

PRIOR AUTHORIZATION POLICY

- POLICY:** Pegylated Interferons
- Pegasys® (peginterferon alfa-2a injection for subcutaneous use – Hoffman-La Roche/Genentech)
 - PegIntron® (peginterferon alfa-2b injection for subcutaneous use – Schering)

TAC APPROVAL DATE: 08/15/2018

OVERVIEW

Pegasys and PegIntron are pegylated interferons (peginterferons) indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and children.¹⁻² The standard of care in hepatitis C is rapidly evolving and the place in therapy for peginterferon very small. The approval of direct-acting antiviral agents (DAAs) has eliminated the need for peginterferon in the majority of patients. Because none of the DAAs are indicated in pediatric patients, peginterferons still have a role in the treatment of pediatric patients with HCV. In the past, the standard of care for patients with HCV consisted of peginterferon and ribavirin (PR) generally administered for 24 to 48 weeks depending on patient factors and genotype.

Clinical Efficacy Data

The clinical efficacy of peginterferon (in combination with ribavirin) has been demonstrated in a variety of clinical settings: treatment-naïve patients, patients previously treated with peginterferon or interferon for hepatitis C, pediatric patients with hepatitis C, and in other special populations including patients with human immunodeficiency virus (HIV) co-infection, cirrhosis/fibrosis, and in patients slow to respond to therapy. In addition, the peginterferons have also been studied in combination with the DAAs (these studies are detailed in the [Hepatitis C Direct-Acting Antiviral Therapy Class Summary](#)).

None of the DAAs are indicated in pediatric patients < 18 years of age. Pegasys (alone or in combination with ribavirin) and PegIntron (in combination with ribavirin) are indicated for the treatment of chronic HCV in patients ≥ 5 years and ≥ 3 years of age, respectively with compensated liver disease previously untreated with interferon alfa.¹⁻² Limited data are available for retreatment in children.

Guidelines

For a summary of American Association for the Study of Liver Diseases (AASLD) guidelines please see [Hepatitis C Direct-Acting Antiviral Therapy Class Summary](#). In summary, peginterferons are no longer recommended.³

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) practice guidelines for the diagnosis and management of hepatitis C infection in infants, children and adolescents (2012) recommend that children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (i.e., liver fibrosis) should be considered for treatment.⁴ The NASPGHAN guidelines state that the recommended therapy for children ages 3 to 17 years of age is with PR. The recommended length of therapy is 48 weeks for children with genotype 1 or 4 CHC and 24 weeks for genotype 2 or 3 CHC.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Pegasys and PegIntron (collectively referred to as “peginterferons” in these criteria) for HCV infection. The intent of this policy

is to provide recommendations for use in hepatitis C *only*. Because of the specialized skills required for evaluation and diagnosis of patients treated with the peginterferons as well as the monitoring required for adverse events (AEs) and efficacy, approval requires peginterferons to be prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pegasys and PegIntron (“peginterferon[s]”) is recommended in patients who meet one of the criteria below (1 through 6).

FDA-Approved Indications

- 1. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6.** Approve peginterferon for up to 48 weeks in patients who meet ALL of the following criteria (A, B, and C):
 - A) The patient is ≥ 2 years of age; AND
 - B) Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician; AND
 - C) Peginterferon is prescribed in combination with ribavirin.

Pegasys and PegIntron are indicated in for the treatment of chronic hepatitis C virus (HCV) in adult and pediatric patients.¹⁻² However, dual therapy has been superseded by use of direct acting antivirals (DAAs) in adults.³ Up to 48 weeks of peginterferon and ribavirin (PR) therapy may be required in patients with genotype 1 using a protease inhibitor or PR therapy alone. Pegasys is also indicated as monotherapy or in combination with ribavirin for 48 weeks (regardless of HCV genotype) for patients co-infected with human immunodeficiency virus (HIV) and HCV.¹

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN, 2012) recommends PR treatment in children and adolescents with chronic HCV.⁴ The recommended duration of therapy in pediatric patients with genotype 1 or 4 chronic HCV is 48 weeks. Note: the American Association for the Study of Liver Diseases (AASLD) 2016 guidance does not address treatment of children. None of the oral DAAs are indicated in children; therefore, the pegylated interferons remain the recommended treatment for pediatric patients.

In the opinion of specialist physicians reviewing the data, we have adopted these criteria.

Other Uses with Supportive Evidence (in the Treatment of Hepatitis C)

2. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Pediatric and Adolescent (≥ 2 years and ≤ 17 years of age).** Approve peginterferon for 48 weeks in patients who meet ALL of the following criteria (A, B, and C):
 - A) The patient is ≥ 2 years of age and < 17 years of age; AND
 - B) Peginterferon is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician; AND
 - C) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician.

In children and adolescents, NASPGHAN recognizes that although rare in children, pediatric liver transplant recipients for end-stage liver disease (ESLD) due to chronic HCV demonstrate allograft survival rates of 72% and 55%, respectively, at 5 years.⁴ Following re-transplantation, these rates decrease to 55% and 34%, respectively. The risk of HCV recurrence in pediatric orthotopic liver transplant recipients is high and is associated with a high rate of re-transplantation. If a decision is made to treat pediatric liver transplant recipients, very close monitoring is warranted.

In the opinion of specialist physicians reviewing the data, we have adopted these criteria.

3. **Chronic Hepatitis C Virus (HCV) – Awaiting Liver Transplantation, Any Viral Genotype - Pediatric and Adolescents (≥ 2 years and ≤ 17 years of age).** Approve peginterferon for 12 months in patients who meet ALL of the following criteria (A, B, and C).
 - A) The patient is ≥ 2 years of age and ≤ 17 years of age; AND
 - B) Peginterferon is prescribed by or in consultation with one of the following prescribers who is affiliated with a liver transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician; AND
 - C) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician.

Regimens containing DAAs are recommended in adults awaiting liver transplant; DAAs are not indicated in pediatric patients.

In the opinion of specialist physicians reviewing the data, we have adopted these criteria. Peginterferon may continue to have a very limited role in patients awaiting liver transplant in the era of DAAs.

4. **Patient has Been Started on Pegasys.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 12 months.
5. **Patient has Been Started on PegIntron.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 12 months.

- 6. Indications other than Hepatitis C.** Approve for 12 months. Pegasys and PegIntron have been used for many off-label indications in adults and for few indications in children.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

The peginterferons have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Hepatitis C Virus (HCV), Maintenance Therapy.** Evidence does not support use. Major published trials have failed to demonstrate a consistent benefit of maintenance therapy in the prevention of hepatocellular carcinoma (HCC).³⁻⁷

In the opinion of a specialist physician reviewing the data, we have adopted this criterion.

- 2. Life Expectancy < 12 Months Due to Non-Liver Related Co-Morbidities.** Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.³ Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

REFERENCES

1. Pegasys® injection [package insert]. Nutley, NJ: Hoffman-La Roche Pharmaceuticals; October 2017.
2. PegIntron® powder for injection [package insert]. Kenilworth, NJ: Schering Corporation; May 2018.
3. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Updated May 24, 2018. Available at: <http://www.hcvguidelines.org>. Accessed on: August 8, 2018.
4. Mack CL, Gonzalez-Peralta RP, Gupta N, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Practice Guidelines: Diagnosis and Management of Hepatitis C Infection in Infants, Children and Adolescents. *J Pediatr Gastroenterol Nutr.* 2012;54(6):838-55.
5. Sherman KE, Anderson JW, Butt A, et al for the AIDS Clinical Trials Group A5178 Study Team. Sustained long-term antiviral maintenance therapy in HCV/HIV co-infected patients (SLAM-C). *J Acquir Immune Defic Syndr.* 2010;55(5):597-605
6. Lok AS, Everhart JE, Wright EC, et al; HALT-C Trial Group. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology.* 2011;140(3):840-849.
7. Di Bisceglie AM, Stoddard AM, Dienstag JL, et al; and The HALT-C Trial group. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. *Hepatology.* 2011;53(4):1100-1108.

History

Type of Revision	Summary of Changes*	TAC Approval Date
Integrated Policy	--	06/12/2012
Selected Revision	--	08/29/2012
Annual Revision	--	06/05/2013
Annual Revision	<p>1. Genotype 1,4,5,6: Reference to “treatment-naïve” was removed; the “note” that a Week 12 titer is needed to determine therapy beyond 48 weeks was removed; a liver transplant physician was added to the list of prescribers.</p> <p>2. Genotype 2, 3: Reference to “treatment-naïve” was removed; a liver transplant physician was added to the list of prescribers; a 48-week approval was removed for patients with HBV co-infection, HIV co-infection, and genotype 3 with high viral load or fibrosis/cirrhosis.</p> <p>3. Retreatment: This indication was removed and these patients are encompassed in criteria based on genotype (note: patients with genotype 2, 3 no longer are approved for 48 weeks for re-treatment).</p> <p>4. Extending therapy for 72 weeks (Genotype 1, 4, 5, 6): This indication was removed.</p> <p>Acute Hepatitis C: A liver transplant physician was added to the list of prescribers.</p> <p>5. Recurrent HCV: “or in consultation with one of the following prescribers who is affiliated with a transplant center” was added; the requirement for patients to have grade 2 fibrosis or greater was removed.</p> <p>6. Patients awaiting liver transplant: “or in consultation with one of the following prescribers who is affiliated with a transplant center” was added.</p> <p>7. Patients already started on Pegasys or PegIntron. The authorization was changed not to exceed 48 weeks (previously 72 weeks).</p>	06/25/2014
Selected revision	<p>Limitations on who to treat were added to the following approval indications: Genotype 1, 2, 3, 4, 5, and 6 CHC adults. Criteria for children 2 through 17 years of age are addressed separately.</p> <p>Exclusion criteria were added for patients with life expectancy < 12 months due to a non-liver related cause.</p>	09/10/2014
Annual revision	<p>1. Chronic Hepatitis C (CHC) Genotype 1, 4, 5, or 6 Chronic Hepatitis C (CHC) – Adults (≥ 18 years of age).</p> <p>-Patients with genotype 1 CHC taking pegylated interferon in combination with Olysio: The approval duration is 48 weeks for prior null or partial responders and 24 weeks for treatment-naïve or relapse patients.</p> <p>-Patients with genotype 1, 4, 5, or 6 CHC taking pegylated interferon in combination with Sovaldi. The approval duration is 12 weeks.</p> <p>-The exception to using ribavirin in combination with pegylated interferon in patients with a contraindication or intolerance to ribavirin according to the prescribing physician was removed from the criteria.</p> <p>2. CHC Genotype 2 or 3 – Adults (≥ 18 years of age). The approval duration was changed to 12 weeks. A requirement was added that patients take pegylated interferon with Sovaldi and ribavirin (previously ribavirin only), and criteria allowing exceptions for using ribavirin were removed.</p> <p>3. Acute Hepatitis C (i.e., Infection within 6 Months of Exposure). The timeframe patients must wait prior to treatment to allow for spontaneous resolution was changed to 12 weeks (previously 8</p>	07/15/2015

	<p>weeks).</p> <p>4. Recurrent HCV Post-Liver Transplantation, Any Viral Genotype. This indication was changed to “Recurrent HCV Post-Liver Transplantation”, “any viral genotype” was removed. For patients ≥ 18 years of age, this indication is only approved for genotypes 5 and 6 (previously all genotypes were approved). For patients ≥ 2 years of age and ≤ 17 years of age, any viral genotype continues to be approved.</p> <p>5. CHC – Awaiting Liver Transplantation, Any Viral Genotype. This indication was modified to “CHC – Awaiting Liver Transplantation, Any Viral Genotype - Pediatric and Adolescents (≥ 2 years and ≤ 17 years of age)”. The criterion for age was changed to only approve in patients ≥ 2 years and ≤ 17 years of age.</p>	
Annual revision	<p><u>Genotype 1, 4, 5, or 6 chronic HCV, adults:</u></p> <ul style="list-style-type: none"> -Added genotype 2 or 3 chronic HCV to this indication (previously, this was a separate indication). -Approval duration changed from 12 to 48 weeks to up to 48 weeks. -Age requirement changed from ≥ 18 years to ≥ 2 years of age. -Requirement for Metavir score F3/F4 or exceptions to Metavir score removed. -Requirement for concomitant therapy (Olysio or Sovaldi) removed from the policy. <p><u>Genotype 1, 4, 5, or 6 chronic HCV, pediatric and adolescent:</u></p> <ul style="list-style-type: none"> -This indication was combined with the prior adult indication (as detailed above). <p><u>Genotype 2 or 3 chronic HCV, adults:</u></p> <ul style="list-style-type: none"> -<u>This indication was combined with genotype 1, 4, 5, and 6 chronic HCV (see above).</u> -Approval duration changed from 12 weeks to up to 48 weeks. -Age requirement changed from ≥ 18 years to ≥ 2 years of age. -Requirement for Metavir score F3/F4 or exceptions to Metavir score removed. <p>Genotype 2 or 3 chronic HCV, pediatric and adolescent:</p> <ul style="list-style-type: none"> -<u>This indication was combined with genotype 1, 4, 5, and 6 chronic HCV (see above).</u> -Approval duration changed from 24 or 48 weeks to up to 48 weeks. <p><u>Acute Hepatitis C:</u></p> <ul style="list-style-type: none"> - This indication was removed from the policy. 	08/10/2016
Annual Revision	No criteria changes	08/16/2017
Annual Revision	Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation: Criteria to approve in adults with genotypes 5 and 6 were removed.	08/15/2018

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; HIV – Human immunodeficiency virus; HBV – Hepatitis B virus; HCV – Hepatitis C virus.