

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

Reference Number: CP.PHAR.89

Effective Date: 10.11

Last Review Date: 08.18

Line of Business: Commercial, HIM, 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 patients 5 years of age and older with compensated liver disease.

Pegasys monotherapy is indicated for:

- CHC only if an adult patient has contraindication to or significant intolerance to other HCV antiviral drugs
- Treatment of 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
- Treatment of 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 chronic hepatitis C (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.

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.

It is the policy of health plans affiliated with Centene Corporation[®] 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 \geq 18 years;
5. Request meets one of the following (a or b):
 - a. Dose does not exceed initial dose of: 6 mcg/kg/week for 8 weeks, then 3 mcg/kg/week;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration:

Medicaid/HIM – 6 months

Commercial – 5 years

B. Myeloproliferative Neoplasms (off-label) (must meet all):

1. Diagnosis of one of the following (a, b, or c):
 - a. Myelofibrosis;
 - b. Polycythemia vera;
 - c. Essential thrombocytopenia;
2. Prescribed by or in consultation with an oncologist;
3. Member meets one of the following:
 - a. For Sylatron: age \geq 18 years;
 - b. For PegIntron: age \geq 3 years;
 - c. For Pegasys: age \geq 5 years;
4. Request meets one of the following (a or b):
 - a. Dose does not exceed (i or ii):
 - i. For PegIntron: 1.5 mcg/kg/week;
 - ii. For Sylatron: 6 mcg/kg/week;
 - iii. For Pegasys: 3 mcg/kg/week;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration:

Medicaid/HIM – Duration of request or 6 months (whichever is less)

Commercial – Length of Benefit

C. Chronic Hepatitis C:

Interferon-based treatment regimens are no longer recommended by the 2017 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.

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

1. Diagnosis of chronic hepatitis B virus infection;
2. Request is for Pegasys;
3. Meets ONE of the following:
 - a. Two elevated ALT lab values within the past 12 months (\geq 60 IU/L for men, \geq 38 IU/L for women) and HBV DNA levels \geq 20,000 IU/ml;
 - b. Patient has cirrhosis (for age \geq 18 years only);
 - c. Patient's liver biopsy showing moderate/severe necroinflammation (Grade 9-18) or significant fibrosis (Stage 3-4);

4. Age \geq 3 years;
 - a. If \leq 17 years, patient is non-cirrhotic;
5. Dose does not exceed 180 mcg/week for adults and 180 mcg/1.73 m² x BSA per week for pediatric patients.

Approval duration: 48 weeks

E. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I except CHC (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving 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 or ii):
 - a. PegIntron: 1.5 mcg/kg/week;
 - b. Sylatron: 6 mcg/kg/week for 8 weeks, then 3 mcg/kg/week;
 - c. Pegasys: 180 mcg/week for adults and 180 mcg/1.73 m² 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*).

Approval duration:

Medicaid/HIM – 12 months (up to 5 years of total treatment for melanoma; up to a total of 48 weeks for HBV)

Commercial – Length of Benefit (up to 5 years of total treatment for melanoma; up to a total of 48 weeks for HBV)

B. Chronic Hepatitis C:

Interferon-based treatment regimens are no longer recommended by the 2017 AASLD-IDSA HCV guidance due to the advent of safe and effective direct acting antivirals.

C. Other diagnoses/indications (1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;
- B. Treatment of chronic hepatitis C;
- C. Pegasys: Uncontrolled autoimmune hepatitis;
- D. Pegasys: Following heart, lung or kidney transplants;
- E. Pegasys: Patients 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 patients 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

HBeAg: hepatitis B e-antigen

CHC: chronic hepatitis C

HCV: hepatitis C virus

FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

Pegasys, PegIntron, and Sylatron are contraindicated in patients with:

- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh score > 6 [class B and C])
- Known hypersensitivity reactions

Pegasys is additionally contraindicated in:

- Neonates/infants

Boxed warning(s):

- Pegasys: risk of serious disorders (may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders)
- PegIntron: risk of serious disorders and ribavirin-associated effects
- Sylatron: depression and other neuropsychiatric disorders

Appendix D: General Information

- Per NCCN Drugs and Biologics Compendium, pegylated interferons have a category 2A rating for treatment of primary myelofibrosis, polycythemia vera, or essential thrombocythemia myelofibrosis.
- According to FDA approved labeling, recent evidence supports dose reduction of pegylated interferon for neutropenic hepatitis C patients treated with combination therapy (pegylated interferon and ribavirin). Treatment with Neupogen[®] is not FDA approved or recommended according to current hepatitis C treatment guidelines.

- 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.
- Genotype 6 is less responsive to treatment than genotypes 2 and 3. Treatment recommendations from Health Net expert reviewers are to treat genotype 6 in a similar manner to genotypes 1 and 4 with the exception of extending therapy to 72 weeks.
- Patient co-infected with HIV should be evaluated by an HIV specialist to see if he/she needs to be treated with a HAART (highly active antiretroviral therapy) regimen that includes a component with activity against HBV (e.g. Viread[®]-tenofovir, Epivir[®]-lamivudine, or Emtriva[®]-emtricitabine).
- According to the American Gastroenterological Association (AGA), recommendations on the treatment of chronic hepatitis B (CHB) are as follows:
 - HBV DNA results should be reported in IU/mL (1 IU/mL = 5.6 copies/mL)
 - The upper limit of normal for serum ALT concentrations for men and women are 30 IU/L and 19 IU/L, respectively.
- According to American Association for the Study of Liver Diseases (AASLD), recommendations on the treatment of CHB are as follows:
 - Pegasys is the only pegylated interferon approved for the treatment of chronic hepatitis B in the United States. However, given the similarity in response rates between 90 and 180 mcg doses in the phase II trial, and the comparable response rates between 24 and 48 week treatment in the phase II and phase III trials, it is possible that lower doses and/or shorter duration of treatment may suffice for HBeAg-positive patients. Whether longer duration of treatment (>48 weeks) will result in higher rates of sustained response in HBeAg negative patients remains to be determined.
 - Hepatitis B treatment is recommended if HBV DNA level or ALT becomes higher from baseline in HBeAg-negative CHB patients with initial HBV DNA levels of ≤ 2,000 IU/mL and normal ALT and
 - Management of anti-viral resistant HBV should include monitoring of serum HBV DNA every 3-6 months during treatment. Prevention of resistance may be a greater benefit of combination therapy than enhanced potency; however, large well-designed studies are needed to confirm this concept. There are insufficient robust data to approve coverage of combination use.
 - 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 2017 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.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Peginterferon alfa-2b (PegIntron, Sylatron)	Myelofibrosis, polycythemia vera, Essential thrombocytopenia	30 mcg/week SC with dose titration upward as tolerated	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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Adults: 180 mcg per week Pediatrics: 180 mcg/1.73 m² 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

VI. Product Availability

Drug	Availability
Peginterferon alfa-2a (Pegasys)	<ul style="list-style-type: none"> Vials: 180 mcg/mL Prefilled syringes: 180 mcg/0.5 mL (4 syringes/pack) Autoinjector: 180 mcg/0.5 mL and 135 mcg/0.5 mL
Peginterferon alfa-2b (PegIntron)	<ul style="list-style-type: none"> Vials (with diluent): 50 mcg/0.5 mL, 80 mcg/0.5 mL, 120 mcg/0.5 mL, 150 mcg/0.5 mL 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

- Sylatron Prescribing Information. Whitehouse Station, NJ: Merck and Co., Inc.; May 2018. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103949Orig1s5310lbl.pdf. Accessed December 14, 2018.

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Updated Background and Safety data to current guidelines Removed Safety concerns table and revised safety section Added Figure 2. Sylatron reauthorization algorithm Added requirement for psych evaluation for reauthorization Added special population information to safety section Expanded Appendix A to contraindicate pediatric patients Expanded Appendix B to include cardiovascular decompensation, hypothyroidism, diabetes, and hepatic impairment Removed Appendix D: Resume dosing at a reduced dose when all of the following are present	12.14	12.14
Converted policy to new template. Criteria: removed dosing question; removed psychiatric evaluation requirement; changed 8 week to 3 month approval period.	10.15	11.15

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>Background: limited to PI and NCCN-based narrative; removed clinical trial and safety discussion.</p> <p>Appendices: limited safety information to contraindications and reasons to discontinue.</p> <p>References: limited to PIs and NCCN guidelines (updated Sylatron PIs to 2015; updated NCCN guidelines to Version 3.2015).</p>		
<p>Policy converted to new template. For FDA-labeled Sylatron use, the time period within which to initiate Sylatron is rounded up from 84 days to 3 months. The two Sylatron PIs are edited to show only one PI with a 0.5 mL deliverable in 3 different strengths: 200 mcg, 300 mcg, 600 mcg.</p> <p>The PegIntron PI is added to the reference section. All NCCN recommended uses are added (melanoma and CML). Information about PegIntron is added to the description and formulations sections.</p>	08.16	09.16
<p>Policy converted to new template. Clinical changes: Added off-label use low risk myeloproliferative neoplasms; deleted off-label use of PegIntron for CML; deleted use for stage III disease with clinical satellite or in-transit metastases, or for local, satellite and/or in-transit recurrence; max dose added. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs.</p>	09.17	09.17
<p>3Q 2018 annual review: combined policy for Commercial and Medicaid lines of business; newly added HIM line of business; summarized NCCN and FDA-approved uses for improved clarity; added age requirement; allowed COC; Medicaid: added specialist involvement in care; removed coverage for CHC; Commercial: removed off-label use for CML, added off-label use for myeloproliferative neoplasms; references reviewed and updated.</p>	05.22.18	08.18
<p>No clinically significant changes; added Pegasys to policy; retired CP.CPA.205 during Q4 2018 P & T</p>	02.01.19	11.18

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.

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