Hepatitis C Treatment with Protease Inhibitors and Interferons and Ribavirin

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Section: Prescription Drugs
Place(s) of Service: Outpatient

I. Description

Hepatitis C virus (HCV) is a genetically complex, single-stranded ribonucleic acid (RNA) virus with six recognized genotypes. Genotypes 1, 2, and 3 are the most common. Seventy percent of patients with HCV infection in the United States have genotype 1.

Genotype 1 has been associated with a poorer response to interferon and ribavirin when compared to other genotypes. It is associated with a higher frequency of cirrhosis and abnormal serum aminotransferases and a 48-week course of treatment is recommended.

The goal of treatment is to prevent complications from chronic HCV infection by eradicating the virus. Treatment responses are defined by surrogate virological parameters:

- Rapid virological response (RVR): HCV RNA negative at week 4 of treatment by sensitive PCR-based quantitative assay.
- Extended rapid virological response (eRVR): HCV RNA is undetectable at week 4 and week 12 of treatment.
- Early virological response (EVR):
  - Complete EVR: HCV RNA negative at week 12 of treatment.
  - Partial EVR: At least a 2 log drop in HCV RNA level at week 12 of treatment compared to baseline HCV RNA level
    - Slow responder: HCV RNA is undetectable at week 24 of treatment
    - Partial responder: HCV RNA is still positive at week 24 of treatment
- Breakthrough: Reappearance of HCV RNA while still on treatment.
- Relapse: Reappearance of HCV RNA after treatment is discontinued.
Nonresponder: Failure to clear HCV after 24 weeks of treatment.
Null responder: Failure to decrease HCV RNA by at least 2 logs after 12 weeks of treatment.

Interferons are glycoproteins that have antiviral, antineoplastic, and immunomodulating properties. Interferons that are chemically joined with polyethylene alcohol are called pegylated interferons. This increases the half-life of the interferons rendering sustained therapeutic levels. Ribavirin is also a synthetic anti-viral agent that has a broad spectrum of anti-viral activity against RNA and DNA viruses. When used together, these drugs are effective in treating hepatitis C. The following drugs have been FDA approved for the treatment of hepatitis C:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example</th>
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<tbody>
<tr>
<td>Interferon alfacon-1</td>
<td>(e.g., Infergen)</td>
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<tr>
<td>Pegylated interferon alfa-2b</td>
<td>(e.g., Peg-Intron)</td>
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<tr>
<td>Pegylated interferon alfa-2a</td>
<td>(e.g., Pegasys)</td>
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<tr>
<td>Pegylated interferon alfa-2b plus ribavirin</td>
<td>(e.g., Peg-Intron/Rebetrol)</td>
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<tr>
<td>Pegylated interferon alfa-2a plus ribavirin</td>
<td>(e.g., Pegasys/Copegus)</td>
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Protease inhibitors, telaprevir (Incivek) and boceprevir (Victrellis) are FDA approved for the treatment of chronic hepatitis C genotype 1 infection in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy. When telaprevir is used, triple therapy with peginterferon alfa, ribavirin and telaprevir is administered for the first 12 weeks followed by dual therapy with peginterferon and ribavirin. The duration of treatment is determined by response to therapy which is based on the patient’s HCV RNA levels at treatment week (TW) 4, 12 and 24. When boceprevir is used, dual therapy with peginterferon and ribavirin is administered for 4 weeks, followed by triple therapy with peginterferon, ribavirin and boceprevir. The duration of therapy is determined by response to therapy which is based on the patient’s HCV RNA levels at TW 4, 8, 12 and 24.

The addition of a protease inhibitor to peginterferon alfa and ribavirin substantially increases the sustained viral response rates in patients with chronic hepatitis C genotype 1. The optimal therapy for chronic hepatitis C genotype 1 infection is the use of telaprevir or boceprevir in combination with peginterferon alfa and ribavirin.

II. Criteria/Guidelines

A. Peg interferon or interferon alfacon-1 with ribavirin or peg-interferon with ribavirin and a protease inhibitor are covered (subject to Limitations/Exclusions and Administrative Guidelines) for the initial treatment (previously untreated patients) or retreatment (previously treated patients) of Hepatitis C when all the following criteria are met:

1. The patient is HCV RNA positive as documented by a quantitative titer obtained within the previous three months.
2. The patient does not have decompensated liver disease. Decompensated liver disease is defined as a Child-Pugh score of greater than six or greater than class A (see Appendix).
3. The patient is currently not drinking alcoholic beverages and has been completely abstinent for at least six months.
4. The patient is currently drug or substance free and has been completely abstinent for six months or is participating in the Ku Aloha Ola Mau or Comprehensive Health and Attitude Management Program (CHAMP) and has agreed to random drug testing.
5. When a protease inhibitor (telaprevir or boceprevir) is used, the patient has genotype 1.
6. For retreatment, treatment is recommended by a gastroenterologist, hepatologist or infectious disease specialist.

B. Continuation of initial treatment and continuation of retreatment beyond week 12 are covered (subject to Limitations/Exclusions and Administrative Guidelines) when the following criteria are met:

1. Peg-interferon or interferon alfacon-1 and ribavirin
   a. Initial treatment
      i. Patient has undetectable virus during week 12 of treatment (complete EVR):
         ▪ Genotype 1, 4, 5, and 6: Continuation for an additional 36 weeks (total course of 48 weeks)
         ▪ Genotype 2 and 3: Continuation for an additional 12 weeks (total course of 24 weeks)
      ii. Patient has at least a 2 log drop in HCV RNA titer from baseline during week 12 of treatment but still has detectable virus (partial EVR)
         ▪ All genotypes: Continuation for an additional 12 weeks (total course of 24 weeks)
      iii. Patient had at least a 2 log drop in HCV RNA from baseline but still had detectable HCV RNA at week 12 and has undetectable virus at week 24 (slow responder):
         ▪ Genotype 1, 4, 5 or 6: continuation for up to an additional 48 weeks (total treatment duration of 72 weeks).
   b. Retreatment
      i. Patient has undetectable virus at week 12:
         ▪ Genotype 1, 4, 5 or 6: Continuation of peginterferon alfa and ribavirin for up to an additional 60 weeks (total treatment duration of up to 72 weeks) or interferon alfacon -1 and ribavirin for up to an additional 36 weeks (total treatment duration of 48 weeks).
         ▪ Genotype 2 and 3: Continuation of peginterferon alfa and ribavirin or interferon alfacon -1 and ribavirin for up to an additional 36 weeks (total treatment duration of 48 weeks).
      ii. Patient has at least a 2 log drop in HCV RNA from baseline at week 12, but still has detectable virus (partial EVR):
         ▪ All genotypes: Continuation of peginterferon alfa and ribavirin or interferon alfacon-1 and ribavirin for an additional 12 weeks (total treatment duration of 24 weeks).
      iii. Patient had at least a 2 log drop in HCV RNA from baseline but still had detectable HCV RNA at week 12 and has undetectable virus at week 24 (slow responder):
- Genotype 1, 4, 5 or 6: Continuation of peginterferon alfa and ribavirin for up to an additional 48 weeks (total treatment duration of up to 72 weeks) or continuation of interferon alfacon-1 and ribavirin for an additional 24 weeks (total treatment duration of 48 weeks).
- Genotype 2 or 3: Continuation of peginterferon alfa and ribavirin or continuation of interferon alfacon-1 and ribavirin for an additional 24 weeks (total treatment duration of 48 weeks).

c. Initial treatment or retreatment should be discontinued in the following situations:
   i. Patient does not have at least a 2 log drop in HCV RNA from baseline at week 12 (null responder).
   ii. Patient has detectable virus at week 24 (nonresponder).

2. Peg-interferon, ribavirin and teleprevir (Incivek) for genotype 1 only
   a. Initial treatment and retreatment of prior relapse patients:
      i. Patient has undetectable virus at weeks 4 and 12 (eRVR): continuation of peg-interferon and ribavirin for an additional 12 weeks (total treatment duration of 24 weeks). Patients with cirrhosis may benefit from peg-interferon and ribavirin for an additional 36 weeks (total treatment duration of 48 weeks).
      ii. Patient has detectable virus with HCV RNA 1000 IU/ml or less at weeks 4 and/or 12: continuation of peginterferon alfa, ribavirin and teleprevir through week 12, followed by continuation of peg-interferon and ribavirin for an additional 36 weeks (total treatment duration of 48 weeks).
   b. Retreatment of prior partial and null responder patients:
      i. Patient has undetectable HCV RNA at week 4 and 12: continuation of peginterferon alfa, ribavirin and teleprevir through week 12, followed by continuation of peg-interferon and ribavirin for an additional 36 weeks (total treatment duration of 48 weeks).
      ii. Patient has detectable virus with HCV RNA 1000 IU/ml or less at week 4 and or 12: Continuation of peginterferon alfa, ribavirin and teleprevir through week 12, followed by continuation of peg-interferon and ribavirin for an additional 36 weeks (total treatment duration of 48 weeks).
   c. Initial treatment and retreatment with all three drugs should be discontinued in the following situations:
      i. Patient has detectable HCV RNA greater than 1000 IU/ml at weeks 4 or 12.
      ii. Patient has detectable HCV RNA at week 24.

3. Peg-interferon, ribavirin and boceprevir (Victrelis) for genotype 1 only
   a. Initial treatment:
      i. Patient has undetectable virus at weeks 8 and 24: continuation of peginterferon alfa, ribavirin and boceprevir through week 28 if patient does not have cirrhosis or through week 48 if patient has compensated cirrhosis.
      ii. Patient has detectable virus at week 8 and undetectable virus at week 24: continuation of peginterferon alfa, ribavirin and boceprevir through week 36, followed by continuation of peginterferon alfa, and ribavirin through week 48. Consideration should be given to treating patients who are poorly interferon responsive (less than 1 log decline in viral load at week 4) with 4 weeks of
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peginterferon alfa and ribavirin followed by 44 weeks of peginterferon alfa, ribavirin and boceprevir.

b. Retreatment of previous partial responders or relapsers:
   i. Patient has undetectable HCV RNA at week 8 and 24: continuation of peginterferon alfa, ribavirin and boceprevir through week 36 if patient does not have cirrhosis or through week 48 if the patient has compensated cirrhosis. (Note: Response guided treatment has not been studied in patients who had less than a 2 log HCV RNA decline by week 12 during prior therapy with peginterferon and ribavirin. If considered for treatment, these patients should receive 4 weeks of boceprevir followed by 44 weeks of peginterferon alfa, ribavirin and boceprevir.)
   ii. Patient has detectable HCV RNA at week 8 and undetectable HCV RNA at week 24: continuation of peginterferon alfa, ribavirin and boceprevir through week 36, followed by peginterferon alfa and ribavirin through week 48.

c. Initial treatment and retreatment with all three drugs should be discontinued in the following situations:
   i. Patient has HCV-RNA greater than or equal to 100 IU/ml at week 12.
   ii. Patient has detectable HCV RNA at week 24.

III. Limitations/Exclusions

A. Treatment should be discontinued as outlined in II.B.1.c, II.B.2.c and II.B.3.c under Criteria/Guidelines.
B. When boceprevir and teleprevir are used, use of a sensitive real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV RNA levels is recommended. The assay should have a lower limit of HCV RNA quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL. For the purposes of assessing response to therapy, a “detectable but below the limit of quantification” HCV RNA result should not be considered equivalent to an “undetectable” HCV RNA result.
C. Quantitative titers and qualitative tests for HCV RNA should be obtained as close to the specified weeks of treatment unless there are extenuating circumstances.
D. If the patient does not respond to treatment with one protease inhibitor, treatment with another protease inhibitor is not covered.
E. Maintenance therapy is not covered.
F. Patients with HCV and human immunodeficiency virus (HIV) coinfection should not be treated with boceprevir or teleprevir in combination with peginterferon alfa and ribavirin as safety and efficacy have not been established.

IV. Administrative Guidelines

A. Precertification is required for the initiation of treatment with peginterferon alfa or interferon alfacon-1 in previously untreated patients (initial treatment) and previously treated patients (retreatment). To precertify, please complete HMSA's Drug Review Request and mail or fax the form and pertinent documentation as indicated.
B. The following documentation must be submitted:
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1. Laboratory reports of HCV RNA quantitative titer obtained in the previous 3 months and HCV genotype.
2. Laboratory reports, imaging and physical examination findings supporting Child-Pugh score of 6 or less.
3. Clinical notes or attestation supporting that the patient is not currently drinking alcoholic beverages and has been completely abstinent for six months and is currently drug or substance free and has been completely abstinent for six months.
4. Clinical notes or letter from Ku Aloha Ola Mau or CHAMP indicating that a patient with drug or substance abuse is participating in the program and has been completely abstinent for six months and has agreed to random drug testing.

C. When criteria for initiation of treatment are met, approval will be given for up to 12 months. HMSA reserves the right to perform retroactive review using the above criteria to validate that the services provided met payment determination criteria. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record and must be made available to HMSA upon request.

D. Precertification is required for treatment beyond 12 months. Documentation, including clinical notes and HCV RNA quantitative titers, supporting the need for continued treatment must be provided.

E. Precertification by Medco is required for the use of boceprevir (Victrellis) and teleprevir (Incivek), see policies in the e-library.

http://www.hmsa.com/portal/provider/MEDCO_HepC_Protease_Inhibitors_Summary_8_2_11.pdf

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J3490</td>
<td>Unclassified drugs (includes peginterferon alfa-2a, peginterferon alfa-2b)</td>
</tr>
<tr>
<td>J9212</td>
<td>Injection, interferon alfacon-1, recombinant, 1 mcg (Infergen)</td>
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<tr>
<td>S0145</td>
<td>Injection, pegylated interferon alfa-2a, 180 mcg per ml (Pegasys)</td>
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<tr>
<td>S0148</td>
<td>Injection, pegylated interferon alfa-2b, 10 mcg per 0.5 ml (Peg Intron)</td>
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V. References

VI. Appendix

Child-Pugh Score

A. Indications
   Evaluating prognosis in cirrhosis

B. Criteria
   1. Total Serum Bilirubin
      a. Bilirubin <2 mg/dl: 1 point
      b. Bilirubin 2-3 mg/dl: 2 points
      c. Bilirubin >3 mg/dl: 3 points
   2. Serum Albumin
      a. Albumin >3.5 g/dl: 1 point
      b. Albumin 2.8 to 3.5 g/dl: 2 points
      c. Albumin <2.8 g/dl: 3 points
   3. PT/IN
      a. PT (seconds prolonged) <4 seconds /INR <1.70: 1 point
      b. PT (seconds prolonged) 4-6 seconds/INR 1.71 to 2.20: 2 points
      c. PT (seconds prolonged) >6 seconds/INR >2.20: 3 points
   4. Ascites
      a. No Ascites: 1 point
      b. Ascites controlled medically: 2 points
      c. Ascites poorly controlled: 3 points
   5. Encephalopathy
      a. No Encephalopathy: 1 point
      b. Encephalopathy controlled medically: 2 points
      c. Encephalopathy poorly controlled: 3 points

C. Interpretation
   1. Child Class A: 5 to 6 points
   2. Child Class B: 7 to 9 points
   3. Child Class C: 10 to 15 points