BlueCross BlueShield of Arizona
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MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

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HEPATITIS C INJECTABLE TREATMENTS

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

Description:

Hepatitis C virus (HCV) is a major cause of chronic liver disease and may progress to acute or chronic hepatitis, cirrhosis, liver failure or liver cancer. Hepatitis C is suspected when anti-HCV is present in the blood. The diagnosis is confirmed by HCV RNA detection. There are at least six major genotypes and more than 50 subtypes of HCV. There is little difference in the severity of disease or outcome of individuals infected with different genotypes. However, individuals with genotypes 2 and 3 are more likely to respond to interferon treatment.

Chronic HCV infections may be treated with combinations of oral and injectable medications.

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Description: (cont.)

Use of a HCV NS3/4A protease inhibitor for the treatment of other HCV genotypes besides genotype 1 has not been fully evaluated. There is no conclusive clinical data on retreating individuals who have failed a HCV NS3/4A protease inhibitor-based treatment, nor are there data on repeated courses.

Duration of HCV drug treatment is determined by HCV genotype, quantitative HCV RNA, previous HCV treatment, and presence or absence of cirrhosis.

Alpha interferon (injectable):
Alpha interferon is a host protein that is made in response to viral infections and has natural antiviral activity. Interferon therapies include:

- Infergen® (Interferon alphacon-1 or consensus interferon CIFN)
- Intron® A (Interferon alpha-2b)
- Rebetron®, combination therapy of Rebetol and Intron A (Interferon alpha-2b/Oral Ribavirin)
- PEG-Intron® (Peginterferon Alpha-2b)
- Pegasys® (Peginterferon Alpha-2a)

Peginterferon alpha is alpha interferon that has been chemically modified by the addition of a large inert molecule of polyethylene glycol. Pegylation changes the uptake, distribution and excretion of interferon, prolonging its half-life.

Peginterferon alphas may be used alone or in combination. Peginterferon alphas may be used for treatment of HCV in individuals coinfected with clinically stable HIV.

Ribavirin (Oral):
Ribavirin is a purine nucleoside analog that interferes with replication of viral RNA. Monotherapy with ribavirin for HCV is not effective and it should not be used alone for this indication. Ribavirin therapies include:

- Copegus®
- Rebetol®
- Ribasphere®
- RibaPak®
- RibaTab®
- Ribavirin - generic

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Description: (cont.)

Hepatitis C Virus NS3/4A Protease Inhibitors (Oral):
NS3/4A serine protease enzyme acts to cut large HCV encoded polyproteins into smaller pieces that are used to build new viruses. It is essential for viral replication. Inhibitors of this essential enzyme are available for use in treating certain HCV genotypes. Current agents available include:

- Incivek® (Telaprevir)*
- Victrelis® (Boceprevir)*
- Olysio (Simeprevir)*

Hepatitis C Virus NS5B Nucleotide Analog Polymerase Inhibitor (Oral):
An additional enzyme that is essential for viral replication is NS5B RNA-dependent RNA polymerase that synthesizes the viral genome. The RNA polymerase initiates RNA synthesis by forming a bond between nucleotides that also begins the elongation process of RNA synthesis. Inhibition of this enzyme is accomplished by insertion of an analog into NS5B polymerase that results in termination of enzyme activity. Current agent available is:

- Sovaldi (Sofosbuvir)*

*** Pharmacy Coverage Guidelines are available for these agents for members with BCBSAZ retail pharmacy prescription benefits**.

Definitions:

Compensated Liver Disease:
Cirrhosis with no evidence of decompensation (ascites, persistent jaundice, wasting, variceal hemorrhage, uncontrolled bleeding, hepatic encephalopathy, end stage disease, etc.) as well as no evidence of loss of liver function (normal liver function as evidenced by the following laboratory values: bilirubin < 1.5 mg/dL, albumin > 3.4 g/dL, INR < 1.5); and low risk for bleeding as evidenced by a platelet count > 75,000/mm3.

Clinically stable HIV:
Antiretroviral therapy is stable or not required.

Treatment Week (TW) HCV RNA:
The Quantitative HCV RNA value obtained at the end of the specified week of treatment. For example, TW 4 HCVRNA is a quantitative sample obtained after completion of 4 weeks of treatment.

Response Guided Therapy:
The Quantitative HCV RNA values, obtained at FDA approved manufacturer predefined points in therapy, which are used to determine duration of HCV treatment.

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Definitions: (cont.)

Treatment Futility:
The Quantitative HCV RNA values, obtained at FDA approved manufacturer predefined points in therapy, which are used to predict failure of HCV treatment.

Treatment Responses:

- Rapid virologic response (RVR): HCV RNA undetectable at TW 4
- Early virologic response (EVR): HCV RNA undetectable at TW 12
- Sustained virologic response (SVR): HCV RNA undetectable 24 weeks after stopping treatment
- Partial response: >2 log decrease in HCV RNA at TW 12 but still detectable HCV RNA at TW 12 and TW 24
- Null response: Failure to decrease HCV RNA by < 2 logs after 24 weeks
- Non-response: Failure to achieve a decline of 2 logs HCV RNA after 12 weeks of treatment or never achieved undetectable HCV RNA during 24 weeks of treatment
- Breakthrough: Reappearance of HCV RNA at any time during treatment
- Relapse: Undetectable HCV RNA at end of treatment but failed to achieve SVR

Criteria:

For oral medications for treatment of Hepatitis C, see BCBSAZ Pharmacy Coverage Guideline, *"Direct Acting Antiviral Agents for Hepatitis C Virus; Oral".*

Interferon Therapy (Non-Peginterferon Alphas):

- **Initial** 6 month course of non-peginterferon alpha for the treatment of chronic hepatitis C with compensated liver disease is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. **ONE** of the following:

     - Infergen, Rebetron: age 18 or older
     - Intron A: age 1 year or older

  2. HCV RNA
  3. Genotype confirmation

- **Continuation** of non-peginterferon alpha for an additional 6 months (total of 12 consecutive months) is considered ***medically necessary*** with documentation of a positive response (i.e., HCV RNA is reduced) to the initial treatment course of 6 months.

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Criteria: (cont.)

Interferon Therapy (Non-Peginterferon Alphas): (cont.)

- **Retreatment** with non-peginterferon alpha for relapse following the initial 12 consecutive months **will be reviewed by the clinical pharmacist and/or medical director(s) and/or clinical advisor(s)** and, if approved, may be authorized for a maximum of 12 additional months (total of 24 consecutive months). Ongoing retreatment, in spite of marginal benefit, may be considered medically necessary in certain circumstances to delay progression of viral damage in individuals with moderate to severe disease, including those individuals who are awaiting liver transplantation.

- Non-peginterferon alpha therapy for the treatment of HCV for all other indications not previously listed is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome.

Peginterferon Alpha Therapy:

Pegasys®:

- **Initial** 6 month course of Pegasys®, alone or in combination with ribavirin, for the treatment of chronic hepatitis C with compensated liver disease with or without clinically stable HIV is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Age 5 or older
  2. HCV RNA
  3. Genotype confirmation

PEG Intron®:

- **Initial** 6 month course of PEG Intron® alone for the treatment of chronic hepatitis C with compensated liver disease is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Age 18 or older
  2. HCV RNA
  3. Genotype confirmation

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Criteria: (cont.)

PEG Intron® with Rebetol®:

- **Initial** 6 month course of PEG Intron® in combination with ribavirin for treatment of chronic hepatitis C with compensated liver disease is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Age 3 or older
  2. HCV RNA
  3. Genotype confirmation

Continuation of Peginterferon Alpha (Pegasys®, PEG Intron®):

- **Continuation** of peginterferon alpha therapy for an additional 6 months (total of 12 consecutive months) is considered medically necessary with documentation of a positive response (i.e., HCV RNA is reduced) to the initial treatment course of 6 months, based on genotype being treated.

Retreatment: PEG Intron® with Ribavirin:

- **Retreatment** with a 6 month course of PEG Intron in combination with ribavirin for treatment of chronic hepatitis C with compensated liver disease is considered ***medically necessary*** with documentation **ANY** of the following:

  1. Responder (HCV RNA negative) to previous treatment but has relapsed after 6 months or more without treatment
  2. Initial course of treatment was standard interferon and individual has not had previous peginterferon alpha therapy
  3. Initial course of treatment with peginterferon alpha was at a dose that was reduced and the individual has not received a full course of standard dose peginterferon alpha.

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Criteria: (cont.)

All Other Indications:

- Peginterferon alpha therapy for the treatment of HCV for all other indications not previously listed is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome.

  These indications include, *but are not limited to:*

  - Continuation beyond the initial 12 consecutive month treatment course
  - Retreatment for relapse following initial interferon therapy for HCV with clinically stable HIV

Resources:

1. 5.01.11 BCBS Association Medical Policy Reference Manual. Treatment of Hepatitis C With Interferon and/or Ribavirin. Re-issue date 09/01/2011, issue date 03/15/1999

2. American Association for the Study of Liver Diseases (AASLD) Practice Guidelines, Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: An Update. *Hepatology.* 2009 Apr;49(4):1335-1374

3. American Gastroenterological Association. Technical Review on the Management of Hepatitis C. January 2006

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Resources: (cont.)

4. American Gastroenterological Association. Medical Position Statement on the Management of Hepatitis C. *Gastroenterology.* January 2006;130(1):225-230

5. Bacon BR, Shiffman ML, Mendes F, et al. Retreating chronic hepatitis C with daily interferon alphacon-1/ribavirin after nonresponse to pegylated interferon/ribavirin: DIRECT results. *Hepatology.* 2009 Jun 2009;49(6):1838-1846

6. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alpha-2b vs standard interferon alpha-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA.* 2004 Dec 15 2004;292(23):2839-2848

7. Dienstag J. The Role of Liver Biopsy in Chronic Hepatitis C. *Hepatology.* 2002 2002;36(No. 5, Suppl. 1):S152-S160

8. Drug Facts and Comparisons®.

9. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* Aug 2011;55(2):245-264

10. External Consultant Review. Gastroenterology. 2006

11. External Consultant Review. Gastroenterology. 2008

12. External Consultant Review. Gastroenterology. 2009

13. Hadziyannis SJ, Sette HJ, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med.* 2004 Mar 2 2004;140(5):346-355

14. Hoofnagle JaS, L. Peginterferon and Ribavirin for Chronic Hepatitis C. *The New England Journal of Medicine.* 12/07/2006 2006;355:2444-2451

15. Manns MP, Wedemeyer H. Treatment of hepatitis C in HIV-infected patients: significant progress but not the final step. *JAMA.* 2004 Dec 15 2004;292(23):2909-2913

16. Marcellin P, Heathcote EJ, Craxi A. Which patients with genotype 1 chronic hepatitis C can benefit from prolonged treatment with the 'accordion' regimen? *J Hepatol.* 2007 Oct 2007;47(4):580-587

HEPATITIS C INJECTABLE TREATMENTS (cont.)

Resources: (cont.)

17. National Institute of Allergy and Infectious Disease Division of Microbiology & Infectious Diseases. A State of the Art Conference, Hepatitis C: A Meeting Ground for the Generalist and the Specialist. *Meeting Summary.* 12/8-9/1998, last updated 01/05/2001, accessed 07/13/2006

18. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health. Chronic Hepatitis C: Current Disease Management. November 2006

19. National Institutes of Health. Management of Hepatitis C Consensus Development Conference Statement. 2002, accessed 07/13/2006

20. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Digestive Diseases Information Clearinghouse. Chronic Hepatitis C: Current Disease Management. 07/2000

21. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Digestive Diseases Information Clearinghouse. Liver Biopsy. *Digestive Diseases A-Z.* 11/2004

22. U.S. Department of Health and Human Services National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases National Digestive Diseases Information Clearinghouse. Liver Biopsy. *Digestive Diseases A-Z.* 2004.