**Cigna Drug and Biologic Coverage Policy**

**Subject**  
Interferon Therapy

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- Oncology Medications

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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.

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**Coverage Policy**

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

**Pegylated Interferon Therapy**

<table>
<thead>
<tr>
<th>Product</th>
<th>Criteria for Use</th>
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| peginterferon alfa-2a (Pegasys) | Treatment for ANY of the following:  
  - Treatment of chronic active hepatitis B in an individual 3 years of age and older for 48 weeks  
  - Treatment of polycythemia vera (PV) when there is a failure of phlebotomy AND there is a failure, contraindication, or intolerance (for example, age less than 60, pregnancy) to cytoreduce therapy (for example, hydroxyurea)  
  - Treatment of essential thrombocythemia (ET) when there is a failure, contraindication, or intolerance (for example, age... |
<table>
<thead>
<tr>
<th>Product</th>
<th>Criteria for Use</th>
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</table>
| peginterferon alfa-2b (PegIntron) | Treatment for ANY of the following:  
- Treatment of chronic active hepatitis B in adults for 48 weeks  
- Treatment of polycythemia vera (PV) when there is a failure of phlebotomy AND there is a failure, contraindication, or intolerance (for example, age less than 60, pregnancy) to cytoreductive therapy (for example, hydroxyurea)  
- Treatment of essential thrombocythemia (ET) when there is a failure, contraindication, or intolerance (for example, age less than 60, pregnancy) to cytoreductive therapy (for example, hydroxyurea) |

### Interferon Therapy

<table>
<thead>
<tr>
<th>Product</th>
<th>Criteria for Use</th>
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| interferon alfa-2b (Intron A) | Treatment for ANY of the following:  
- Treatment of chronic active hepatitis B in an individual 1 year of age or older for 24 weeks  
- Treatment of polycythemia vera (PV) when there is a failure of phlebotomy AND there is a failure, contraindication, or intolerance (for example, age less than 60, pregnancy) to cytoreductive therapy (for example, hydroxyurea)  
- Treatment of essential thrombocythemia (ET) when there is a failure, contraindication, or intolerance (for example, age less than 60, pregnancy) to cytoreductive therapy (for example, hydroxyurea)  
- Condylomata acuminata, intralesional only, after failure, contraindication or intolerance of podofilox (adults 18 and older) |
| interferon alfa-n3 (Alferon N) | Treatment for EITHER of the following:  
- Condylomata acuminata, intralesional only, after failure, contraindication or intolerance of podofilox (adults 18 and older)  
- Recurrent respiratory papillomatosis (recurrent laryngeal papillomas, juvenile laryngeal papillomatosis) as adjunct to surgery |

Cigna does not cover the use of Interferon Therapies for any other indication including the following because it is considered experimental, investigational, or unproven (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
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.

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 (for non-Hepatitis C and non-oncology indications)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Approved Indication</th>
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<tbody>
<tr>
<td><strong>Pegylated Interferon Therapy</strong></td>
<td></td>
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</tbody>
</table>
| Pegasys | Chronic Hepatitis B  
Pegasys monotherapy is indicated for the treatment of adult patients with HBeAg positive and HBeAg negative chronic hepatitis B infection who have compensated liver disease and evidence of viral replication and liver inflammation.  
Pediatric Patients: Pegasys 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). |
| PegIntron | FDA approved indications are for hepatitis C. All other covered indications are considered off-label use. |
| **Interferon Therapy** | |
| Alferon N | Alferon N is indicated for the intralesional treatment of refractory or recurring external condylomata acuminata in patients 18 years of age or older. Alferon N is particularly useful for patients who have not responded satisfactorily to other treatment modalities, e.g., podophyllin resin, surgery, laser or cryotherapy. There have been no studies with this product in adolescents. This product is not recommended for use in patients less than 18 years of age. |
| Intron A | Condylomata Acuminata  
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.  
Chronic Hepatitis B  
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. |
### Pegylated Interferon Therapy

#### Pegsys

**Chronic Hepatitis B**

**Adult Patients** - The recommended dose of Pegsys monotherapy for hepatitis B is 180 mcg once weekly for 48 weeks. The dose of is not weight-based; it is dosed as a weekly subcutaneous (SC) injection of 180 mcg. The dose of ribavirin is weight-based, with patients < 75 kg receiving 1000 mg/day and patients > 75 kg receiving 1200 mg/day in divided doses. The recommended length of therapy with Pegsys and ribavirin varies with genotype. Patients with genotype 2 and 3 may only require 800 mg/day of ribavirin in divided doses. The recommended dose of for treatment of hepatitis B is 180 mcg once weekly by SC administration.

**Pediatric Patients** - The recommended Pegsys 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.

Maintain the recommended pediatric dosage through the entire duration of therapy in patients who turn 18 years of age during therapy.

#### PegIntron

FDA approved indications are for hepatitis C. All other covered indications are considered off-label use.

#### Alferon N

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).

#### Intron A

**Condyloma Acuminatum**

Intralesional, one million units (using only the 10-million-units-per-mL strength) per wart (up to five warts) three times a week on alternate days for three weeks. If response is not satisfactory 12 to 16 weeks after the initial treatment course, a second course may be given. Patients with six to 10 warts may be given a second (sequential) course of treatment at the same dose to treat up to five additional warts per course; for patients with more than 10 warts, additional courses may be given as needed with up to five additional warts per course.

**Chronic Hepatitis B**

**Adults** - Subcutaneous or intramuscular, 30 to 35 million units per week, either as five million units per day or 10 million units three times per week, for 16 weeks.

**Children/ Adolescents** - 3 million units per square meter of body surface area, subcutaneously, three times per week for 1st week, then escalate to 6 million units per square meter of body surface area (maximum 10 million), subcutaneously, three times per week for 16-24 weeks.

### Drug Availability

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Availability</th>
</tr>
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<tbody>
<tr>
<td><strong>Pegylated Interferon Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Pegsys</td>
<td>Each Pegsys single use vial package contains a box containing 180 mcg per 1 mL solution in a single use vial. Each Pegsys prefilled syringe monthly convenience pack contains a box containing four 180 mcg per 0.5 mL (½ cc) single use prefilled syringes. Each Pegsys ProClick Autoinjector package contains a box containing one 180 mcg per 0.5 mL; Pegsys ProClick single use autoinjector contains one 135 mcg per 0.5 mL single use autoinjector.</td>
</tr>
<tr>
<td>PegIntron</td>
<td>Peginterferon alfa-2b is available in single-use vial and Redipen, an injectable pen.</td>
</tr>
<tr>
<td><strong>Interferon Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Alferon N</td>
<td>Alferon N is available in an injectable solution with each vial containing 1 ml of interferon alfa-n3 injection.</td>
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</tbody>
</table>
| Intron A | **Intron A Powder for Injection**
Intron A Powder for Injection - 10 million IU per vial 1 mL per vial; 18 million IU per vial; and 50 million IU per vial. **Intron A Solution for Injection in Multidose Pens** |
**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, i.e., 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 acuminate.

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.

**Guidelines**

**Essential Thrombocythemia (ET) and Polycythemia Vera (PV)**

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 thrombocytemia (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 T and Finazzi G, 2006)

The British Committee for Standards in Haematology has published guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. In individuals intolerant to phlebotomy or demonstrating symptoms of disease progression, the committee recommends Interferon alfa as first-line treatment for PV patients who are < 40 years of age. In persons aged 40 to 75, Interferon alfa is considered second-line treatment. The committee does not endorse cytoreductive therapy in pregnancy, but in pregnant women who are at increased risk of complications due to PV, Interferon alfa is considered the treatment of choice. (McMullin M, et al., 2005)
**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 it’s 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 et al, 2016)

**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 et al, 2015)

**Clinical Efficacy**

**Other Covered Uses**

**Laryngeal papillomas**

The American Society of Health-Systems Pharmacists in AHFS Drug Information describes interferon alfa (alfa-n3, alfa-n1 [no longer commercially available in the US]) in recurrent respiratory papillomatosis (recurrent laryngeal papillomas, juvenile laryngeal papillomatosis) as adjunct to surgery. (AHFS Drug Information 2014)

**Experimental, Investigational, Unproven Uses**

Interferon alfa therapy in neuroinvasive West Nile Virus has not been demonstrated efficacious in controlled clinical studies. (AHFS Drug Information 2014).

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 Drug Information 2015)

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 Drug Information 2015)

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 randomised, 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 et al 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, et al, 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:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>J9214</td>
<td>Injection, interferon alfa-2b, recombinant, 1 million units</td>
</tr>
</tbody>
</table>

References