Clinical Policy: Peginterferon Alfa-2a,b (Pegasys, PegIntron, Sylatron)

Reference Number: ERX.SPA.200
Effective Date: 01.11.17
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Peginterferon alfa-2a (Pegasys®) is a covalent conjugate of recombinant alfa-2a interferon. Peginterferon alfa-2b (PegIntron®, Sylatron™) is an alpha interferon.

FDA Approved Indication(s)
Pegasys is indicated for the treatment of:
- Chronic hepatitis C (CHC) as part of a combination regimen with other hepatitis C virus (HCV) antiviral drugs in adult patients with compensated liver disease
- CHC as monotherapy in adult patient that have contraindication to or significant intolerance to other HCV antiviral drugs
- CHC in combination with ribavirin in pediatric patients 5 years of age and older with compensated liver disease
- Adult patients with HBeAg positive and HBeAg negative chronic hepatitis B (CHB) infection who have compensated liver disease and evidence of viral replication and liver inflammation
- HBeAg-positive CHB in non-cirrhotic pediatric patients 3 years of age and older with evidence of viral replication and elevations in serum alanine aminotransferase (ALT)

PegIntron is indicated for treatment of CHC infection in patients with compensated liver disease.

Sylatron is indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.

Limitation(s) of use:
- Pegasys alone or in combination with ribavirin without additional HCV antiviral drugs is not recommended for treatment of patients with CHC who previously failed therapy with an interferon-alfa
- Pegasys is not recommended for treatment of patients with CHC who have had solid organ transplantation

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Pegasys, PegIntron, and Sylatron are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all)**:**

1. Diagnosis of melanoma;
2. Request is for Sylatron;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Request meets one of the following (a or b):*

a. Dose does not exceed initial dose of 6 mcg/kg per week for 8 weeks, then 3 mcg/kg per week;
b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 6 months

B. NCCN-Recommended Off-Label Uses (off-label) (must meet all)**:**

1. Diagnosis of one of the following (a, b, c, or d, e, f, g, h, i, j, or k):
   a. Myelofibrosis, low risk and symptomatic;
   b. Polycythemia vera;
   c. Essential thrombocythemia;
   d. Systemic mastocytosis with associated hematologic malignancy;
   e. Aggressive systemic mastocytosis;
   f. Hairy cell leukemia;
   g. Erdheim-Chester disease;
   h. Osteopenia or osteoporosis with refractory bone pain and/or decreasing bone mineral density on bisphosphonate therapy;
   i. Primary cutaneous CD30+ T-cell lymphoproliferative disorder as substitution for other interferon preparations;
   j. Adult T-cell leukemia or lymphoma as substitution for other interferon preparations;
   k. Mycosis fungoides or Sézary syndrome as substitution for other interferon preparations;
2. Prescribed by or in consultation with an oncologist;
3. For polycythemia vera, inadequate response or loss of response to hydroxyurea or to interferon therapy if peginterferon alfa-2b or peginterferon alfa-2a naive;
4. For essential thrombocythemia, inadequate response or loss of response to hydroxyurea, anagrelide, or interferon therapy if peginterferon alfa-2b or peginterferon alfa-2a naive;
5. For hairy cell leukemia, used as a single agent following following initial treatment with cladribine or pentostatin;
6. For Erdheim-Chester disease, used as a single agent for disease that is both symptomatic and relapsed/refractory;
7. Member meets one of the following (a, b, or c):
   a. For Sylatron: Age ≥ 18 years;
   b. For PegIntron: Age ≥ 3 years;
   c. For Pegasys: Age ≥ 5 years;
8. Request meets one of the following (a or b):*
   a. Dose does not exceed (i, ii, or iii):
      i. For Sylatron: 6 mcg/kg per week;
      ii. For PegIntron: 1.5 mcg/kg per week;
      iii. For Pegasys: 3 mcg/kg per week;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 6 months

C. Chronic Hepatitis C

1. Interferon-based treatment regimens are no longer recommended by the 2019 American Association for the Study of Liver Diseases/Infectious Disease Society of America (AASLD-IDSA) HCV guidance due to the advent of safe and effective direct acting antivirals.

Approval duration: Not applicable

D. Chronic Hepatitis B Infection (must meet all)**:**

1. Diagnosis of chronic hepatitis B virus infection;
2. Prescribed by or in consultation with gastroenterologist, hepatologist, or infectious disease specialist;
3. Request is for Pegasys;

4. Member meets ONE of the following (a, b, or c):
   a. Two elevated ALT lab values within the past 12 months (≥ 70 IU/L for men, ≥ 50 IU/L for women) and HBV DNA levels ≥ 20,000 IU/mL in HBeAg positive patients or > 2,000 IU/mL in HBeAg negative patients;
   b. Diagnosis of cirrhosis, HBV DNA level > 2,000 IU/mL, and age ≥ 18 years;
   c. Liver biopsy shows moderate/severe necroinflammation (Grade 9-18) or significant fibrosis (Stage 3-4);
5. Age ≥ 3 years;
6. If age ≤ 17 years, member does not have cirrhosis;
7. Dose does not exceed 180 mcg per week for adults and 180 mcg/1.73 m^2 x BSA per week for pediatric patients.

Approval duration: 48 weeks

E. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I except CHC (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Pegasys, PegIntron, or Sylatron for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed (i, ii, or iii):
      i. PegIntron: 1.5 mcg/kg per week;
      ii. Sylatron: 6 mcg/kg per week for 8 weeks, then 3 mcg/kg per week;
      iii. Pegasys: 180 mcg per week for adults and 180 mcg/1.73 m^2 x BSA per week for pediatric patients;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 12 months (up to 5 years total for melanoma; up to a total of 48 weeks for HBV)

B. Chronic Hepatitis C
1. Interferon-based treatment regimens are no longer recommended by the 2019 AASLD-IDSA HCV guidance due to the advent of safe and effective direct acting antivirals.

Approval duration: Not applicable

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;
B. Treatment of CHC;
C. Pegasys: Uncontrolled autoimmune hepatitis;
D. Pegasys: Following heart, lung or kidney transplants;
E. Pegasys: Members with previous history of drug or alcohol abuse who have not abstained for at least 3 months before starting therapy;

F. Pegasys: To solely reduce the risk of developing hepatocellular carcinoma (HCC) in members with cirrhosis.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AASLD/IDSA: American Association for the Study of Liver Diseases/Infectious Disease Society of America
CHB: chronic hepatitis B
CHC: chronic hepatitis C
FDA: Food and Drug Administration
HBeAg: hepatitis B e-antigen
HCV: hepatitis C virus

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Pegasys, Pegintron, and Sylatron: autoimmune hepatitis; hepatic decompensation (Child-Pugh score > 6 [class B and C]); hypersensitivity
  - Pegasys: neonates/infants
- Boxed warning(s): risk of serious disorders (may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders)

Appendix D: General Information

- Per NCCN Drugs and Biologics Compendium, pegylated interferons have a category 2A rating for treatment of Erdheim-Chester disease, hairy cell leukemia, myelofibrosis, polycythemia vera, essential thrombocythemia, and systemic mastocytosis.
- Patients who develop anemia may be treated with epoetin to ensure that 80% of the original ribavirin dose is maintained throughout the course of therapy.
- According to the American Association for the Study of Liver Diseases (AASLD) the upper limit of normal for serum ALT concentrations for men and women are 35 IU/L and 25 IU/L, respectively.
- Grading and staging a liver biopsy for chronic hepatitis patients are as follows:
  - The grade is given a number based on the amount of inflammation (Knodell Scoring System).
    0 = no inflammation
    1-4 = minimal inflammation
    5-8 = mild inflammation
    9-12 = moderate inflammation
    13-18 = marked inflammation
  - The stage is scored based on the amount of fibrosis or scarring (Metavir Scoring System).
    0 = no scarring
    1 = minimal scarring
    2 = scarring has occurred and is outside the areas of the liver which include blood vessels
    3 = bridging fibrosis
    4 = cirrhosis or advanced scarring of the liver
- The 2018 AASLD/IDSA Hepatitis C treatment guidelines do not recommend treatment of CHC with PEG-interferon as this treatment has been superseded by treatments incorporating direct-acting antiviral agents and should not be used.
- 2018 AASLD technical remarks on peginterferon: contraindicated in persons with autoimmune disease, uncontrolled psychiatric disease, cytopenia, severe cardiac disease, uncontrolled seizures, and decompensated cirrhosis.
- According to the ASSLD 2018 guidelines: Chronic Hepatitis B (CHB): Subdivided into HBeAg positive and negative. HBV-DNA levels are typically >20,000 IU/mL in HBeAg-positive CHB, and lower values (2,000-20,000 IU/mL) are often seen in HBeAg-negative CHB. CHB therapy is recommended for persons with immune-active CHB and cirrhosis if HBV DNA is >2,000 IU/mL, regardless of ALT level.

V. Dosage and Administration

rug Name	Indication	Dosing Regimen	Maximum Dose
Peginterferon alfa-2b (PegIntron, Sylatron)	Myelofibrosis, polycythemia vera, Essential thrombocytopenia	See NCCN dosing regimen.	N/A
Peginterferon alfa-2b (Sylatron)	Melanoma	6 mcg/kg/week SC for 8 doses, followed by 3 mcg/kg/week SC for up to 5 years	• 6 mcg/kg/week for the first 8 doses • 3 mcg/kg/week for up to 5 years
Peginterferon alfa-2a (Pegasys)	Chronic hepatitis B infection	Adults: 180 mcg SQ per week as monotherapy Pediatrics: 180 mcg/1.73 m^2 x BSA per week as monotherapy	• Adults: 180 mcg per week • Pediatrics: 180 mcg/1.73 m^2 x BSA per week
	Myelofibrosis	Dose varies: 2-3 mcg/kg SQ/week	Treatment continues until no longer clinically beneficial or until unacceptable toxicity occurs
	Polycythemia vera, essential thrombocytopenia	See NCCN dosing regimen.	N/A

VI. Product Availability

Drug Name	Availability
Peginterferon alfa-2a (Pegasys)	• Vials: 180 mcg/mL • Prefilled syringes: 180 mcg/0.5 mL (4 syringes/pack)
Peginterferon alfa-2b (PegIntron)	• Vials (with diluent), Redipen: 50 mcg/0.5 mL, 80 mcg/0.5 mL, 120 mcg/0.5 mL, 150 mcg/0.5 mL
Peginterferon alfa-2b (Sylatron)	Single-use vials: 200 mcg/0.5 mL, 300 mcg/0.5 mL, 600 mcg/0.5 mL

VII. References

1. Sylatron Prescribing Information. Whitehouse Station, NJ: Merck and Co., Inc.; December 2018. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103949s5312lbl.pdf. Accessed May 16, 2021.
2. PegIntron Prescribing Information. Whitehouse Station, NJ: Merck Sharp and Dohme Corp.; January 2019. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103949s5313lbl.pdf. Accessed May 16, 2021.
3. Pegasys Prescribing Information. South San Francisco, CA: Genentech USA, Inc, March 2021. Available at: https://www.gene.com/download/pdf/pegasys_prescribing.pdf. Accessed May 16, 2021.
4. Peginterferon alfa-2a/b. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed May 16, 2021.
5. American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD-IDSA). HCV guidance: recommendations for testing, managing, and treating hepatitis C. Last updated March 12, 2021. Available at: https://www.hcvguidelines.org/. Accessed May 16, 2021.
6. Silver RT, Kiladjian JJ, Hasselbalch HC. Interferon and the treatment of polycythemia vera, essential thrombocythemia and myelofibrosis. Expert Review of Hematology 2013; 6(1):49-58. DOI: 10.1586/ehm.12.69.
7. Terrault NA, Lok ASF, McMahon BJ, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology. 2018; 67 (4):1560-99.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q17 Annual Review Added max dose and age. Updated approval duration from 3/6 to 6/12 months.	10.10.17	11.17
3Q 2018 annual review: summarized NCCN and FDA-approved uses for improved clarity; added separate age requirements for PegIntron and Sylatron; allowed COC; added specialist involvement in care; removed coverage for CHC; removed off-label use for CML; added off-label use for myeloproliferative neoplasms; references reviewed and updated.	05.22.18	08.18
3Q 2019 annual review: added Pegasys to policy; added criteria set for Hepatitis B; added NCCN Compendium supported use in systemic mastocytosis; references reviewed and updated.	05.14.19	08.19
3Q 2020 annual review: added systemic mastocytosis with associated hematologic malignancy, aggressive systemic mastocytosis, osteopenia or osteoporosis with refractory bone pain and/or decreasing bone mineral density on bisphosphonate therapy as per NCCN compendium; specified myelofibrosis as low risk and symptomatic as per NCCN compendium; added specialist involvement for chronic hepatitis B infection; updated chronic hepatitis B criteria to include > 2,000 IU/mL in HBeAg negative patients and HBV DNA level > 2,000 IU/mL; references reviewed and updated.	07.27.20	08.20
Added inadequate response or loss of response to hydroxyurea or interferon therapy if peginterferon alfa-2b or peginterferon alfa-2a naïve for polycythemia vera; added inadequate response or loss of response to hydroxyurea, anagrelide, or interferon therapy if peginterferon alfa-2b or peginterferon alfa-2a naïve for essential thrombocytopenia; added NCCN-recommended (with Category 2A or above) off-label uses: primary cutaneous CD30+ T-cell lymphoproliferative disorder, adult T-cell leukemia or lymphoma; Mycosis fungoides or Sezary syndrome; NCCN references reviewed and updated.	08.24.20	11.20
3Q 2021 annual review: Pegasys autoinjector discontinued and removed from section V; added off-label indications of hairy cell leukemia and Erdheim-Chester disease and corrected essential thrombocytopenia to essential thrombocythemia per NCCN; references reviewed and updated.	05.16.21	08.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.