



Drug and Biologic Coverage Policy

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Interferon Therapy

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Related Coverage Resources

- [Hepatitis C Therapy](#)
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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Please refer to coverage policy (CP) 1316, Hepatitis C Therapy, for all hepatitis C criteria for interferon and pegylated interferon therapy.

Please refer to coverage policy (CP) 1403, Oncology Medications, for all oncology criteria for interferon and pegylated interferon therapy.

Please refer to coverage policy (CP) 1402, Multiple Sclerosis Therapy, for all multiple sclerosis criteria for interferon therapy.

Interferon Therapy includes the following products:

- Pegylated Interferon Therapy:
 - Peginterferon alfa-2a (**Pegasys®**) – Preferred Brand [Employer group plans only, and plans using Advantage Prescription Drug List]
 - Peginterferon alfa-2b (**Peg-Intron®**) – Preferred Brand [Employer group, Individual & Family Plans]
- Interferon Therapy:
 - Interferon alfa-n3 (**Alferon® N**)
 - Interferon alfa-2b (**Intron® A**)

Pegylated interferon therapy (Pegasys, Peg-Intron) is considered medically necessary when use is defined by ANY of the following:

- **Chronic active hepatitis B** and EITHER of the following:
 - Individual is 3 years of age and older for Pegasys
 - Individual is 18 years of age and older for Peg-Intron
(*Authorization is for 48 weeks.*)
- **Polycythemia vera (PV) AND:**
 - Documented failure of phlebotomy
- **Essential thrombocythemia (ET)**

Interferon alfa-2b (Intron A) is considered medically necessary when use is defined by ANY of the following:

- **Chronic active hepatitis B, AND:**
 - Individual is 1 year of age and older
(*Authorization is for 24 weeks.*)
- **Polycythemia vera (PV) AND:**
 - Documented failure of phlebotomy
- **Essential thrombocythemia (ET)**
- **Condylomata acuminata** and ALL of the following:
 - Individual is 18 years of age and older
 - Intralesional treatment
 - Documented failure, contraindication per FDA label, or intolerance of podofilox

Interferon alfa-n3 (Alferon N) is considered medically necessary when use is defined by EITHER of the following:

- **Condylomata acuminata** and ALL of the following:
 - Individual is 18 years of age and older
 - Intralesional treatment
 - Documented failure, contraindication per FDA label, or intolerance of podofilox
- **Recurrent respiratory papillomatosis** (recurrent laryngeal papillomas, juvenile laryngeal papillomatosis), AND
 - Adjuvant treatment to surgery

Initial is up to 12 months unless otherwise stated.

Interferon Therapy products are considered medically necessary for continued use when the individual continues to meet the initial criteria.

Reauthorization is up to 12 months unless otherwise stated.

Interferon Therapy products are considered experimental, investigational, or unproven for treatment of any other use including the following (this list may not be all inclusive):

- Bechet's disease
- Chronic uveitis
- Hepatitis E
- Idiopathic thrombocytopenic purpura (adults, adolescents, children)
- Middle East respiratory syndrome
- Peyronie's disease
- Vernal keratoconjunctivitis
- West Nile virus infection

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Interferon Therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication (for non-Hepatitis C and non-oncology indications)

Brand Name	Approved Indication
Pegylated Interferon Therapy	
Pegasys (peginterferon alfa-2a)	<p>Chronic Hepatitis B (CHB)</p> <p><u>Adult Patients:</u> Pegasys is indicated for the treatment of adults with HBeAg-positive and HBeAg-negative CHB infection who have compensated liver disease and evidence of viral replication and liver inflammation.</p> <p><u>Pediatric Patients:</u> Pegasys is indicated for the 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).</p>
Peg-Intron (peginterferon alfa-2b)	An antiviral indicated for treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease. All other covered uses are non-FDA labeled uses.
Interferon Therapy	
Alferon N (interferon alfa-n3)	Alferon N is indicated for the intralesional treatment of external genital and perianal exophytic warts (condylomata acuminata) due to human papillomavirus (HPV) in adults.
Intron A (interferon alfa-2b)	<p>Chronic Hepatitis B</p> <p>Intron A is indicated for the treatment of chronic hepatitis B in patients 1 year of age or older with compensated liver disease. Patients who have been serum HBsAg positive for at least 6 months and have evidence of HBV replication (serum HBeAg positive) with elevated serum ALT are candidates for treatment.</p> <p>Condylomata Acuminata</p> <p>Intron A is indicated for intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal area. The use of this product in adolescents has not been studied.</p>

Recommended Dosing

FDA Recommended Dosing

Brand Name	FDA Recommended Dosing
Pegylated Interferon Therapy	
Pegasys (peginterferon alfa-2a)	<p>Chronic Hepatitis B (CHB)</p> <p><u>Adult Patients:</u> The recommended Pegasys dosage in adults with CHB is 180 mcg subcutaneously once weekly in the thigh or abdomen for 48 weeks.</p> <p><u>Pediatric Patients:</u> The recommended Pegasys dosage in pediatric patients for HBeAg-positive CHB is 180 mcg/1.73 m² x BSA subcutaneously once weekly to a maximum dose of 180 mcg. The recommended duration of therapy is 48 weeks.</p> <p>Maintain the recommended pediatric dosage through the entire duration of therapy in patients who turn 18 years of age during therapy.</p>
Peg-Intron (peginterferon alfa-2b)	An antiviral indicated for treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease. All other covered uses are non-FDA labeled uses.
Interferon Therapy	
Alferon N (interferon alfa-n3)	The recommended dose of Alferon N for the treatment of condylomata acuminata is 0.05 ml (250,000 IU) per wart. Alferon N should be administered twice weekly for up to 8 weeks. The maximum recommended dose per treatment session is 0.5 ml (2.5 million IU).

Brand Name	FDA Recommended Dosing
Intron A (interferon alfa-2b)	<p>Condyloma Acuminatum The recommended dose is 1.0 million IU per lesion in a maximum of 5 lesions in a single course. The lesions should be injected three times weekly on alternate days for 3 weeks. An additional course may be administered at 12 to 16 weeks.</p> <p>Chronic Hepatitis B <u>Adult Patients:</u> The recommended dose of INTRON A for the treatment of chronic hepatitis B is 30 to 35 million IU per week, administered subcutaneously or intramuscularly, either as 5 million IU daily (QD) or as 10 million IU three times a week (TIW) for 16 weeks.</p> <p><u>Pediatric Patients:</u> The recommended dose of INTRON A for the treatment of chronic hepatitis B is 3 million IU/m² three times a week (TIW) for the first week of therapy followed by dose escalation to 6 million IU/m² TIW (maximum of 10 million IU TIW) administered subcutaneously for a total duration of 16 to 24 weeks.</p>

General Background

Pharmacology

Interferon alfa is a family of proteins that possess antiviral, antitumor and immunomodulating effects. Generally, interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Plasma concentrations of interferon below the detection limit of the assay, that is, less than or equal to 3 IU/ml were observed in a study of intralesional use of interferon alfa-n3 for the treatment of condylomata acuminata.

There is no convincing data to indicate a significant clinical difference between the various alpha interferons. Pegylated interferons including interferon alfa-2a and interferon alfa-2b are pure clones of single interferon subspecies. In pegylated interferons, polyethylene glycol (PEG) is attached to interferon as a protein modifying agent to decrease renal clearance and extend duration of action. This allows for once-weekly administration. Peginterferon alfa-2a has a mean systemic clearance approximately 100-fold lower than for interferon alfa-2a. The time to maximum serum concentration occurs between 72–96 hours. Peginterferon alfa-2b has an approximately seven-fold lower mean apparent clearance and a five-fold greater mean half-life than interferon alfa-2b, allowing a reduced dosing frequency.

Professional Societies/Organizations

Essential Thrombocythemia (ET) and Polycythemia Vera (PV)

The National Comprehensive Cancer Network (NCCN) has published guidelines for myeloproliferative neoplasms (MPNs). MPNs are disorders of the hematopoietic system that include polycythemia vera (PV) and essential thrombocythemia (ET). Characteristic to PV and ET are significant thrombotic and hemorrhagic complications, and increased risks of conversion to acute myeloid leukemia. The treatment goal is to reduce the risk of thrombohemorrhagic events. Use of cytoreductive therapy, including hydroxyurea and interferon alfa, is based on risks as identified by age, thrombosis history and cardiovascular risk factors. Routine monitoring of disease-related symptoms and need-assessment for cytoreductive therapy should be part of the treatment management plan for individuals with PV and ET. (NCCN, 2020)

The Nordic MPN (myeloproliferative neoplasms) Study Group has published a care program for individuals with essential thrombocytopenia, polycythemia vera and primary myelofibrosis. Recommendations are based upon review of the evidence for the diagnosis and treatment of patients with these diseases. The guidelines recommend both pegylated and conventional forms of interferon alfa in the treatment of polycythemia vera (PV). In individuals less than 60 years of age, pegylated interferon alpha is preferred as first-line cytoreductive treatment for PV. For individuals between 60 and 75 years of age, first-line cytoreductive therapy is either hydroxyurea or interferon alfa. In younger populations, interferon alfa is considered superior to other cytoreductive therapies because it is not leukemogenic and may result in PV remission. Because interferon alfa has not been demonstrated to be teratogenic, it is recommended in pregnant women who are at high risk of complications due to PV. In pediatric MPN, interferon is recommended as first line treatment because of the long-term leukemogenicity risk associated with hydroxyurea. In essential thrombocythemia (ET), interferon alfa is mentioned

as first and second line treatment in persons less than 60 years of age. In individuals over 60 years of age, interferon alfa is considered as second line therapy. (Ahlstrand, 2017)

Evidence-based management recommendations of polycythemia vera also include stratifying patients into risk categories based upon age, thrombosis history and cardiovascular risk factors. Low-risk patient recommendations include phlebotomy and aspirin. High-risk patients include myelosuppression therapy. Hydroxyurea is recommended in patients at high risk for thrombosis or with evidence of disease progression. Interferon alfa may be recommended in high-risk patients younger than 40 years of age, women of childbearing age, and patients with intractable pruritus. (Barbui, 2006)

Chronic Hepatitis B

The American Association for the Study of Liver Disease (AASLD) Practice Guidelines for chronic hepatitis B mention that pegylated interferon, entecavir and tenofovir are first line therapies in this disease state. When evaluating therapeutic options, consideration should be given to the safety/efficacy and potential resistance of the drug, as well as, its direct and indirect costs. Other factors to guide treatment selection include the preferences of the prescriber, patient, and in women, consideration of family planning. The organization does give preference to pegylated interferon over nonpegylated forms for simplicity of dosing regimen. (Terrault, 2018)

Peyronie's Disease

The American Urological Association (AUA) Practice Guidelines for Peyronie's disease state that clinicians may administer intralesional interferon alfa-2b to patients with Peyronie's disease. This statement was provided as a moderate recommendation with an evidence strength, grade C. The AUA recommendation was based on one randomized controlled trial of moderate quality (n=117), one randomized design without a placebo group (n=30), and eight observational studies. Of the two randomized trials taken into consideration, only one demonstrated statistically significant changes in Peyronie's disease as a result of interferon therapy. In this study, patients who received interferon therapy achieved an average curvature improvement of nine degrees compared to placebo. (Nehra, 2015)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:

No recommendations are available for the use of interferon alpha in the treatment of hepatitis B, myeloproliferative neoplasms, condylomata acuminata, or respiratory papillomatosis.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for interferon alpha therapy.

Off Label Uses

The American Hospital Formulary Service (AHFS) Drug Information 2020 Edition supports the following off-label uses: acute hepatitis C virus, chronic hepatitis D virus, chronic hepatitis E virus infections, and recurrent respiratory papillomatosis (recurrent laryngeal papillomas, juvenile laryngeal papillomatosis) as adjunct to surgery. However, interferon alpha therapy is not recommended in the following area: Middle East Respiratory Syndrome. (AHFS, 2020)

Experimental, Investigational, Unproven Uses

Interferon alfa therapy in neuroinvasive West Nile Virus has not been demonstrated efficacious in controlled clinical studies. (AHFS, 2020)

Pegylated interferon alfa has been used for the treatment of chronic hepatitis E virus infection in solid organ transplant patients however its use has not been substantiated by controlled clinical trials of significant size demonstrating efficacy. The available clinical literature is primarily limited to trials enrolling less than five patients with inconsistent virologic response data and uncertainty to the curative agent. (AHFS, 2020)

Pegylated interferon alfa has been used in combination with ribavirin for the treatment of Middle East respiratory syndrome caused by the Middle East respiratory syndrome coronavirus. The Center for Disease Control has not identified a specific treatment for this viral infection. The available data for this indication is limited to a single retrospective cohort study with no significant difference in survival after 28 days between individuals who received interferon therapy and those who received supportive care. (AHFS, 2020)

Interferon in Peyronie's disease was the subject of a systematic review in 2007, which used Oxford criteria and analyzed intra-plaque injection therapies. Of the seven interferon studies reviewed, six were deemed level 4 evidence (case series or poor-quality cohort or case-control studies), while only one was considered level 1 evidence (meta-analysis or narrow confidence interval randomized, controlled trials). The authors call attention to factors which contribute to difficulty in conducting quality studies in this disease, such as the heterogeneity of patients enrolled in studies of Peyronie's, due to the natural phases of the disease, as well as a lack of agreement as to what are the important outcomes to assess and exactly how these should be evaluated. The studies available for evaluation are not conducted in a controlled manner and are often under powered. The review concludes that although the vast majority of studies for treatment of Peyronie's have reported positive outcomes, the data is weak and does not support the findings. (Russell, 2007)

Interferon alfa use in children and adolescents with ITP is no longer supported due to the paucity of evidence of efficacy and an abundance of reports of toxicities. In the adult population with ITP, available evidence confirms that interferon alfa is not effective and results in a disproportionate amount of toxicities. (Provan, 2010)

There is insufficient evidence in the peer-reviewed published scientific literature to support safety and efficacy of interferon use in Behcet's disease, chronic uveitis and vernal keratoconjunctivitis.

Coding/ Billing Information

Note: Non-Hepatitis C Interferon Therapy is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions. Interferon alfa-2b (Intron® A)] requires medical drug coding and is listed as follows:

- Note:** 1) This list of codes may not be all-inclusive.
 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

HCPCS Codes	Description
J9214	Injection, interferon alfa-2b, recombinant, 1 million units

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

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