BlueCross BlueShield of Louisiana

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Treatment of Hepatitis C with Triple Therapy (Ribavirin Plus Pegylated Interferon Alfa Plus telaprevir [Incivek®] or boceprevir [Victrelis®])

Policy # 00373
Original Effective Date: 11/01/2013
Current Effective Date: 09/17/2014

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 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.

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 triple therapy (combination of ribavirin plus pegylated interferon alfa [Pegasys® and PegIntron®] plus an HCV NS3/4A protease inhibitor telaprevir [Incivek®] OR boceprevir [Victrelis®])‡ 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 triple therapy (as defined above) when the following criteria are met:

- Patient has diagnosis of chronic hepatitis C virus (HCV) Genotype 1; and
- Patient has detectable hepatitis C virus (HCV) ribonucleic acid (RNA) levels; and
- Patient is greater than 18 years of age; and
- Patient has compensated liver disease (including those with cirrhosis); and
- Patient is treatment-naïve OR has been previously treated with interferon-based (including pegylated interferon) treatment, including prior null responders, partial responders, and relapsers; and
- Patient must NOT have previously failed therapy with a treatment regimen that includes other HCV NS3/4A protease inhibitors (e.g. telaprevir, boceprevir); and
    - For boceprevir (Victrelis): Patient must have a 4 week "lead in period" of ribavirin plus pegylated interferon alfa; and
    - For boceprevir (Victrelis)/telaprevir (Incivek): Patient must use in combination with ribavirin plus pegylated interferon alfa.

Note: An initial authorization will be granted and based on the HCV NS3/4A protease inhibitor prescribed, re-authorization will be granted based on HCV RNA levels submitted (per the table below):

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Drug Based Regimen:	At Treatment Week:	Submit:
boceprevir (Victrelis)	12 (1st Re-auth)	HCV RNA levels from treatment weeks 8 and 12
	24 (2nd Re-auth)	HCV RNA levels from treatment week 24
telaprevir (Incivek)	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 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 table below:

Victrelis Based Regimen:

Patient-Type	Week 8 HCV Results	Week 24 HCV Results	Length of Therapy (V = Victrelis, P = Pegylated interferon alpha, R = Ribavirin)	Approvals
Previously Untreated	Not Detected	Not Detected	28 weeks (4 weeks of P/R + 24 weeks of V/P/R)	Initial Auth Time: Approve through treatment week 12 1st Re-auth Time (based on 8 and 12 week levels): Approve through treatment week 24 2nd Re-auth Time (based on 8, 12, and 24 week levels): Approve through treatment week 28
	Detected	Not Detected	48 weeks (4 weeks of P/R + 32 weeks of V/P/R) + 12 weeks of P/R)	Initial Auth Time: Approve through treatment week 12 1st Re-auth Time (based on 8 and 12 week levels): Approve through treatment week 24 2nd Re-auth Time (based on 8, 12, and 24 week levels): Approve through treatment week 48
Previously Partial Responders OR Relapsers	Not Detected	Not Detected	36 weeks (4 weeks of P/R+ 32 weeks of V/P/R)	Initial Auth Time: Approve through treatment week 12 1st Re-auth Time (based on 8 and 12 week levels): Approve through treatment week 24 2nd Re-auth Time (based on 8, 12, and 24 week levels):

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				Approve through treatment week 36
	Detected	Not Detected	48 weeks (4 weeks of P/R + 32 weeks of V/P/R)+ 12 weeks of P/R)	Initial Auth Time: Approve through treatment week 12 1st Re-auth Time (based on 8 and 12 week levels): Approve through treatment week 24 2nd Re-auth Time (based on 8, 12, and 24 week levels): Approve through treatment week 48
Previous Null Responders OR Patients With Cirrhosis OR HIV Co-Infected Patients	Detected OR Not Detected	Not Detected	48 weeks (4 weeks of P/R + 44 weeks V/P/R)	Initial Auth Time: Approve through treatment week 12 1st Re-auth Time (based on 8 and 12 week levels): Approve through treatment week 24 2nd Re-auth Time (based on 8, 12, and 24 week levels): Approve through treatment week 48

Note: If at any time treatment week 12 levels are greater than or equal to 100 IU/mL OR treatment week 24 levels are detectable, all drugs should be discontinued.

Incivek Based Regimen:

Patient-Type	**Week 4 HCV Results**	**Week 12 HCV Results**	**Length of Therapy** (I = Incivek, P = Pegylated interferon alpha, R = Ribavirin)	**Approvals**
Previously Untreated OR Prior Relapse	Not Detected	Not Detected	24 weeks (12 weeks of I/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 24
	Detectable (1000 IU/mL or less) AND/OR	Detectable (1000 IU/mL or less)	48 weeks (12 weeks of I/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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Previously Partial Responders OR Null Responders	Not Detected/ Detectable (1000 IU/mL or less) AND/OR	Not Detected/ Detectable (1000 IU/mL or less)	48 weeks (12 weeks of I/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
Cirrhosis Patients OR HIV Co-Infected Patients	Not Detected/ Detectable (1000 IU/mL or less) AND/OR	Not Detected/ Detectable (1000 IU/mL or less)	48 weeks (12 weeks of I/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

Note: If at any time treatment week 4 or 12 levels are greater than 1000 IU/mL OR treatment week 24 levels are detectable, all drugs should be discontinued.

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 triple therapy (combination of ribavirin + pegylated interferon alfa [Pegasys and PegIntron] + an HCV NS3/4A protease inhibitor [telaprevir (Incivek) OR boceprevir [Victrelis]) for the treatment of individuals with chronic hepatitis C virus (HCV) genotype 1 when patient selection criteria are not met to be **investigational.***

Background/Overview

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.

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®)ǂ, 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

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doubled sustained virologic response 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 inferferon alfa and ribavirin for a variety of timeframes depending on the patient's hepatitis C treatment status.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. Victrelis and Incivek were approved in 2011. They have an indication for the treatment of hepatitis C in combination with pegylated interferon alfa and ribavirin.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. 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.

Incivek
ADVANCE included 1,095 treatment-naïve patients randomized to a) the telaprevir regimen (above) for 24 to 48 weeks based on response to treatment at 4 and 12 weeks, b) telaprevir + pegylated-interferon + ribavirin for 8 weeks followed by pegylated-interferon + ribavirin for 16 or 40 weeks based on response to treatment at 4 and 12 weeks, or c) control [pegylated interferon (Pegasys) + ribavirin (Copegus)] for 48 weeks. Sustained viral response (SVR) rates were 75%, 69% and 44% for groups a, b and c, respectively. 58% of patients in the treatment groups met criteria for 24-week total treatment. A follow-up ILLUMINATE study found that that there was no benefit in extending therapy to 48 weeks in patients who had an early response to therapy. Rash was the most concerning side effect, occurring in more than 25% of patients in the treatment groups. 92% of the rash cases were mild and were treated effectively with topical corticosteroids or antihistamines.

REALIZE included 662 patients who failed prior therapy. Three groups were randomized to receive a) the telaprevir regimen (above) for 48 weeks, b) 4 weeks of pegylated-interferon + ribavirin, followed by 12 weeks of telaprevir + pegylated-interferon + ribavirin, followed by 32 weeks of pegylated-interferon + ribavirin, or c) control (pegylated interferon + ribavirin) for 48 weeks. Overall SVR for the telaprevir-based treatment arms were 65% compared to 17% for those in the control arm. The safety and tolerability results of the telaprevir-based regimens were similar to those reported from ADVANCE and ILLUMINATE.

Victrelis
SPRINT-2 included 1,097 treatment-naïve patients randomized to receive a) the boceprevir regimen (above) for 48 weeks, b) the boceprevir regimen using response-guided therapy (treatment to stop at 28 weeks in patients with undetectable virus at week eight), or c) control [pegylated interferon (Peg-Intron) +

ribavirin (Rebetol)] for 48 weeks. Sustained viral response rates were 66%, 63% and 38% in groups a, b and c, respectively. Anemia was the most concerning side effect affecting 49%, 49% and 29% of patients in the 3 groups, respectively.

RESPOND-2 included 403 patients who failed prior therapy. Three groups were randomized to receive a) the boceprevir regimen (above) for 48 weeks, b) the boceprevir regimen using response-guided therapy for 36 weeks, or c) control for 48 weeks. Sustained viral response rates were 66%, 59% and 21% in groups a, b and c, respectively. Anemia occurred in 47%, 43% and 20% of patients in the 3 groups, respectively.

Treatment

According to the American Association for the Study of Liver Diseases (AASLD), combination therapy with a pegylated interferon alfa and ribavirin and either Incivek or Victrelis is the standard of care for patients with genotype 1. Current guidelines do not address which pegylated interferon is preferred.

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30-April 3, 2011.

Policy History

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09/05/2013 Medical Policy Committee review
09/18/2013 Medical Policy Implementation Committee approval. New policy. One of three policies that replace medical policies 00171 Treatment of Hepatitis C and B with Pegylated Interferon and/or Ribavirin and 00310 Treatment of Hepatitis C with Pegylated Interferon, Ribavirin and/or Telaprevir (Incivek) and Boceprevir (Victrelis).
09/04/2014 Medical Policy Committee review
09/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 09/2015

*****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.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.