peginterferon alfa-2a (Pegasys®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO213

Description

Peginterferon alfa-2a (Pegasys) is a subcutaneous pegylated interferon which induces cellular activities related to binding specific cell-surface membrane receptors. These include suppression of cell proliferation, antiviral activity, and immunomodulating effects.

Length of Authorization

- Initial:
  - Chronic Hepatitis B: 48 weeks
  - All other indications: 12 months
- Renewal:
  - i. For Polycythemia Vera AND Essential Thrombocythemia: 12 months
  - ii. For all other indications: None

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Peginterferon Alfa-2a (Pegasys; Pegasys ProClick)	180 µg/mL vial	Chronic Hepatitis B; Chronic Hepatitis D; Polycythemia Vera; Essential Thrombocythemia	4 vials/30 days
	180 µg/0.5 mL prefilled syringe		4 syringes/30 days
	135 µg/0.5 mL autoinjector		4 autoinjectors/30 days
	180 µg/0.5 mL autoinjector		4 autoinjectors/30 days

Initial Evaluation

I. **Peginterferon Alfa-2a (Pegasys)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a gastroenterologist, hepatologist, infectious disease specialist, hematologist, or an oncologist; **AND**
   B. The medication will be used as monotherapy; **AND**
   C. Member has not previously experienced disease progression while on peginterferon Alfa-2a (Pegasys) for the treatment of indications listed in this policy; **AND**
   D. Provider attestation that the member does **not** have any of the following:
      i. Hepatic decompensation (Child-Pugh Score> 6, Class B and C)
      ii. Autoimmune hepatitis

iii. Depression or other neuropsychiatric disorders; **AND**

E. A diagnosis of one of the following:

1. **Chronic Hepatitis B; AND**
   i. Member is 3 to 17 years old; **AND**
      a. Provider attests to **ALL** of the following:
         i. Member is hepatitis B e-antigen (HBeAg) positive; **AND**
         ii. Member is noncirrhotic; **AND**
         iii. Member has elevated serum alanine aminotransferase (ALT) more than twice the upper limit of normal (ULN); **OR**
   ii. Member is 18 years of age or older; **AND**
      a. Documentation of hepatitis B (HBV) viral load less than 12 months old (i.e. serum HBV > 100,000 copies/mL or HBV DNA levels > 2000 IU/mL); **OR**
2. **Chronic Hepatitis D; AND**
   i. Diagnosis of chronic hepatitis D (HDV) confirmed by a quantifiable HDV RNA; **AND**
   ii. Provider attests the member has active liver disease (e.g. elevated serum ALT, or liver biopsy); **OR**
3. **Polycythemia Vera; OR Essential Thrombocythemia; AND**
   i. Member is 18 years of age or older; **AND**
   ii. Provider attests that the member has high-risk disease; **AND**
   iii. Treatment with generic hydroxyurea has been ineffective, contraindicated, or not tolerated

II. Peginterferon Alfa-2a (Pegasys) is considered not medically necessary when used for:

A. Treatment of chronic hepatitis C (HCV)

III. Peginterferon Alfa-2a (Pegasys) is considered investigational when used for all other conditions, including but not limited to:

A. Malignant melanoma
B. Renal cell carcinoma
C. Hairy cell leukemia
D. Myelofibrosis
E. Systemic mastocytosis
F. Chronic myelogenous leukemia (CML)

Renewal Evaluation

I. Member has not been established on therapy by use of free samples, manufacturer coupons or otherwise; **AND**
II. Member has received previous prior authorization for this agent through THIS health plan; **AND**
III. Provider attestation that the member does **not** have any of the following:
    i. Hepatic decompensation (Child-Pugh Score> 6, Class B and C)
    ii. Autoimmune hepatitis
    iii. Depression or other neuropsychiatric disorders; **AND**
IV. Member has diagnosis of **Polycythemia Vera, or Essential Thrombocythemia; AND**
V. Member has experienced response to therapy such as disease stabilization or remission (e.g. complete or partial response)

Supporting Evidence

I. Interferons, a family of naturally occurring small protein molecules or glycoproteins, are produced by cells in response to viral infections or various synthetic or biologic inducers. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. Interferons have been found to mediate antiviral, antiproliferative, and immunomodulatory activities. Peginterferon alfa-2a (Pegasys®) is a covalent conjugate of recombinant alfa-2a interferon. Other types of alfa interferon such as Peginterferon alfa-2b (PegIntron®, Sylatron™) are covered under separate PA policies based on their respective indications.
II. Given the treatment complexities associated with the indications listed in this policy, use of peginterferon alfa-2a (Pegasys) should be prescribed by a specialist practicing in the respective area of specialty.
III. Patients with chronic hepatitis B are at an increased risk to develop cirrhosis, liver failure, and liver cancer. Hepatitis B e-antigen (HBeAg) and Hepatitis B viral DNA (HBV DNA) are both markers of HBV replication and their presence provides a rationale for initiating therapy to stop the progression of liver disease. In the past, the ability to detect HBV DNA in the serum by hybridization assays was a major factor in determining which patients should be treated. This assay is sensitive enough to detect viral DNA when it is present in amounts ≥ 105 copies/ml and consequently this viral level became an important benchmark in treatment algorithms. As improvements in viral detection have advanced it has become apparent that it is not possible to designate a single HBV DNA value that can differentiate between inactive hepatitis B carriers and patients suffering from chronic hepatitis B.
IV. There are several agents currently indicated for treatment of chronic HBV. They include Peg-interferon, lamivudine, telbivudine, entecavir, tenofovir and adefovir. AASLD guidelines recommend peginterferon alfa-2a, entecavir, or tenofovir as preferred initial therapy for adults with immune-active chronic HBV infection. peginterferon alfa-2b is not FDA approved for

chronic hepatitis B; however, there are studies that support its use for this indication. Overall, the quality of evidence is considered low for this setting.

V. Interferon therapy is not recommended in patients with decompensated cirrhosis because it increases their risk for developing bacterial infections and it can potentially worsen their condition.

VI. Peginterferon alfa-2a (Pegasys) was evaluated in multiple phase 3, randomized clinical trials, as monotherapy and in combination with lamivudine, for patients with HBV infection. All subjects were adults with compensated liver disease, had chronic HBV infection and evidence of HBV replication (serum HBV greater than 500,000 copies/mL for HBeAg-positive patients and greater than 100,000 copies/mL for HBeAg-negative patients). All subjects had serum ALT between 1 and 10 times the upper limit of normal (ULN). Treatment with peginterferon alfa-2a (Pegasys) exhibited significant serological, virological, and histological responses at the treatment interval of 24 weeks. Co-administration of lamivudine with Pegasys did not result in additional sustained response as compared to Pegasys monotherapy.

VII. In the setting of chronic hepatitis C (HCV), the sustained virological response (SVR) is defined as undetectable HCV RNA in 12 weeks (SVR 12) or 24 weeks (SVR 24) after treatment completion. Cure rate, which achieves SVR, is more than 99%. SVR is generally associated with resolution of liver disease in patient without cirrhosis, but in the patient with cirrhosis there remains risk of life-threatening complications.

VIII. Ppeginterferon alfa-2a (Pegasys) has been studied as monotherapy and in combination with ribavirin in seven randomized, active-controlled clinical trials. Pooled population analysis showed the participants in these trials had HCV genotype 1 through 6, were of ages 5 years and above, and had detectable viral load at treatment initiation. Therapeutic responses were observed at median 12 weeks of treatment and durability of response sustained up to the 48-week trial window. Recommended total duration of therapy for peginterferon alfa-2a (Pegasys) is up to 48 weeks (per FDA-approval).

IX. The only guideline recommended treatment of chronic hepatitis D is interferon alfa (IFN-a). Peginterferon alfa is the drug of choice without clear differences in efficacy between peginterferon alfa-2a (Pegasys) or peginterferon alfa-2b (Pegintron). Treatment success, defined as undetectable HDV RNA at 24 weeks after completing treatment, ranges from 23% to 57%. Late relapses can occur with longer follow-up, leading to very low rates of sustained HDV-RNA undetectability. In the multicenter HIDIT-1 (Hep-Net-International-Delta-Hepatitis-Intervention-Study 1) study of peginterferon alfa-2a (Pegasys) for 48 weeks with or without adefovir, 40% of patients achieved an undetectable HDV-RNA level 24 weeks after completing therapy, but at a mean follow-up 4.3 years later, only 12% remained undetectable.

X. Although not FDA-approved, use of peginterferon alfa-2a (Pegasys) is supported by NCCN guidelines (category 2A recommendation) for the treatment of essential thrombocythemia (ET) and polycythemia vera (PV). PV and ET are BCR-ABL1–negative myeloproliferative neoplasms. Both diseases are characterized by a clonal myeloid proliferation with excessive production of blood elements. The hallmarks of ET and PV include an increased risk of thrombohemorrhagic complications, and a variable risk of transformation to myelofibrosis (MF) and/or acute myeloid leukemia (AML). Recommended use of peginterferon alfa-2a (Pegasys) in these settings is based

on multiple clinical trials and retrospective studies. Notably, a phase 2 open-label clinical trial assessed Pegasys for induction of complete (CR) and partial (PR) hematologic responses in patients with high-risk ET (n=65) or PV (n=50), who were either refractory or intolerant to HU. The overall response rates (ORRs; CR/PR) at 12 months were 69.2% (43.1% and 26.2%) in ET patients and 60% (22% and 38%) in PV patients. This clinical trial was further extended to a confirmatory phase 3 trial using hydroxyurea as active comparator (N=168), wherein similar ORR was observed in the treatment arm. The treatment efficacy was comparable to hydroxyurea.

XI. For PV and ET patient populations, high-risk disease is defined by a history of thrombosis, age >60 years, a history of bleeding (ET only), platelet counts >1500 X 10^9/L in ET and >1000 X 10^9/L in PV, vasomotor symptoms (erythromelalgia, severe migraine headaches), significant or symptomatic splenomegaly, and the presence of diabetes or uncontrolled hypertension. However, younger patients (<60 years) without any other defining factors may qualify for cytoreductive therapy with peginterferon alfa-2a (Pegasys) when hydroxyurea is contraindicated (e.g. during pregnancy).

XII. There is lack of efficacy and safety data for use of peginterferon alfa-2a (Pegasys) in pediatric population with ET and/ or PV.

Investigational or Not Medically Necessary Uses

I. Peginterferon alfa-2a (Pegasys) has been investigated for safety and efficacy in some the following indications. Safety and efficacy have not been established in all of the following:

A. Chronic hepatitis C: Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of chronic hepatitis C (HCV) infection in compensated liver disease, the WHO and AALSD guidelines no longer recommend interferon-based regimens for HCV infection. Recently updated 2019 AASLD guidelines for treatment of hepatitis C recommend use of newer direct antiviral agents (DAA) as preferred treatment regimens. Overall, it is guideline consensus that peginterferon alfa-2a based treatments have relatively lower efficacy, longer onset of action and higher safety concerns. Therefore, use of peginterferon alfa-2a is recommended for limited situations when all DAA are contraindicated.

B. Myelofibrosis: NCCN guideline for myeloproliferative neoplasms recommends use of peginterferon alfa-2a (Pegasys) as ‘useful in certain circumstances’ as a possible alternative to ruxolitinib (Jakafi) and hydroxyurea, only when cytoreduction is considered symptomatically beneficial. This recommendation stems from a retrospective case study and observational single-center open-label trial in 30 patients, wherein 7% CR and 30% PR were reported. Overall quality of evidence is considered low.

C. Systemic mastocytosis: peginterferon alfa-2a (Pegasys) was included in NCCN guidelines for systemic mastocytosis (SM) (category 2A recommendation) as a possible treatment option for advanced SM patients. This recommendation is restricted to patients with slowly

progressing disease without need for rapid cytoreduction. Tyrosine kinase inhibitors (TKI), midostaurine (Rydapt), and cladribine remain preferred therapeutic options in this space. Guidelines note that alfa interferon has recently fallen out of favor because of its slow onset of action and poor tolerability. Given the potential harmful effects of kinase inhibitors on germ cells and cladribine on the fetus (both pregnancy category D), alfa interferon may be an option in pregnancy. However, there are no supporting clinical trials to establish the efficacy and safety of peginterferon alfa-2a (Pegasys) in this patient population.

D. Chronic myelogenous leukemia (CML): NCCN guidelines recommend use of interferon alfa for management of CML during pregnancy due to contraindication to use of tyrosine kinase inhibitors (TKI) and hydroxyurea in this population. It is noted that if introduced earlier (during 1st trimester), the use of interferon may preserve molecular remission after discontinuation of TKI or HU. However, data are insufficient to establish the use of peginterferon alfa-2a (Pegasys) in pregnancy.
E. Renal cell carcinoma (RCC): interferon-alfa was studied in RCC as an adjuvant therapy for high-risk, clear cell, localized RCC post nephrectomy. Randomized trials in patients who had locally advanced, completely resected RCC showed no delay in time to relapse or improvement in survival with adjuvant therapy.
F. Malignant melanoma: Interferon alfa-2b (Intron A) and peginterferon alfa-2b (Sylatron) have supporting clinical evidence and are FDA-approved for malignant melanoma. Safety and efficacy of peginterferon alfa-2a (Pegasys) has not been established in these settings.
G. Hairy cell leukemia: NCCN guidelines for hairy cell leukemia recommend peginterferon alfa-2a as a possible alternative for the treatment of relapsed/ refractory hairy cell leukemia. However, purine analogs (cladribine, pentostatin) and rituximab remain preferred therapeutic options in this space. In a 1995 phase III intergroup study (N=319), efficacy and safety of pentostatin was compared with that of interferon alfa with a treatment follow-up of median 57 months. Subjects receiving Pentostatin reported higher complete remission (CR) rates versus those with interferon alfa treatment (76% vs 11%; p< 0.0001) along with longer relapse-free survival (RFS) (not reached vs 20 months; p< 0.0001). NCCN guidelines note that with the advent of purine analogs, the role of interferon alfa as a treatment option for hairy cell leukemia is limited.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria update: Transition from criteria to policy format and review of FDA-approved and guideline supported indications for peginterferon alfa-2a (Pegasys). Added supporting evidence for all indications listed in the policy. Removed indication of chronic hepatitis C per current AALSD and WHO guideline recommendation. Reviewed available evidence for indications listed under not medically necessary and investigational uses and added relevant clinical information to supporting evidence section	12/2020
Previous reviews and updates	12/2012; 08/2012; 12/2011; 12/2008; 11/2007
Criteria created	01/2006