UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

<table>
<thead>
<tr>
<th>Program</th>
<th>Notification - Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>interferon alfacon-1 (Infergen®), interferon alpha-2b (Intron® A), peginterferon alfa-2a (Pegasys®), peginterferon alfa-2b (PegIntron® and Sylatron™), ribavirin (Copegus® and Rebetol®)</td>
</tr>
<tr>
<td>Date Approved</td>
<td>2/2004, 4/2012</td>
</tr>
</tbody>
</table>

1. **Background:**
   
   **Indications**
   
   Interferon alfacon-1 (Infergen) is FDA approved for the treatment of chronic hepatitis C virus infection in patients ≥ 18 years old with compensated liver disease. This indication is based on clinical trials using interferon alfacon-1 alone, and on a single trial of interferon alfacon-1 in combination with ribavirin in patients who failed to respond to previous treatment with a pegylated interferon and ribavirin. However, the clinical trials using interferon alfacon-1 alone were conducted before combination therapy was the standard of care, and use of monotherapy is not recommended unless a patient is unable to take ribavirin.¹

   Interferon alfa-2b (Intron A) is FDA indicated for treatment of adults 18 years of age or older with chronic hepatitis C with compensated liver disease, hairy cell leukemia, malignant melanoma, follicular Non-Hodgkin’s lymphoma, condylomata acuminata (genital and perianal), and AIDS-related Kaposi’s sarcoma. Interferon alfa-2b is also FDA approved for the treatment of chronic hepatitis B in patients 1 year of age or older with compensated liver disease. Interferon alfa-2b has additional FDA labeling for combination use with ribavirin for the treatment of chronic hepatitis C in patients ≥ 3 years old with previously untreated compensated liver disease or in patients ≥ 18 years old who have relapsed following alpha interferon therapy.²

   The NCCN (National Comprehensive Cancer Network) also approves of the use of interferon alpha-2b (Intron A) for chronic myelogenous leukemia, kidney cancer, multiple myeloma, systemic light chain amyloidosis, other types of NHL including mycosis fungoides/Sézary syndrome, carcinoid neuroendocrine tumors, desmoid soft tissue sarcomas, meningiomas, and in combination with zidovudine for adult T-cell leukemia/lymphoma.³ Interferon alfa has also been used for treatment of progressive kaposiform hemangioendothelioma.⁴

   Peginterferon alfa-2a (Pegasys) is FDA approved as monotherapy or in combination with ribavirin for the treatment of patients 5 years of age and older with compensated liver disease who have chronic hepatitis C virus infection not previously treated with interferon alpha.⁵ Peginterferon alfa-2b (Peg-Intron) is FDA approved as monotherapy or in combination with ribavirin for the treatment of adult patients with compensated liver disease who have chronic hepatitis C virus infection not previously treated with interferon alpha.⁶ It is also approved in combination with ribavirin for the
treatment of chronic hepatitis C in pediatric patients ≥ 3 years old with compensated liver disease previously untreated with interferon alpha as well as in combination with ribavirin for retreatment after previously failing a course of therapy. Peginterferon alfa-2a is also indicated for the treatment of adults with HBeAg positive and HBeAg negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation. The American Association for the Study of Liver Diseases (AASLD) Chronic Hepatitis B Practice Guideline suggests that similar efficacy in hepatitis B is seen with peginterferon alfa-2b. The NCCN also approves the use of peginterferon alfa-2a and peginterferon alfa-2b for chronic myelogenous leukemia and peginterferon alfa-2b for melanoma. Additional evidence supports the use of peginterferon alfa-2a in patients with myeloproliferative neoplasms (MPNs) such as essential thrombocytopenia (ET), polycythemia vera (PV), and primary myelofibrosis (PM).

Another formulation of peginterferon alfa-2b (Sylatron) is FDA approved for the adjuvant treatment of malignant melanoma.

Ribavirin (Copegus and Rebetol) is indicated for use in combination with interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b for the treatment of chronic hepatitis C virus infection with compensated liver disease.

Evidence

- The combination of pegylated interferon alfa and oral ribavirin is the current standard of care for the treatment of chronic hepatitis C.
- Patients with genotype 1 HCV have a very small chance (0-3%) of sustained viral response (SVR) if early viral response (EVR) is not achieved by week 12 of pegylated interferon therapy.
- Retreatment SVR rates with peginterferon/ribavirin in relapsers previously treated with interferon/ribavirin may be 40-50%. For previous interferon monotherapy nonresponders, SVR with retreatment with peginterferon/ribavirin is about 20%, and about 10% for previous interferon/ribavirin nonresponders. Retreatment of peginterferon/ribavirin nonresponders leads to an SVR of 5% or less. Retreatment of peginterferon/ribavirin relapsers led to a 33% SVR in one trial.
- Longer term peginterferon has also been investigated for treatment nonresponders and is currently unproven.
- Up to 38% of patients treated with a peginterferon regimen post liver transplant achieve SVR.
- Optimal length of therapy for HIV patients coinfected with HCV is 48 weeks, regardless of genotype.

2. Coverage Criteria:

<table>
<thead>
<tr>
<th>INTERFERON ALFACON-1 (INFERGEN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient has chronic hepatitis C virus infection</td>
</tr>
<tr>
<td>Patient has compensated liver disease</td>
</tr>
<tr>
<td>Ribavirin will be taken in combination with interferon alfacon-1 or patient has documented medical reason why ribavirin will not be used.</td>
</tr>
</tbody>
</table>
### Coverage Criteria:

<table>
<thead>
<tr>
<th>INTERFERON ALPHA-2B (INTRON A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient has chronic hepatitis C</td>
</tr>
<tr>
<td>• Patient has compensated liver disease</td>
</tr>
<tr>
<td>• Ribavirin will be taken in combination with interferon alpha-2b or patient has documented medical reason why ribavirin will not be used.</td>
</tr>
<tr>
<td>• Patient is ≥ 18 years old</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>• Patient has chronic hepatitis C</td>
</tr>
<tr>
<td>• Patient has compensated liver disease</td>
</tr>
<tr>
<td>• Patient is ≥ 3 years old and &lt; 18 years old</td>
</tr>
<tr>
<td>• Intron A will be used in combination with ribavirin</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>• Patient has chronic hepatitis B</td>
</tr>
<tr>
<td>• Patient has compensated liver disease</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>• Patient has a diagnosis of one of the following:</td>
</tr>
<tr>
<td>- Hairy cell leukemia</td>
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<tr>
<td>- Malignant melanoma</td>
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<tr>
<td>- Condylomata acuminata (genital or perianal)</td>
</tr>
<tr>
<td>- AIDS-related Kaposi’s sarcoma</td>
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<tr>
<td>- Chronic myelogenous leukemia</td>
</tr>
<tr>
<td>- Kidney cancer</td>
</tr>
<tr>
<td>- Multiple myeloma</td>
</tr>
<tr>
<td>- Systemic light chain amyloidosis</td>
</tr>
<tr>
<td>- Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>- Mycosis fungoides or Sézary syndrome</td>
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<tr>
<td>- Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>- Carcinoid neuroendocrine tumor</td>
</tr>
<tr>
<td>- Desmoid soft tissue sarcoma</td>
</tr>
<tr>
<td>- Meningiomas</td>
</tr>
<tr>
<td>- Progressive kaposiform hemangioendothelioma</td>
</tr>
</tbody>
</table>

### Coverage Criteria:

<table>
<thead>
<tr>
<th>PEGINTERFERON ALFA-2A (PEGASYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient has chronic hepatitis B</td>
</tr>
<tr>
<td>• Patient has compensated liver disease</td>
</tr>
<tr>
<td>• Patient is ≥ 18 years old</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>• Patient has chronic myelogenous leukemia</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>• Patient has chronic hepatitis C virus infection</td>
</tr>
<tr>
<td>• Patient is treatment naïve</td>
</tr>
<tr>
<td>• Patient has compensated liver disease</td>
</tr>
<tr>
<td>• Ribavirin will be taken in combination with peginterferon alfa-2a or patient</td>
</tr>
</tbody>
</table>
has documented medical reason why ribavirin will not be used.
- Patient is ≥ 5 years old

OR
- Patient has chronic hepatitis C virus infection
- Patient has compensated liver disease
- Patient is currently receiving peginterferon and is requesting completion of recommended therapy, or is an adult currently receiving interferon alpha for chronic HCV and is requesting switch to peginterferon.

OR
- Patient has chronic hepatitis C virus infection
- Patient has compensated liver disease
- Retreatment is requested due to relapse or non-response to interferon monotherapy, interferon/ribavirin, or peginterferon monotherapy.

OR
- Patient has chronic hepatitis C virus infection
- Patient has compensated liver disease
- Retreatment is requested due to relapse after peginterferon/ribavirin therapy.

OR
- Patient has chronic hepatitis C virus infection
- Patient has compensated liver disease
- Retreatment is requested due to non-response to peginterferon/ribavirin therapy.
- Peginterferon will be used in combination with boceprevir (Victrelis™) or telaprevir (Incivek™)

OR
- Patient has a diagnosis of myeloproliferative neoplasms (MPNs) such as essential thrombocytopenia (ET), polycythemia vera (PV), and primary myelofibrosis (PM)

Coverage Criteria:

PEGINTERFERON ALFA-2B (PEGINTRON)
- Patient has chronic hepatitis B
- Patient has compensated liver disease
- Patient is ≥ 18 years old

OR
- Patient has chronic myelogenous leukemia

OR
- Patient has malignant melanoma

OR
- Patient has chronic hepatitis C virus infection
- Patient is treatment naïve
- Patient has compensated liver disease
- Ribavirin will be taken in combination with peginterferon alfa-2b or patient has documented medical reason why ribavirin will not be used.
• Patient is ≥ 18 years old
  OR
• Patient has chronic hepatitis C virus infection
• Patient is treatment naïve
• Patient has compensated liver disease
• Patient is ≥ 3 years old and < 18 years old
• Peginterferon alfa-2b will be used in combination with ribavirin
  OR
• Patient has chronic hepatitis C virus infection
• Patient has compensated liver disease
• Patient is currently receiving peginterferon and is requesting completion of recommended therapy, or is currently receiving interferon alpha for chronic HCV and is requesting switch to peginterferon
  OR
• Patient has chronic hepatitis C virus infection
• Patient has compensated liver disease
• Retreatment is requested due to relapse or non-response to interferon monotherapy, interferon/ribavirin, or peginterferon monotherapy
  OR
• Patient has chronic hepatitis C virus infection
• Patient has compensated liver disease
• Retreatment is requested due to relapse after peginterferon/ribavirin therapy.
  OR
• Patient has chronic hepatitis C virus infection
• Patient has compensated liver disease
• Retreatment is requested due to non-response to peginterferon/ribavirin therapy.
• Peginterferon will be used in combination with boceprevir (Victrelis) or telaprevir (Incivek)

Coverage Criteria:

PEGINTERFERON ALFA-2B (SYLATRON)
• Patient has malignant melanoma

Coverage Criteria:

RIBAVIRIN (COPEGUS AND REBETOL)
• Patient has chronic hepatitis C
• Patient has compensated liver disease
• Ribavirin will be used in combination with interferon or peginterferon

Approvals/Renewals (refer to tables for response-guided therapy rules):
Table 1: Duration of therapy using Response-Guided Therapy (RGT) guidelines in patients without cirrhosis receiving boceprevir (Victrelis) triple drug regimen\textsuperscript{19}

<table>
<thead>
<tr>
<th></th>
<th>Assessment* (HCV-RNA Results)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Treatment Week 8</td>
<td>At Treatment Week 24</td>
</tr>
<tr>
<td>Previously Untreated Patients</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td>Detectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Partial Responders or Relapsers</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td>Detectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

*Treatment Futility
If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

For the purposes of assessing Response-Guided Therapy milestones, a confirmed “detectable but below limit of quantification” HCV-RNA result should not be considered equivalent to an “undetectable” HCV-RNA result.

- Pegasys or PegIntron requested as part of boceprevir (Victrelis) triple therapy regimen for hepatitis C genotype 1 in treatment naïve patients:\textsuperscript{19}
  - Initial 28 week approval
  - HCV-RNA report required at weeks 8 and 24.
    - If HCV-RNA is detectable (1,000 IU/mL or less) at week 8 and undetectable at week 24, renewal will be given for an additional 20 weeks for a total treatment duration of 48 weeks.

- Pegasys or PegIntron requested as part of boceprevir (Victrelis) triple therapy regimen for hepatitis C genotype 1 in previous partial responder or relapse patients:\textsuperscript{19}
  - Initial 28 week approval
  - HCV-RNA report required at weeks 8 and 24.
    - If HCV-RNA is undetectable at week 8 and undetectable at week 24, renewal will be given for an additional 8 weeks for a total treatment duration of 36 weeks.
• If HCV-RNA is detectable (1,000 IU/mL or less) at week 8 and undetectable at week 24, renewal will be given for an additional 20 weeks for a total treatment duration of 48 weeks.

• Pegasys or PegIntron requested as part of boceprevir (Victrelis) triple therapy regimen for hepatitis C genotype 1 in patients with compensated cirrhosis, previous null response to peginterferon/ribavirin therapy, or poor interferon responsiveness as determined at treatment week 4:
  o Initial 28 week approval
  o HCV-RNA report required at weeks 8 and 24
  o If HCV-RNA is undetectable at week 24, renewal will be given for an additional 20 weeks for a total treatment duration of 48 weeks.

Table 2: Duration of therapy using Response-Guided Therapy (RGT) guidelines in patients without cirrhosis receiving telaprevir (Incivek) triple drug regimen

<table>
<thead>
<tr>
<th>Treatment-naïve and prior relapse patients</th>
<th>HCV-RNA</th>
<th>Triple therapy (telaprevir, peginterferon alfa, and ribavirin)</th>
<th>Dual therapy (peginterferon alfa and ribavirin)</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable at weeks 4 and 12</td>
<td>First 12 weeks</td>
<td>Additional 12 weeks</td>
<td>24 weeks</td>
<td></td>
</tr>
<tr>
<td>Detectable (1000 IU/mL or less) at weeks 4 and/or 12</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
<td>48 weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior partial and null responder patients</th>
<th>HCV-RNA</th>
<th>Triple therapy (telaprevir, peginterferon alfa, and ribavirin)</th>
<th>Dual therapy (peginterferon alfa and ribavirin)</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
<td>48 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Futility (all patients)
Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12 (discontinue Incivek, peginterferon alfa, and ribavirin); or (2) confirmed detectable HCV-RNA levels at Treatment Week 24 (discontinue peginterferon alfa and ribavirin)

For the purposes of assessing Response-Guided Therapy milestones, a confirmed “detectable but below limit of quantification” HCV-RNA result should not be considered equivalent to an “undetectable” HCV-RNA result.

• Pegasys or PegIntron requested as part of telaprevir (Incivek) triple therapy regimen for hepatitis C genotype 1 in treatment naïve or prior relapse patients:
  o Initial 16 week approval
HCV-RNA report required at weeks 4 and 12.

- If HCV-RNA is undetectable at weeks 4 and 12, renewal will be given for an additional 8 weeks for a total treatment duration of 24 weeks.
- If HCV-RNA is detectable (1,000 IU/mL or less) at weeks 4 and/or 12, renewal will be given for an additional 12 weeks.
  - HCV-RNA report required at week 24.
  - If HCV-RNA is undetectable at week 24, renewal will be given for an additional 20 weeks for a total treatment duration of 48 weeks.
  - If the patient has confirmed, detectable HCV-RNA at treatment week 24, then no additional therapy will be authorized (discontinue peginterferon and ribavirin).

- Pegasys or PegIntron requested as part of telaprevir (Incivek) triple therapy regimen for hepatitis C genotype 1 in prior partial or null responder patients or in patients with compensated cirrhosis.¹⁸
  - Initial 16 week approval
  - HCV-RNA report required at weeks 4, 12, and 24
  - If HCV-RNA is 1,000 IU/mL or less at weeks 4 and 12, renewal will be given for an additional 12 weeks.
  - If HCV-RNA is 1,000 IU/mL or less at weeks 24, renewal will be given for an additional 20 weeks for a total treatment duration of 48 weeks.

- Pegasys or PegIntron requested for hepatitis C, treatment naïve or switching from interferon (non-pegylated):
  - Initial 16 week approval for genotypes 1, 4, 5, or 6.
  - HCV-RNA report required at week 12.
    - If HCV-RNA is undetectable at week 12, renewal will be given for an additional 32 weeks for a total treatment duration of 48 weeks.
    - Upon at least 2-log decrease in HCV-RNA, renewal will be given for an additional 12 weeks at which time a negative HCV-RNA will be required at week 24 for approval of an additional 24 to 48 weeks, for maximum 72 weeks of therapy.

- Pegasys or PegIntron in combination with ribavirin requested for hepatitis C, treatment naïve or switching from interferon (non-pegylated): Initial and total of 6 months approval for genotypes 2 or 3.

- Pegasys or PegIntron monotherapy requested for hepatitis C, treatment naïve or switching from interferon (non-pegylated):
  - Initial 16 week approval for genotypes 2 and 3.
  - HCV-RNA report required at week 12.
    - If HCV-RNA is undetectable at week 12, renewal will be given for an additional 32 weeks for a total treatment duration of 48 weeks.
    - Upon at least 2-log decrease in HCV-RNA, renewal will be given for an additional 12 weeks at which time a negative HCV-RNA will be required at week 24 for approval of an additional 24 weeks for a total treatment duration of 48 weeks.
• Pegasys or PegIntron requested for retreatment:
  o Initial 16 week approval.
  o HCV-RNA report required at week 12.
    ▪ If HCV-RNA is undetectable at week 12, renewal will be given for
      an additional 32 weeks for a total treatment duration of 48
      weeks.
    ▪ Upon at least 2-log decrease in HCV-RNA, renewal will be given
      for an additional 12 weeks at which time a negative HCV-RNA
      will be required at week 24 for approval of an additional 20
      weeks for a total treatment duration of 48 weeks.
• Pegasys or PegIntron requested for hepatitis C in a liver transplant recipient or
  a patient co-infected with HIV:
  o Initial and total approval for 48 weeks in a treatment naïve patient.
  o In a patient who is currently receiving treatment, initial and total
    approval to complete 48 weeks of therapy.
• Pegasys or PegIntron for hepatitis B: 12 months approval
• Infergen: 12 months approval
• Intron A: 12 months approval
• Ribavirin (Copegus, Rebetol): 12 months approval

3. **Additional Clinical Rules:**
   **Supply Limits:** In place for Infergen, Pegasys, and PegIntron
   **Progression Rx:** In place for PegIntron

4. **Definitions:**

<table>
<thead>
<tr>
<th>Early virologic response (EVR)</th>
<th>≥ 2-log_{10} decline in HCV-RNA level compared to baseline HCV-RNA level (partial EVR) or HCV-RNA negative at treatment week 12 (complete EVR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained virologic response (SVR)</td>
<td>HCV-RNA negative 24 weeks after cessation of treatment</td>
</tr>
<tr>
<td>Treatment-naïve patients</td>
<td>Untreated for HCV infection</td>
</tr>
<tr>
<td>Non-responders / Partial responders to peginterferon alfa and ribavirin therapy</td>
<td>≥ 2-log_{10} decline in HCV-RNA by week 12 of prior peginterferon alfa and ribavirin therapy, but with detectable HCV-RNA level during therapy</td>
</tr>
<tr>
<td>Relapsers to peginterferon alfa and ribavirin therapy</td>
<td>Undetectable HCV-RNA level at the end of previous peginterferon alfa and ribavirin treatment, but HCV-RNA detectable within 24 weeks of treatment follow-up (i.e., absence of an SVR)</td>
</tr>
<tr>
<td>Null responders to peginterferon alfa and ribavirin therapy</td>
<td>&lt; 2-log_{10} decline in HCV-RNA by week 12 of prior peginterferon alfa and ribavirin therapy</td>
</tr>
<tr>
<td>Poor interferon response at treatment week 4</td>
<td>&lt; 1-log_{10} decline in HCV-RNA at treatment week 4 (i.e., at the end of treatment)</td>
</tr>
</tbody>
</table>
5. References:

3. The NCCN Drugs and Biologics Compendium (NCCN Compendium™). http://www.nccn.org/professionals/drug_compendium/content/contents.asp