

Infergen[®] Prior Authorization Criteria

Brand	Generic	Dosage Form
Infergen [®]	interferon alfacon-1	injection

SUMMARY OF PRIOR AUTHORIZATION CRITERIA

It is the intent of the Infergen Prior Authorization Criteria to ensure that patients who are prescribed Infergen (interferon alfacon-1) therapy for treatment of hepatitis C are appropriately selected for treatment and appropriate duration of therapy. Infergen may also be approved for other indications. The following is a summary of the criteria for approval of Infergen (interferon alfacon-1).

Infergen will be approved for INITIAL therapy if ONE of the following criteria is met:

- Patient is using Infergen for a non-hepatitis C indication
- OR**
- Patient has a diagnosis of hepatitis C AND ALL of the following:
 - Patient has never completed a course of 24 months of interferon alfa, interferon alfacon-1, or pegylated interferon therapy AND
 - Interferon alfacon-1 therapy has not been prescribed as a maintenance dose for HCV AND
 - HCV infection has been confirmed by the detection of serologic markers.

Length of approval: 6 months for hepatitis C, initial therapy
 Remainder of 24 months for hepatitis C, for continuing a course of therapy
 12 months for all other indications

Infergen will be approved for RENEWAL of therapy if ONE of the following criteria is met:

- Patient is using Infergen for a non-hepatitis C indication
- OR**
- Patient has a diagnosis of hepatitis C AND ALL of the following:
 - Patient had met the criteria for initial therapy above AND
 - Interferon alfacon-1 therapy has not been prescribed as a maintenance dose for HCV AND
 - HCV RNA level at or before six (6) months (24 weeks) of therapy became negative or decreased by at least 2-log₁₀ units (e.g., from 2,000,000 IU to 20,000 IU or less).

Length of approval: for the remainder of 24 months total therapy for hepatitis C
 12 months for all other indications

PRIOR AUTHORIZATION FOR APPROVAL

The PA criteria for the IFN alfacon-1 will approve an initial 6 months of therapy if testing confirms HCV infection. IFN alfacon-1 therapy will be approved beyond the initial 6 months only if a second serum HCV RNA level shows a 2-log drop. To accommodate this extended length of therapy and to allow for possible disruptions in therapy, the PA process will allow for up to 24 months of therapy for a diagnosis of HCV. The value of continuation of therapy beyond 24 months is currently unproven and considered investigational or experimental.

The decision to treat members who have had previous IFN alfa therapy will be referred to the health plan for determination of coverage. Until recommendations can be made on retreatment of relapsing patients and non-responders to IFN or PEG IFN therapy, the decision to retreat or continue therapy beyond the initial treatment course will be referred to the health plan for determination of coverage.

IFN alfacon-1 therapy is not FDA-approved for any other indication but will be covered for other non-hepatitis C indications.

Infergen

Initial Evaluation

1. Has the patient been previously approved for Infergen through the Prime Therapeutics prior authorization approval process?
If yes, see renewal criteria. If no, continue to 2.
2. What is the diagnosis?
 - a. Acute or chronic hepatitis C (HCV) infection
 - b. OtherIf a, continue to 3. If b, approve for 12 months.
3. Has the patient previously received a course of interferon (including consensus interferon or interferon alfacon-1) or peginterferon therapy?
If yes, deny. If no, continue to 4.
4. Has the diagnosis of HCV been confirmed by detection of serologic markers for the infection?
If yes, continue to 5. If no, deny.
5. Has Infergen been prescribed as a maintenance dose for HCV?
If yes, deny. If no, continue to 6.
6. Is Infergen being continued to finish a treatment course (member is currently receiving Infergen)?
If yes, approve for remainder of course, up to 24 months. If no, approve for 6 months.

Renewal Evaluation

1. Has the patient been previously approved for Infergen through the Prime Therapeutics prior authorization approval process?
If yes, continue to 2. If no, see initial criteria.
2. What is the diagnosis?
 - a. Acute or chronic hepatitis C (HCV) infection
 - b. OtherIf a, continue to 3. If b, approve for 12 months.
3. Has the HCV RNA level at or before 6 months (24 weeks) of therapy become negative or decreased by at least two log₁₀ units (such as from 2 million IU to 20,000 IU or less)?
If yes, continue to 4. If no, deny.
4. Has Infergen been prescribed as a maintenance dose for HCV?
If yes, deny. If no, approve for the remainder of 24 months.

RATIONALE FOR PRIOR AUTHORIZATION

The intent of the Infergen Prior Authorization (PA) criteria is to ensure that patients with hepatitis C are appropriately selected and treated for an appropriate duration of therapy according to parameters defined in product labeling and/or clinical evidence and/or guidelines. In current FDA-approved labeling, Infergen is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease that have anti-HCV serum antibodies and/or the presence of HCV RNA. Infergen may be approved for other indications also.

Guidelines

According to FDA-approved labeling and published guidelines, patients who react positively to enzyme immunoassay for antibody to HCV or HCV RNA, and have compensated liver disease are potential candidates for peginterferon (PEG IFN) or interferon (IFN) alfacon-1 therapy.¹⁻⁵ Antiviral therapy is not recommended routinely for patients with decompensated liver disease, patients with a history of severe, uncontrolled psychiatric disorder, or patients with severe hematologic cytopenia.⁴

Standard outcome measures include:³⁻⁵

- Sustained Virologic Response (SVR), which is defined as the absence of detectable qualitative HCV RNA in the serum by reverse transcriptase PCR 24 weeks after the end of treatment, is currently the best indicator of effective therapy. While there is little correlation between disease severity or progression with the absolute titer of HCV RNA, quantitative determination of the HCV titer provides important information in assessing response to treatment.³⁻⁵
- Sustained Alanine Transaminase (ALT), which is defined as the normalization of ALT in the serum during treatment and maintenance of normal ALT for 6 months after the end of treatment. Although loss or reduction in HCV RNA is the primary indicator of response to antiviral therapy, the resolution of elevated ALT levels with antiviral therapy appears to be an important indicator of disease response.³⁻⁵

The American Association for the Study of Liver Diseases (AASLD) (endorsed by the AASLD, the Infectious Diseases Society of America, and the American College of Gastroenterology and the American Gastroenterological Association) has made the following recommendations:⁵

- The optimal treatment for chronic hepatitis C (CHC) is PEG IFN plus ribavirin (RBV). Guidelines do not prefer one PEG IFN product over the other. This recommendation is based on the results of 3 pivotal, randomized, clinical trials that demonstrated the superiority of this combination treatment over standard IFN alfa and RBV.⁶⁻⁸ In general, duration of therapy is recommended as follows:
 - Genotype 1, 4, 6: treat for 48 weeks
 - Genotype 2 and 3: 24 weeks
 - Genotype 5: not enough data to make a recommendation for duration of therapy⁵
- Retreatment of persons who failed to respond to previous treatment may be recommended. Approximately 20-50% of patients treated with PEG IFN and RBV will not achieve an SVR. Retreatment with PEG IFN + RBV in patients who did not achieve an SVR after a prior full course of PEG IFN + RBV is not recommended, even if a different type of PEG IFN is administered. Retreatment with PEG IFN + RBV can be considered for non-responders or relapsers who have previously been treated with non-PEG IFN with or without RBV, or with PEG IFN monotherapy, particularly if they have bridging fibrosis or cirrhosis. Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of PEG IFN and RBV.⁵
- For acute hepatitis C, guidelines recommend consideration of an IFN-based anti-viral therapy. Treatment can be delayed for 8-12 weeks after acute onset hepatitis to allow for spontaneous resolution. Clinicians should consider the use of PEG IFN over standard IFN because of its greater ease of administration. Treatment should be for at least 12 weeks, and 24 weeks of therapy may be considered. No recommendation can be made for or against the addition of RBV and the decision will therefore need to be considered on a case-by-case basis.⁵

The American Gastroenterological Association (AGA) statement on management of hepatitis C supports the recommendations of the AASLD stated above.⁴ It states that knowledge of the severity of the underlying liver disease is important in recommending re-treatment. Patients with advanced fibrosis or cirrhosis have

an increased risk of hepatic decompensation and should be considered for re-treatment, especially if they were originally treated with IFN monotherapy.⁷ Expectations for responsiveness to re-treatment are lower in patients with genotype 1, cirrhosis, high baseline HCV RNA levels, and black ethnicity.⁴

Patients who achieve undetectable HCV RNA during and at the end of therapy but relapse are likely to respond and relapse again with subsequent treatment with the same therapy.⁴ There are currently several trials in progress evaluating the long-term effect of low-dose PEG IFN for patients with chronic HCV and advanced fibrosis. The results of these trials will determine future recommendations for chronic maintenance therapy in those patients with advanced fibrosis who fail to achieve a sustained virologic response.⁴

The NIH 2002 hepatitis C consensus conference statement³ also recommends combination therapy, stating that combination therapy results in better treatment responses than monotherapy. The highest response rates have been achieved with PEG IFN in combination with RBV. Three large trials have shown that overall PEG IFN plus RBV was more effective than standard IFN-RBV combination or PEG IFN alone. SVR rates were similar with both forms of PEG IFN (alfa-2a and alfa-2b) when used in combination with RBV. On duration of therapy, the guidelines state "... 24 weeks of treatment and an 800 mg dose of RBV [with PEG IFN] appears to be sufficient for persons with genotypes 2 and 3, while patients with genotype 1 need 48 weeks of treatment and standard doses of RBV [with PEG IFN]." The guidelines also add, "Among patients with genotypes 2 or 3, SVRs with standard IFN and RBV were comparable to those with PEG IFN and RBV, and thus standard IFN and RBV could be used in treating patients with these genotypes."³

Guidelines from the National Institute for Clinical Excellence (NICE -UK)⁹ and recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office: Management and treatment of hepatitis C virus infection in HIV-Infected adults.¹⁰ also recommend combination therapy with a PEG IFN product and RBV.

Laboratory Testing, Duration of Therapy, Retreatment

Current treatment guidelines³⁻⁵ recommend a quantitative serum HCV RNA be performed at the initiation of or shortly before, treatment and also at week 12 of therapy. Persons who achieve a SVR almost always have a dramatic earlier reduction in the HCV RNA level defined often as a 2-log drop or loss of HCV RNA 12 weeks into therapy.^{4,5} In the absence of this type of response, the likelihood of an SVR is 0-3%.

Proper duration of treatment is 12 continuous months for infection with HCV genotype 1, 4, 5, or 6 if there is a response to therapy at 12 weeks and six continuous months for genotype 2 and 3 which may be extended to 12 continuous months if there is evidence of cirrhosis, high viral load, or delayed response (response at 24 weeks versus 12 weeks).^{3,5} There is evidence that patient's considered slow responders (positive HCV RNA after 12 weeks of treatment but HCV RNA negative after 24 weeks) may benefit from a 72 week course of therapy.^{11,12}

Infergen Efficacy

Infergen - IFN alfacon-1 or consensus IFN - is a recombinant non-naturally occurring type-1 IFN. The 166-amino acid sequence of IFN alfacon-1 was derived by scanning the sequences of several natural IFN alpha subtypes and assigning the most frequently observed amino acid in each corresponding position. Four additional amino acid changes were made to facilitate the molecular construction, and a corresponding synthetic DNA sequence was constructed using chemical synthesis methodology. IFN alfacon-1 differs from IFN alfa-2b at 20 of 166 amino acids.^{1,2} [See also Chapter 1.10D Antivirals Hepatitis C Agents²]

Randomized controlled trials comparing IFN alfacon-1 to IFN alpha-2a and 2b have demonstrated similar reductions in ALT and HCV RNA.¹³ An open-label, randomized, controlled clinical trial in patients with chronic hepatitis C compared the efficacy of IFN alfacon-1/RBV to INF-alfa-2b/ribavirin in achieving SVR at week 72 (24 weeks post-treatment).¹⁴ There was no statistical significance between the two groups, but there was a trend towards more SVR in the IFN alfacon-1/ribavirin group. At week 72, 36 patients (57%) in the INF alfacon-1/RBV treated patients had undetectable serum HCV RNA levels, compared to 26 (40%) patients in the IFN alfa-2b/RBV (p=0.052).

IFN alfacon-1 has been studied in patients who relapsed after IFN therapy. In general, retreatment of non-responders with conventional IFN alpha and RBV leads to a low SVR of about 7%. Treatment with PEG IFN

alpha + RBV is similar.¹⁵ A study assessed the efficacy of IFN alfacon-1 daily dosing and induction therapy followed by RBV combination treatment in combination therapy non-responders (n=182).¹⁵ The SVR was 38-45% in conventional IFN/RBV non-responders (n=121) and 27-31% (n=61) in PEG-IFN/RBV non-responders. The authors conclude that IFN alfacon-1 may be an effective treatment modality for this patient population.¹⁵

A study of daily administration of IFN alfacon-1 + RBV resulted in a 21% and 35% SVR in patients who were non-responders to PEG IFN alfa-2b and PEG IFN alfa-2a, respectively. Daily IFN alfacon-1 and RBV therapy also induced a higher SVR than PEG alfa-2a in patients who had relapsed after PEG IFN therapy (69% vs 44%).^{16,17}

A earlier randomized study compared the effect of IFN alfacon-1 and IFN-alpha 2b + RBV in patient relapsing after treatment with IFN-alpha 2b alone.¹⁸ The following results were seen:

- Group A: IFN-alpha 2b + RBV (n=34) – The end of treatment response (24 weeks) clearance of HCV-RNA was seen in 23 patients (68%); SVR (48 weeks) was 29% (10/34)
- Group B: IFN alfacon-1 (n=40) – The end of treatment response (24 weeks) clearance of HCV-RNA was seen in 33 patients (82%); SVR (48 weeks) was 58% (23/40) (p<0.03 when compared to SVR of group A)

An additional randomized study (n=45) evaluated the effect of IFN alfacon-1 + RBV in retreating CHC patients who relapsed after conventional IFN monotherapy.¹⁹ Intention to treat analysis showed a SVR was obtained in only 26.7% of all patients, with no effect in favor of higher doses. One-third of the patients discontinued their regimen due to adverse reactions.

FDA APPROVED INDICATIONS

Infergen¹

Infergen (interferon alfacon-1), is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients 18 years of age or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA. Other causes of hepatitis, such as viral hepatitis B or autoimmune hepatitis should be ruled out prior to initiation of therapy with Infergen. In some patients with chronic HCV infection, Infergen normalizes serum ALT, reduces serum HCV RNA concentrations to undetectable quantities (<100 copies/mL), and improves liver histology.

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Document History

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