



Horizon BCBSNJ
Medical Necessity Guideline

Section Drugs
Policy Number
Effective Date 12/22/08
Review Date

BRAND NAME Alferon N
(interferon alfa-n3)

IMPORTANT NOTE:

The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. Outpatient prescription drugs are not covered under all Horizon benefit plans. If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.

Horizon BCBSNJ pharmacy guidelines do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.

FDA-APPROVED INDICATIONS

Alferon-N

Condylomata acuminata

Alferon-N (Interferon alfa-n3, human leukocyte derived, is indicated for the intralesional treatment of refractory or recurring external condylomata acuminata (genital warts) in patients 18 years of age or older.

The physician should select patients for treatment with Alferon N Injection after consideration of a number of factors: the locations and sizes of the lesions, past treatment and response thereto, and the patient's ability to comply with the treatment regimen. Alferon N Injection 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.

Compendial Uses for Alferon-N:

- Multiple Myeloma
 - as a component of first-line treatment to induce remission
 - as maintenance therapy to prolong response and survival in patients who have responded to first-line therapy or conventional induction chemotherapy
- Mycosis Fungoides

- Polycythemia Vera
- Cutaneous T Cell Lymphoma
- Renal Cell Carcinoma
- Carcinoid Syndrome
- Bladder Cancer (intravesical)
- Basal Cell Carcinoma (intralesional)
- Ovarian Cancer (intraperitoneal)
- Respiratory Papillomatosis including Laryngeal Papillomatosis
- Essential Thrombocytosis
- Cervical Cancer
- Chronic Hepatitis D
- Human Papilloma virus Infections
- Chronic myelocytic leukemia
- Hemangiomas
- AIDS-related Kaposi's sarcoma
- Chronic hepatitis B
- Chronic hepatitis C
- Follicular lymphoma
- Malignant melanoma
- Hairy cell leukemia

CRITERIA FOR APPROVAL

Alferon-N

1. Is the physician aware that labeling recommends that all patients be monitored for evidence of depression?	Yes	No
2. Does the patient have a diagnosis of autoimmune hepatitis? [If the answer to this question is yes, then no further questions required.]	Yes	No
3. Does the patient have a diagnosis of any of the following: • AIDS-related Kaposi's sarcoma • Hairy cell leukemia • Malignant melanoma • Condylomata acuminata (also known as genital warts) • Aggressive low-grade (follicular) or intermediate-grade non-Hodgkin's lymphoma where Intron A will be prescribed in combination with cytotoxic agents as first-line therapy [If the answer to this question is yes, then no further questions required.]	Yes	No
4. Does the patient have the diagnosis of chronic hepatitis B? [If the answer to this question is no, then skip to question 16.]	Yes	No
5. Is the patient <u>less</u> than 18 years old? [If the answer to this question is no, then skip to question 9.]	Yes	No
6. Has the patient been HBsAg (hepatitis B surface antigen) positive for greater than 6 months?	Yes	No
7. Does the patient have persistent or intermittent elevation in serum aminotransferase (ALT) levels > 2 times the upper limits of normal?	Yes	No
8. Is the patient HBeAg (hepatitis Be antigen) positive for greater than 6 months? [No further questions required]	Yes	No

9. Has the patient been HBsAg (hepatitis B surface antigen) positive for greater than 6 months?	Yes	No
10. Is the patient HBeAg (hepatitis Be antigen) positive? [If the answer to this question is yes, then skip to question 12.]	Yes	No
11. Does the patient have Hepatitis B viral DNA > 20,000 IU/mL? [If the answer to this question is no, then skip to question 13.]	Yes	No
12. Does the patient have persistent or intermittent elevation in serum aminotransferase (ALT) levels > 2 times the upper limit of normal? [If the answer to this question is yes, no further questions required.] [If the answer to this question is no, may skip to question 15.]	Yes	No
13. Does the patient have Hepatitis B viral DNA of 2,000-20,000 IU/mL?	Yes	No
14. Does the patient have persistent or intermittent elevation in serum aminotransferase (ALT) levels 1-2 times the upper limit of normal?	Yes	No
15. Does the patient have moderate to severe hepatitis on liver biopsy? [No further questions required.]	Yes	No
16. Does the patient have the diagnosis of chronic hepatitis C? [If the answer to this question is no, then skip to question 28.]	Yes	No
17. Is the patient less than 3 years of age? [if the answer to this question is yes, no further questions required]	Yes	No
18. Would either of these describe the patient's liver condition: • the patient does not have cirrhosis • the patient has a diagnosis of cirrhosis, but it is it considered compensated cirrhosis	Yes	No
19. Do any of the following apply to the patient: • the patient will be taking ribavirin (e.g., Copegus, Rebetol, Ribasphere) concurrently with alpha interferon therapy • treatment with ribavirin is contraindicated (e.g., pregnancy or men whose female partners are pregnant, hemoglobinopathies, hepatic decompensation, creatinine clearance < 50mL/mon, unstable heart disease) • the patient is intolerant to ribavirin therapy [If the answer to this question is no, then no further questions required.]	Yes	No
20. Does the patient have a diagnosis of HIV? [If the answer to this question is yes, then skip to question 27.]	Yes	No
21. Is the patient Genotype-2 or 3? [If the answer to this question is no, then skip to question 23.]	Yes	No
22. Has the patient had 24 weeks total of alpha interferon therapy with this treatment? [If the answer to this question is no, then skip to question 31.] [If the answer to this question is yes, then no further questions required.]	Yes	No
23. Has the patient received at least 12 weeks of alpha interferon therapy	Yes	No

in the past 3 months? [If the answer to this question is no, then skip to question 31.]		
24. Did the patient experience at least a 2-log decrease in serum hepatitis C RNA levels (viral load) since the initiation of Hepatitis C therapy? [Skip to question 33.]	Yes	No
25. Has the patient tried pegylated (e.g., Pegasys, PEG-Intron) interferon therapy for hepatitis C in the past and found to be intolerant to pegylated therapy. [If the answer to this question is no, then skip to question 27.]	Yes	No
26. At the end of prior drug treatment for hepatitis C, did the patient have detectable levels of hepatitis C RNA (a viral load) in the serum? the patient intolerant to pegylated (e.g., Pegasys, PEG-Intron) interferons? [If the answer to this question is no, then no further questions required.]	Yes	No
27. Has the patient had 48 weeks total of alpha interferon therapy? [No further questions required.]	Yes	No
28. Will Alferon-N be used to induce remission of multiple myeloma as a component of first-line treatment? [If the answer to this question is yes, no further questions required.]	Yes	No
29. Will Alferon-N be prescribed for multiple myeloma to provide maintenance therapy to prolong response and survival after the patient responded to first-line therapy or conventional induction chemotherapy?	Yes	No
[If the answer to this question is yes, then no further questions required.]		
30. Does the patient have a diagnosis of any of the following: <ul style="list-style-type: none"> • Mycosis fungoides • Polycythemia vera • Cutaneous T cell lymphoma • Renal cell carcinoma • Carcinoid syndrome • Respiratory papillomatosis, including laryngeal papillomatosis • Essential thrombocytosis • Cervical cancer • Chronic hepatitis D • Human papilloma virus infection • Chronic myelocytic leukemia • Hemangiomas [If the answer to this question is yes, then no further questions required.]	Yes	No
31. Will Alferon-N be given for any of the following <ul style="list-style-type: none"> • intravesically for the diagnosis of bladder cancer • intralesionally for the diagnosis of basal cell carcinoma • intraperitoneally for the diagnosis of ovarian cancer 	Yes	No

GUIDELINES FOR APPROVAL
Alferon-N
Duration of Approval 12 Months

Set 1 Kaposi's sarcoma/hairy cell leukemia/ malignant melanoma/ condylomata acuminata		Set 2 – Hep B under 18 y/o		Set 3- hep B adult HBeAg + ALT x2			
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)		
1	2	1	2	1	2		
3		4	3	4	3		
		5		9	5		
		6		10			
		7		12			
		8					
Duration of Approval 16 Weeks			Duration of Approval 12 months				
Set 4 adult hep B HBe Ag +, ALT 1-2, biopsy			Set 5 adult hep B HBe Ag neg HBV>20,000				
Yes to question(s)	No to question(s)	1		2			
1	2	4		3			
4	3	9		5			
9	5	11		10			
10	12	12					
15							
Set 6 adult hep B HBe Ag neg, HBV2-20, biopsy							
1	2						
4	3						
9	5						
13	10						
14	11						
15							
Chronic Hepatitis C							
Genotype 1 or 4							
Duration of Approval 12 weeks			Duration of Approval 24 weeks				
Set 7 genotype 1-4 initial		Set 8 genotype 1-4 initial		Set 9 genotype 1-4 renewal		Set 10 genotype 1-4 renewal	
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)
1	2	1	2	1	2	1	2
16	3	16	3	16	3	16	3
18	4	18	4	18	4	18	4
19	17	19	17	19	17	19	17
	20	25	20	23	20	23	20
	21		21	24	21	24	21
	23		23		27	25	26
	25		26				
	27						
Duration of Approval 32 weeks Genotype 2 & 3				Duration of Approval 12 months Hepatitis C + HIV			
Set 11 w/Riba-Peds				Set 12			
Yes to question(s)	No to question(s)			Yes to question(s)	No to question(s)		

1	2			1	2		
16	3			16	3		
18	4			18	4		
19	17			19	17		
21	20			20	27		
	22						
	27						
Duration of Approval				12 months			
Set 13 multiple myeloma first line		Set 14 multiple myeloma maintenance		Set 15 mycosis fungoides, polycythemia		Set 16 bladder CA, basal cell CA, ovarian CA	
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)
1	2	1	2	1	2	1	2
28	3	29	3	30	3	31	3
	4		4		4		4
	16		16		16		16
			28		28		28
					29		29
							30

Horizon BCBSNJ Pharmacy Guideline Development Process: This Horizon BCBSNJ Pharmacy Guideline (the "Pharmacy Guideline") has been developed by Horizon BCBSNJ's Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

RATIONALE

These criteria meet the Medicare Part D definition of a medically accepted indication. This definition includes uses which are approved by the FDA or supported by a citation included, or approved for inclusion, in one of the Medicare approved compendia.

ADDITIONAL INFORMATION

Interferons are a family of naturally occurring, small protein molecules and glycoproteins that are produced and secreted by cells in response to viral infections or to various synthetic and biological

inducers. Interferons share common biological activities generated by binding of interferon to the cell-surface receptor, leading to the production of several interferon-stimulated gene products. Interferons induce pleiotropic biologic responses which include antiviral, antiproliferative, and immunomodulatory effects, induction of certain enzymes, regulation of cell surface major histocompatibility antigen expression, regulation of cytokine expression, and upregulates the Th1 T-helper cell subset. The clinical relevance of these findings is not known. While all alpha interferons have similar biological effects, not all the activities are shared by each alpha interferon and, in many cases, the extent of activity varies substantially for each interferon subtype.

DOSAGE AND ADMINISTRATION

The recommended dose of Alferon N Injection® for the treatment of condylomata acuminata is 0.05 ml (250,000 IU) per wart. Alferon N Injection® 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). Alferon N Injection® should be injected into the base of each wart, preferably using a 30 gauge needle. For large warts, Alferon N Injection® may be injected at several points around the periphery of the wart, using a total dose of 0.05 ml per wart.

STORAGE

Alferon N Injection® should be stored at 2° to 8°C (36° to 46°F). Do not freeze. Do not shake.

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

Contraindications:

Alferon N Injection® is contraindicated in patients with known hypersensitivity to human interferon alpha proteins or any component of the product. The product is also contraindicated in patients who have anaphylactic sensitivity to mouse immunoglobulin (IgG), egg protein or neomycin.

Warnings/Precautions

Because of the fever and other "flu-like" symptoms associated with Alferon N Injection®, it should be used cautiously in patients with debilitating medical conditions such as cardiovascular disease (e.g., unstable angina and uncontrolled congestive heart failure), severe pulmonary disease (e.g., chronic obstructive pulmonary disease), or diabetes mellitus with ketoacidosis.

Alferon N Injection® should be used cautiously in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism and hemophilia), severe myelosuppression, or seizure disorders. Acute, serious hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have not been observed in patients receiving Alferon N Injection®. However, if such reactions develop, drug administration should be discontinued immediately and appropriate medical therapy should be instituted.

Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Patients being treated with Alferon N Injection® should be informed of the benefits and risks associated with the treatment. Because the manufacturing process, strength, and type of interferon (e.g., natural, human leukocyte interferon versus single-species recombinant interferon) may vary for different interferon formulations, changing brands may require a change in dosage. Therefore, physicians are cautioned not to change from one interferon product to another without considering these factors.

Pregnancy Category C

Animal reproduction studies have not been conducted with Alferon N Injection®. It is also not known whether Alferon N Injection® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Alferon N Injection® should be given to a pregnant woman only if clearly needed.

Changes in the menstrual cycle and abortions have been reported to occur in non-human primates given extremely high doses of recombinant interferon alpha. In these studies, *Macaca mulatta* (rhesus monkeys) were given interferon daily by intramuscular injection. Abortifacient effects were noted when

the recombinant interferon alpha was given daily during early to mid-gestation at intramuscular doses of 978 times the average intralesional dose of Alferon N Injection® (360 times the maximum recommended dose).

Nursing Mothers

It is not known whether Alferon N Injection® is excreted in human milk. Studies in mice have shown that mouse interferons are excreted in milk.⁷ Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to not initiate drug treatment, taking into account the importance of the drug to the mother and the potential risks to the infant.

Pediatric Use

Safety and effectiveness have not been established in patients below the age of 18 years.

ADVERSE REACTIONS

Adverse Reactions in Patients with Condylomata Acuminata

A total of 104 patients with condylomata acuminata was treated with Alferon N Injection® during the double-blind clinical trial. Adverse reactions were reported to be likely, unlikely, or not known to be related to Alferon N Injection®. Adverse reactions consisted primarily of "flu-like" symptoms (myalgias, fever, and/or headache) which were in most cases mild or moderate, and transient, and did not interfere with treatment.

The "flu-like" adverse reactions, consisting of fever, myalgias, and/or headache, occurred primarily after the first treatment session and were reported by 30% of the patients. The frequency of "flu-like" adverse reactions abated with repeated dosing of Alferon N Injection® so that the incidences due to Alferon N Injection® and placebo were similar after three to four weeks of treatment (after six to eight treatment sessions). "Flu-like" symptoms were relieved by administration of acetaminophen.

Adverse reactions were reported at least once during the course of treatment in the following percentages of patients in each treatment group:

**Table 2
Percent of Patients With Adverse Reactions**

Adverse Reactions:	Alferon (n=104)	Placebo (n=85)
<i>Autonomic Nervous System</i>		
Sweating	2%	1%
Vasovagal Reaction	2%	0%
<i>Body as a Whole</i>		
Fever	40%	19%
Chills	14%	2%
Fatigue	14%	6%
Malaise	9%	9%
<i>Skin</i>		
Generalized Pruritis	2%	0%
<i>Central & Peripheral Nervous System</i>		
Dizziness	9%	4%
Insomnia	2%	1%
<i>Gastrointestinal System</i>		
Nausea	4%	7%
Vomiting	3%	0%
Dyspepsia/		

Heartburn	3%	1%
Diarrhea	2%	2%
Musculoskeletal System		
Arthralgia	5%	1%
Back Pain	4%	1%
Myalgias	45%	15%
Headache	31%	15%
Psychiatric Disorders		
Depression	2%	1%
Nasopharyngeal		
Nose/sinus		
Drainage	2%	2%

Most of the systemic adverse reactions were mild or moderate. Severe systemic adverse reactions were reported by 18% of Alferon N Injection®-treated patients and 13% of placebo-treated patients (not a statistically significant difference). Most of the severe systemic adverse reactions reported were "flu-like". Other severe systemic adverse reactions included back pain, insomnia, and sensitivity to allergens. Those adverse reactions which were reported by 1% of patients treated with Alferon N Injection® in the double-blind trial include: left groin lymph node swelling, tongue hyperaesthesia, thirst, tingling of legs/feet, hot sensation on bottom of feet, strange taste in mouth, increased salivation, heat intolerance, visual disturbances, pharyngitis, sensitivity to allergens, muscle cramps, nosebleed, throat tightness, and papular rash on neck. Additional adverse reactions which were reported by 1% of patients treated with placebo include: pharyngitis, oral pain, penile discharge, cold, knuckle stiffness, herpes outbreak, cough, disorientation, and weight/appetite loss.

Additional adverse reactions which occurred only in open clinical trials of intralesional use of Alferon N Injection® for treatment of condylomata acuminata were herpes labialis, hot flashes, nervousness, decrease in concentration, dysuria, photosensitivity, and swollen lymph nodes. These reactions occurred in 1% of the patients. One patient with a history of epilepsy, who was not taking anticonvulsant medication, had a grand mal seizure while being treated with Alferon N Injection®; this seizure was judged to be unrelated to Alferon N Injection® administration.

Application Site Disorders

The frequency of application site disorders (such as itching and pain) for patients treated with Alferon N Injection® was significantly less than that reported with placebo (12% versus 26%). No severe application site disorders were reported by patients treated with Alferon N Injection®, while 7% of placebo-treated patients reported severe disorders.

Laboratory Test Values

Abnormalities were seen with statistically equivalent frequencies in both the Alferon N Injection® and placebo groups. None of the laboratory abnormalities were considered clinically significant. The abnormalities in the Alferon N Injection®-treated patients consisted primarily of decreased WBC (11%). Decreases also occurred in 4% of the placebo patients (not a statistically significant difference). The abnormalities in Alferon N Injection®-treated patients involved increases of only one WHO grade.

Adverse Reactions in Patients with Cancer

Thirty-one (31) patients with cancer were treated with a maximum of ten intramuscular injections of Alferon N Injection® in doses of 3 million IU, 9 million IU, or 15 million IU per treatment session. The occurrence of adverse reactions was judged to be unrelated to the dose of Alferon N Injection®.

The following adverse reactions were reported at least once (the percentage of patients experiencing the reaction is indicated in parentheses): chills (87%), fever (81%), anorexia (68%), malaise (65%), nausea (48%), vomiting (29%), myalgias (16%), arthralgia (10%), chest pains (10%), soreness at injection site (10%), sleepiness (10%), headache (10%), diarrhea (6%), fatigue (6%), low blood

pressure (6%), sore mouth/stomatitis (6%), and blurred vision (6%). Those adverse reactions which were each reported by only one patient treated with Alferon N Injection® include: stiff shoulders, flushed face, edema, dry mouth, mucositis, coughing, numbness, numbness in hands, numbness in fingers, pain on ocular rotation, shakes/shivers, ringing in ears, cramps, constipation, muscle soreness, confusion, light-headedness, depression, upset stomach, and sweating. The following adverse reactions were reported as severe by at least one patient (the percentage of patients experiencing the reaction is indicated in parentheses); fever (55%), malaise (54%), anorexia (45%), chills (45%), nausea (16%), myalgias (13%), vomiting (10%), fatigue (6%), low blood pressure (6%), chest pains (6%), sore mouth/stomatitis (6%), headache (3%), diarrhea (3%), sleepiness (3%), arthralgia (3%), blurred vision (3%), stiff shoulders (3%), numbness (3%), pain on ocular rotation (3%), muscle soreness (3%), confusion (3%), light-headedness (3%), depression (3%), and sweating (3%). The number and percentage of patients with cancer who experienced a significant abnormal laboratory test value (values that changed from WHO Grades 0, 1, or 2 at baseline to WHO Grades 3 or 4 during or after treatment) at least once during the trials are shown in the following table:

Table 3 Abnormal Laboratory Test Values	Cancer (n=31)
Hemoglobin Level	2(7%)
White Blood Cell Count	1(3%)
Platelet Count	1(3%)
GGT	1(6%)
SGOT	1(3%)
Alkaline Phosphatase	2(8%)
Total Bilirubin	1(4%)

HISTORY

12/22/08

Original Policy

REFERENCES

1. Alferon-N Product Information. Hemispherx Biopharma, Inc. June 2008.
2. Micromedex. Thomson MICROMEDEX. Greenwood Village, CO. 2008.
3. American Hospital Formulary Service. American Society of Health-System Pharmacists. 2008.

Pharmacy Guidelines can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician or pharmacist, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.

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