Medical Policy Manual

Topic: Pegasys®, peginterferon alfa-2a
Committee Approval Date: March 14, 2014
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Date of Origin: October 2001
Next Review Date: March 2015

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Peginterferon alfa-2a (Pegasys®) is a pegylated form of interferon alfa-2a used in the treatment of both chronic hepatitis B and chronic hepatitis C.
Policy / Criteria

I. Most contracts require prior authorization approval of peginterferon alfa-2a prior to coverage. Peginterferon alfa-2a may be considered medically necessary when one of the following criteria (A, B, C, or D) is met.

ADMINISTERED WITH A HCV PROTEASE INHIBITOR

A. Peginterferon alfa-2a will be used in combination with a hepatitis C virus (HCV) protease inhibitor (e.g. boceprevir, simeprevir, or telaprevir) and criteria 1 through 3 below are met:
   1. There is a diagnosis of chronic genotype 1 HCV infection.
   AND
   2. Prior authorization has been approved for boceprevir (Victrelis), simeprevir (Olysio), or telaprevir (Incivek).
   AND
   3. There is documentation of the member’s treatment history (see Appendix 2).

OR

ADMINISTERED WITH SOFOSBUVIR (SOVALDI)

B. Peginterferon alfa-2a will be used in combination with sofosbuvir (Sovaldi) and criteria 1 and 2 below are met:
   1. There is a diagnosis of chronic genotype 1 or genotype 4 hepatitis C virus (HCV) infection.
   AND
   2. Prior authorization has been approved for sofosbuvir (Sovaldi).

OR

ADMINISTERED WITHOUT A HCV PROTEASE INHIBITOR OR SOFOSBUVIR

C. Peginterferon alfa-2a will be used without a hepatitis C virus (HCV) protease inhibitor (e.g. boceprevir, simeprevir, or telaprevir) or sofosbuvir (Sovaldi) and criteria 1 through 4 below are met:
   1. There is a diagnosis of chronic HCV infection (any genotype).
   AND
   2. Peginterferon alfa-2a will be used in combination with ribavirin, unless ribavirin is contraindicated (see Appendix 1).
   AND
   3. The member has not received previous treatment with peginterferon alfa-2a or peginterferon alfa-2b.
4. There is documentation that peginterferon alfa-2a will not be used with a HCV protease inhibitor (e.g. boceprevir, simeprevir, or telaprevir) or sofosbuvir (Sovaldi).

OR

D. Peginterferon alfa-2a will be used for the treatment of chronic hepatitis B and criteria 1 and 2 below are met:
   1. There is a confirmed diagnosis of compensated chronic hepatitis B.
   AND
   2. Patient has not received previous treatment with peginterferon alfa-2a or peginterferon alfa-2b.

II. Administration and Authorization Period

A. RegenceRx considers peginterferon alfa-2a to be a self-administered medication.

B. When prior authorization is approved, peginterferon alfa-2a may be authorized as follows:
   1. Use with boceprevir (Victrelis) or telaprevir (Incivek): up to 48 weeks.
   2. Use with simeprevir (Olysio):
      a. Treatment-naïve members and prior relapsers: up to 24 weeks.
      b. Prior partial and null responders: up to 48 weeks.
   3. Use with sofosbuvir (Sovaldi): up to 12 weeks.
   4. Use without a hepatitis C virus (HCV) protease inhibitor (e.g. boceprevir, simeprevir, or telaprevir) or sofosbuvir (Sovaldi): up to 48 weeks.

III. Peginterferon alfa-2a is considered not medically necessary when used for the following conditions:

A. Clinically decompensated cirrhosis due to hepatitis C

B. Chronic myelogenous leukemia

C. Kidney, liver, heart, or other solid organ transplant

D. Retreatment of chronic hepatitis B or C in relapsers or non-responders to peginterferon alfa-2a or peginterferon alfa-2b, except when used in combination with boceprevir (Victrelis), simeprevir (Olysio), or telaprevir (Incivek) for the retreatment of chronic hepatitis C genotype 1, or in combination with sofosbuvir (Sovaldi) for the treatment of chronic hepatitis C genotype 1 or 4.

E. Treatment of chronic hepatitis B or C beyond 48 weeks

IV. Peginterferon alfa-2a is considered investigational when used for all other conditions, including, but not limited to:

A. Advanced renal cell carcinoma
B. Chronic hepatitis C genotype 1 in combination with boceprevir (Victrelis), simeprevir (Olysio), or telaprevir (Incivek), but without ribavirin.

C. Chronic hepatitis C genotype 1 or 4 in combination with sofosbuvir (Sovaldi), but without ribavirin.

D. Thrombocytosis

E. Melanoma

F. Multiple myeloma

G. Polycythemia vera

H. Status post liver transplant

Position Statement

Summary

- Peginterferon alfa is used as part of standard of care treatment for chronic genotype 1, 4, 5, or 6 hepatitis C virus (HCV) infection.

- The duration of treatment ranges from 12 to 48 weeks depending on the genotype of HCV and concomitant HCV therapies.

- There is no reliable evidence that treatment beyond 48 weeks provides any additional benefit.

- Peginterferon alfa-2a has been studied in several other conditions; however there is no reliable evidence establishing it as a treatment option for conditions other than chronic HCV infection and hepatitis B virus (HBV) infection at this time.

Clinical Efficacy

In Combination with a HCV Protease Inhibitor (e.g. boceprevir, simeprevir, telaprevir)

- The addition of simeprevir to peginterferon and ribavirin improves viral cure rates as compared to peginterferon and ribavirin alone in patients with chronic genotype 1 hepatitis C virus (HCV) infection. There are three unpublished, phase III randomized controlled trials and one published, phase II trial demonstrating that simeprevir improves viral cure rates in both treatment-naïve patients and patients who failed prior treatment with peginterferon and ribavirin. [62,63]

  * The primary endpoint evaluated in clinical trials of simeprevir was the rate of viral cure, defined as a sustained virologic response (SVR) 12 weeks following the completion of therapy. Although SVR is measured by a series of HCV RNA levels and is considered a surrogate endpoint, it is accepted as a measure of efficacy for the treatment of HCV.

  * Patients were excluded from clinical trials with simeprevir if they had decompensated liver disease or HIV co-infection.

  * Treatment-naïve patients: One fair and one low confidence randomized controlled trial (QUEST-1 and QUEST-2; unpublished) demonstrated that the addition of a 12 week course of simeprevir to peginterferon and ribavirin significantly improved SVR rates in treatment naïve patients with

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chronic genotype 1 HCV infection as compared to peginterferon and ribavirin alone (80-81% vs 50%, respectively; P < 0.001).

- SVR rates were lower in simeprevir-treated patients with the HCV genotype 1a Q80K polymorphism than in patients without the Q80K polymorphism (pooled QUEST-1 and QUEST-2 data: 84% and 58%, respectively). The Q80K polymorphism is common in the U.S. HCV population, and was detected in 48% of genotype 1a patients with sequencing data in the simeprevir clinical trials.

* Treatment-experienced patients: One low confidence, unpublished randomized controlled trial and one fair confidence, published randomized controlled trial demonstrated that the addition of a 12 week course of simeprevir to peginterferon and ribavirin significantly improved SVR rates in patients who relapsed after or did not respond to prior therapy with peginterferon and ribavirin as compared to peginterferon and ribavirin alone (67-79% vs 23-37%, respectively; P < 0.001).

- SVR rates were lower in simeprevir-treated patients with the HCV genotype 1a Q80K polymorphism than in patients without the Q80K polymorphism.

The addition of boceprevir to response-guided peginterferon plus ribavirin improves viral cure rates as compared to peginterferon and ribavirin alone in patients with chronic genotype 1 HCV infection. There are three published, phase III randomized controlled trials demonstrating that boceprevir improves viral cure rates in both treatment-naïve patients and patients who failed prior treatment with peginterferon and ribavirin. [55-58]

* The primary endpoint evaluated in clinical trials of boceprevir was the rate of viral cure, defined as a sustained virologic response (SVR) 24 weeks following the completion of therapy. Although SVR is measured by a series of HCV RNA levels and is considered a surrogate endpoint, it is accepted as a measure of efficacy for the treatment of HCV.

* Patients were excluded from clinical trials with boceprevir if they had decompensated liver disease or hepatocellular carcinoma.

* Treatment-naïve patients: Two unreliable phase III trials demonstrated that the addition a 24- to 44-week course of boceprevir to peginterferon and ribavirin significantly improved SVR rates in patients with previously untreated chronic genotype 1 HCV infection compared to peginterferon and ribavirin alone. There were also fewer virologic failures and relapses reported in the boceprevir treatment groups. [56, 58]

- The two trials of boceprevir in treatment-naïve patients were appraised as unreliable due to the high percentage of study participants who did not complete the studies (> 20%). Because the studies are unreliable, the magnitude of benefit demonstrated by the addition of boceprevir to peginterferon and ribavirin cannot be accurately estimated.

* Treatment-experienced patients: One reliable phase III trial demonstrated that the addition of a 32- to 44-week course of boceprevir to peginterferon and ribavirin significantly improved SVR rates in patients who relapsed after, or only partially responded to, prior treatment with peginterferon plus ribavirin as compared to peginterferon and ribavirin alone (60-65% vs 21%, respectively; NNT = 2 to 3). There were also fewer virologic failures and relapses reported in the boceprevir treatment group. [57]
The addition of telaprevir to response-guided peginterferon plus ribavirin improves viral cure rates as compared to peginterferon and ribavirin alone in patients with chronic genotype 1 HCV infection. There are two published, reliable phase III randomized controlled trials demonstrating that telaprevir improves viral cure rates in both treatment-naïve patients and patients who failed prior treatment with peginterferon and ribavirin. [59-61]

* The primary endpoint evaluated in clinical trials of telaprevir was the rate of viral cure, defined as a sustained virologic response (SVR) 24 weeks following the completion of therapy. Although SVR is measured by a series of HCV RNA levels and is considered a surrogate endpoint, it is accepted as a measure of efficacy for the treatment of HCV.

* Patients were excluded from clinical trials with telaprevir if they had decompensated liver disease or hepatocellular carcinoma.

* Treatment-naïve patients: The addition of a 12-week course of telaprevir to peginterferon and ribavirin significantly improved SVR rates in patients with previously untreated chronic genotype 1 HCV infection compared to peginterferon and ribavirin alone (78% vs 46%, respectively; NNT = 3). There were also fewer virologic failures and relapses reported in the telaprevir treatment groups. [59,60]

* Treatment-experienced patients: The addition of a 12-week course of telaprevir to peginterferon and ribavirin significantly improved SVR rates in patients who relapsed after, or did not respond to, prior treatment with peginterferon and ribavirin as compared to peginterferon and ribavirin alone (66% vs 17%, respectively; NNT = 2). There were also fewer virologic failures and relapses reported in the telaprevir treatment group. [59,61]

In Combination with Sofosbuvir (Sovaldi)

- The addition of sofosbuvir to peginterferon and ribavirin produces high viral cure rates in treatment-naïve patients with chronic genotype 1, 4, 5, or 6 HCV infection. One low confidence, single-arm published trial evaluated a 12 week treatment course of sofosbuvir, peginterferon, and ribavirin in treatment-naïve patients with chronic genotype 1, 4, 5, or 6 HCV infection. [64]

* The primary endpoint evaluated in clinical trials of sofosbuvir was the rate of viral cure, defined as a sustained virologic response (SVR) 12 weeks following the completion of therapy. Although SVR is measured by a series of HCV RNA levels and is considered a surrogate endpoint, it is accepted as a measure of efficacy for the treatment of HCV.

* The reported SVR rate was 90% with sofosbuvir, peginterferon, and ribavirin. SVR rates for genotypes 1, 4, 5, and 6 were 89%, 96%, 100%, and 100%, respectively.

  ▪ According to the FDA medical review, too few patients with genotypes 5 and 6 were included in the trial to establish efficacy, safety, and appropriate dosing for those genotypes. [65] Sofosbuvir did not receive FDA-approval for the treatment of HCV genotypes 5 and 6.

Use without a HCV Protease Inhibitor or Sofosbuvir (Sovaldi)

- Three large pivotal trials have demonstrated that peginterferon plus ribavirin was more effective than standard interferon-ribavirin combination or peginterferon alone. [1, 4, 5]

- The optimal duration of therapy depends on HCV genotype. [1]
* Patients infected with genotype 1 HCV who achieve an early viral response require 48 weeks of combination peginterferon and ribavirin therapy. \[^{1,22}\]

* Patients infected with genotype 4 HCV who achieve an early viral response require 36 to 48 weeks of combination peginterferon and ribavirin therapy. \[^{26}\]

* A 24-week treatment course of peginterferon and ribavirin is equally effective as a 48-week course of therapy in patients with HCV genotypes 2 or 3. \[^{1}\]

**Clinical Practice Guidelines** \[^{66}\]
- Clinical practice guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend the combination of sofosbuvir, peginterferon and ribavirin as the preferred regimen for treatment-naïve patients with chronic genotype 1 HCV infection and as an alternative regimen for treatment-experienced chronic genotype 1 HCV infection. This regimen is also listed as the preferred therapy for treatment-naïve or treatment-experienced chronic genotype 4, 5, or 6 HCV infection.
- The guidelines recommend simeprevir, peginterferon, and ribavirin as an alternative regimen for treatment-naïve and treatment-experienced patients with chronic genotype 1 or 4 HCV infection.
- The guidelines do not recommend triple therapy regimens that include the addition of boceprevir or telaprevir to peginterferon and ribavirin.
- Dual therapy with peginterferon and ribavirin is recommended as an alternative regimen for treatment-naïve patients with chronic genotype 5 or 6 HCV infection.

**Patient Characteristics**
- Quantitative determination of the HCV level provides important information on the likelihood of response to treatment in patients undergoing antiviral therapy. \[^{1}\]
- Determination of the HCV genotype provides important information on the duration of therapy. \[^{1}\]

**Dosing Considerations and Treatment Duration**
- A 48 week treatment course is recommended, regardless of genotype, for patients treated with peginterferon monotherapy (those with contraindications to ribavirin - see appendix 1). \[^{9}\]
- A reduced ribavirin dosage of 800 mg daily appeared to be adequate for patients with genotypes 2 and 3, but the higher, standard dosage of 1,000 mg to 1,200 mg daily yielded better response rates in patients with genotype 1. \[^{1}\]
- Peginterferon alfa is dosed for 24 – 48 weeks when given concomitantly with boceprevir (Victrelis) or telaprevir (Incivek). The duration of treatment is response-guided and based on HCV RNA levels at designated check points. \[^{55,59}\]
  * Peginterferon and ribavirin are administered for 4 weeks prior to initiating treatment with boceprevir. \[^{55}\]
  * The dosing regimen for telaprevir does not include a 4-week peginterferon/ribavirin lead-in. \[^{59}\]
  However, a phase III trial of telaprevir in prior treatment failures of peginterferon/ribavirin demonstrated similar rates of sustained virologic response (SVR) in patients treated with a 4-week lead-in as compared to those without a lead-in. \[^{61}\] A lead-in period may be useful in
certain patients, including prior null responders and those with an unknown response to prior treatment, for assessing interferon sensitivity and determining whether to start a HCV protease inhibitor.

- Peginterferon alfa is dosed for 12 – 48 weeks when given concomitantly with simeprevir. The duration of treatment with peginterferon is dependent on patient treatment history. [67]

- Peginterferon alfa is dosed for 12 weeks when given concomitantly with sofosbuvir for all patients. [68]

- Doses in excess of FDA-approved doses have not been proven to be more effective in well-designed clinical studies, yet may be accompanied by more frequent adverse effects. [23, 24, 51]

  * No difference in SVR was demonstrated in a study comparing peginterferon alfa-2b plus ribavirin given for 48 weeks versus 72 weeks in patients with HCV genotype 1 who had a slow virologic response. [51]

Treatment of Patients Co-Infected with HIV

- The chance of achieving a SVR in a patient co-infected with human immunodeficiency virus (HIV) is lower than in a patient who is not co-infected. [1, 4, 5, 10-14] Clinical studies have evaluated up to 48 weeks of treatment in patients with HIV, regardless of HCV genotype. [21]

- EVR is predictive of treatment success in patients with HIV. Patients who do not have an EVR are unlikely to experience a sustained response to therapy. Therefore, additional treatment is not likely to be of value. [11, 12, 13]

- While HCV genotype is of prognostic value, it is unclear if differences in genotype can be useful in influencing duration of therapy.

Retreatment of Patients

- "Relapsers" achieve an initial end of treatment response, but it is not sustained over time. "Non-responders" never achieve an end of treatment response. [1]

- Only 15 to 20 percent of non-responders treated with standard interferon and ribavirin achieve an SVR on re-treatment with peginterferon and ribavirin. [1, 25]

- Only 9 to 16 percent of non-responders treated with peginterferon alfa-2b and ribavirin achieve and SVR on re-treatment with peginterferon alfa-2b and ribavirin. [49]

- Most patients relapse again if they are re-treated with the same regimen that was originally used. [1, 25]

- Long-term continuous therapy for patients with peginterferon (or ribavirin or both) for non-responders is considered investigational. [1, 50]

- Patients with advanced fibrosis or cirrhosis have an increased risk of hepatic decompensation and may be considered for re-treatment, especially if they were initially treated with interferon monotherapy. [1] In addition, patients with genotype 2 or 3 and absence of cirrhosis may have improved chances of success with retreatment. [16]
In patients with chronic HCV genotype 1 who failed prior treatment with peginterferon plus ribavirin (relapsers or non-responders), the addition of a HCV protease inhibitor (e.g. boceprevir or telaprevir) to standard therapy resulted in significantly improved SVR rates as compared to standard therapy alone. [57,61]

**Treatment After Liver Transplant**

- Treatment of HCV after liver transplantation is considered experimental and should be carried out in the context of clinical trials. [1] The effectiveness of peginterferon for the treatment of chronic hepatitis C that is present after orthotopic liver transplantation (OLT) has not been established. Treatment has not been shown to decrease the chance of re-transplantation or increase the survival of the allograft.

- Two randomized controlled trials have evaluated either prophylaxis or treatment in patients who have undergone OLT. Sustained viral response rates were 8% and 12%, respectively. Although histological improvements were correlated with treatment, the impact on allograft function or survival has not been demonstrated. [15]

- In a non-randomized, open-label study of 47 liver transplant patients with recurring HCV infection, 23% achieved an SVR. Twenty-one percent of patients discontinued therapy due to adverse events, despite the use of darbepoetin alpha. [37]

- A randomized, open-label trial compared peginterferon alfa-2a monotherapy to combined therapy with ribavirin in 42 patients transplanted for HCV-related cirrhosis.
  * Medication dose reductions occurred frequently. Forty-eight percent of patients failed to complete the entire 48 weeks of therapy.
  * Sustained viral response (SVR) occurred in 38% of monotherapy patients and 33% of combination therapy patients. [38]

- Two active clinical trials are investigating patients with recurrent hepatitis C after orthotopic liver transplantation. One trial is investigating prophylactic treatment with pegylated interferon and the other trial is assessing the efficacy and safety of combination therapy with pegylated interferon and ribavirin. [39]

**Treatment of Hepatitis B**

- Peginterferon alfa-2a is recommended as an option for initial treatment of chronic compensated hepatitis B. [33,34]

- Peginterferon alfa-2a has been studied up to 60 weeks in duration for treatment of hepatitis B. However well-conducted randomized controlled trials are needed to assess if longer treatment durations are more effective than standard regimens. [40]

- Peginterferon appears to be effective in treating some measures of chronic hepatitis B. However, it is unclear if peginterferon is more effective for most patients than other available treatments such as standard interferon or Hepsera®. [17-19]

- Combination therapy of peginterferon alfa-2a and lamivudine failed to demonstrate additional benefit over peginterferon alfa-2a monotherapy. [27]
**Other Investigational Uses**

- Peginterferon alfa-2a has been studied in the treatment of hepatitis D virus when used in combination with adefovir. \[^{52}\] Hepatitis D is a defective RNA virus that requires coinfection with hepatitis B in order to replicate. Because peginterferon alfa is already an established treatment for the treatment of hepatitis B virus, this finding has little impact on the treatment of these patients.

- Several studies have evaluated peginterferon alfa in the treatment of chronic myelogenous leukemia (CML):
  * An open-label randomized study comparing the efficacy and tolerability of pegylated interferon alfa-2a compared to interferon alfa-2a concluded that pegylated interferon alfa-2a resulted in higher rates of hematologic and cytogenetic response rates. However, differences in overall survival were not statistically significant. \[^{42}\]
  * An unreliable, open-label randomized trial evaluated imatinib, imatinib plus cytarabine, and imatinib plus peginterferon alfa-2a in the treatment of CML. \[^{53}\] The study reported improved molecular response rates in the peginterferon treatment arm at one year. Cytogenetic response rates were similar between treatment groups. The tolerability of the regimen is poor as 93% and 83% of patients dropped out of the imatinib plus peginterferon and imatinib plus cytarabine treatment arms, respectively. The high rate of attrition makes these data highly unreliable.
  * A small (n = 27), phase I study looked at tumor response in patients with renal cell carcinoma following therapy with peginterferon alfa-2a. Well-designed comparative studies are necessary to determine whether peginterferon has a role in this setting. \[^{54}\]

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**Appendix 1: Ribavirin contraindications:**

| - Women who are pregnant or men whose female partners cannot practice birth control. |
| - Patients with a history of hypersensitivity to ribavirin or any component of the capsule. |
| - Patients with autoimmune hepatitis. |
| - Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) should not be treated with ribavirin. |
Appendix 2: Definition of Member Treatment History

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<tr>
<th>Treatment-naive</th>
<th>Patients who have never received therapy for the treatment of hepatitis C.</th>
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<tbody>
<tr>
<td>Relapser</td>
<td>Patients who had an undetectable HCV RNA level at the end of prior therapy with peginterferon and ribavirin, but had a subsequent detectable HCV RNA level during the follow-up period.</td>
</tr>
<tr>
<td>Partial responder</td>
<td>Patients who had a HCV RNA reduction of $\geq 2 \log_{10}$ after 12 weeks of prior therapy with peginterferon and ribavirin, but still had a detectable HCV RNA level during the treatment period.</td>
</tr>
<tr>
<td>Null responder</td>
<td>Patients who had a $&lt; 2 \log_{10}$ reduction in HCV RNA after 12 weeks of prior therapy with peginterferon and ribavirin.</td>
</tr>
</tbody>
</table>

Cross References

- PEG-Intron®, peginterferon alfa-2b dru144
- Incivek™, telaprevir dru254
- Olysio™, simeprevir dru331
- Sovaldi™, sofosbuvir dru332
- Victrelis™, boceprevir dru253

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References

5. Fried MW et al. "Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection." *NEJM* 2002;347:975-82

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65. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Medical Review; NDA 204-671; Sovaldi (sofosbuvir). [cited 2/28/2014]; Available from: [link to document].

66. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C. January 29, 2014. [cited 2/24/14]; Available at: [link to document].
