin.

Response rates were represented by the sustained viral response (SVR) at 12 weeks, also known as SVR12. In the pooled data of QUEST 1 and QUEST 2, there were 521 patients that received Olysio with pegylated interferon (P) and ribavirin (R) and there were 264 patients that received placebo, pegylated interferon (P), and ribavirin (R). The overall SVR12 was 80% in the treatment group vs. 50% in the placebo+PR group. The FDA recommends that HCV genotype 1a patients with the Q80K mutation be

placed on alternate therapy. This stems from the fact that only 58% of patients in the Olysio based treatment group achieved an SVR12 vs. 52% of those patients in the placebo+PR group. Looking at individuals with genotype 1a without the Q80K mutation, 84% of those patients treated with the Olysio based regimen achieved an SVR12 vs. 43% in the placebo+PR group. Looking at the genotype 1b population (which doesn't have any label wording regarding mutations), 85% of those patients treated with Olysio achieved an SVR12 vs. 53% in the placebo+PR treated group. In the pooled data of the two trials, there was an 8% on-treatment failure (met stopping rules and/or experienced viral breakthrough) in the Olysio based treatment group vs. 33% in the placebo+PR group. Viral relapse occurred in 11% of Olysio treated subjects vs. 23% of placebo+PR treated subjects.

Adult Subjects with HCV Genotype 1 Infection who Failed Prior Therapy
The PROMISE trial was a randomized, double-blind, placebo-controlled, 2-arm, multicenter, Phase 3 trial in subjects with HCV genotype 1 infection who relapsed after prior interferon-based therapy. All subjects received 12 weeks of once daily treatment with 150 mg Olysio or placebo, plus pegylated interferon alfa-2a and ribavirin, followed by 12 or 36 weeks of therapy with pegylated interferon alfa-2a and ribavirin in accordance with the protocol-defined RGT criteria. Subjects in the control group received 48 weeks of pegylated interferon alfa-2a and ribavirin.

Response rates for the PROMISE trial were represented by the SVR at 12 weeks, also known as SVR12. There were 260 patients that received Olysio with pegylated interferon (P) and ribavirin (R) and there were 133 patients that received placebo, pegylated interferon (P), and ribavirin (R). The overall SVR12 was 79% in the treatment group vs. 37% in the placebo+PR group. As mentioned in previous paragraphs, the FDA recommends that HCV genotype 1a patients with the Q80K mutation be placed on alternate therapy. This continues to hold true as only 47% of patients in the Olysio based treatment group achieved an SVR12 vs. 30% of those patients in the placebo+PR group. Looking at individuals with genotype 1a without the Q80K mutation, 78% of those patients treated with the Olysio based regimen achieved an SVR12 vs. 26% in the placebo+PR group. Looking at the genotype 1b population (which doesn't have any label wording regarding mutations), 86% of those patients achieved an SVR12 vs. 43% in the placebo+PR treated group. There was a 3% on-treatment failure (met stopping rules and/or experienced viral breakthrough) in the Olysio based treatment group vs. 27% in the placebo+PR group. Viral relapse occurred in 18% of Olysio treated subjects vs. 48% of placebo+PR treated subjects

The ASPIRE trial was a randomized, double-blind, placebo-controlled, 7-arm, Phase 2b trial in subjects with HCV genotype 1 infection, who failed prior therapy with pegylated interferon alfa and ribavirin (including prior relapsers, partial responders or null responders). Subjects received 12, 24 or 48 weeks of 100 mg or 150 mg Olysio in combination with 48 weeks of pegylated interferon alfa 2a and ribavirin, or 48 weeks of placebo in combination with 48 weeks of pegylated interferon alfa 2a and ribavirin.

Response rates for the ASPIRE trial were represented by the SVR at 24 weeks, also known as SVR24. Pooled data of both doses of an Olysio based regimen show that 83% of prior relapse subjects receiving an Olysio based regimen (N = 132) achieved SVR24 vs. 37% of patients that received placebo+PR. Sixty-seven percent (67%) of prior partial responders in the Olysio based regimen group achieved an SVR24 vs.

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9% in the placebo+PR group. In the prior null responders group, 45% of patients receiving an Olysio based regimen achieved an SVR24 vs. 19% of those in the placebo+PR group.

Treatment
The most recent AASLD (American Association for the Study of Liver Diseases) guidelines do not address the most recent approvals of the new Hepatitis C medications such as Olysio.

References.

1. The Centers for Disease Control and Prevention. Hepatitis C for health care professionals. Last updated: March 14, 2011. Available at: http://www.cdc.gov/hepatitis/HCV/index.htm.
2. Olysio [package insert]. Cambridge, MA: Vertex Pharmaceuticals; November 2013.

Policy History

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Current Effective Date: 01/15/2014
01/09/2014 Medical Policy Committee review
01/15/2014 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 01/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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