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Interferons

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Policy

Subject to the qualification described below regarding length of treatment and response to treatment, Aetna considers interferon alfa, pegylated interferon, interferon beta, and interferon gamma medically necessary for persons who meet the criteria for each drug specified below.

Interferon alfa 2a and 2b

Aetna considers interferon alfa 2a and 2b medically necessary for the following indications:

1. Adult T-cell leukemia/lymphoma (chronic, smoldering or acute);
2. AIDS-associated Kaposi's sarcoma;
3. Carcinoid syndrome;
4. Condylomata acuminata (genital warts) (intralesional only);
5. Desmoid tumors (aggressive fibromatosis);
6. Essential thrombocythemia;
7. Giant cell tumor of bone;
8. Hairy cell leukemia, relapsed or refractory;
9. Hepatitis C (non-A, non-B hepatitis). Continued treatment with interferon alfa is considered not medically necessary for persons with HCV genotypes 1 and 4 through 6 who have failed to attain an early virologic response after 12 weeks of treatment (where early virologic response is indicated by achievement of at least a 100-fold (2 log10) decrease in serum

Policy History

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Review History

Definitions

HCV from pretreatment baseline). Up to a maximum of 24 weeks of interferon alfa is considered medically necessary for persons with HCV genotypes 2, 3 and up to a maximum of 48 weeks of interferon alfa is considered medically necessary for persons with HCV genotypes 1 and 4 through 6. A course of standard interferon alfa in persons with hepatitis C who have failed to respond or relapsed after an adequate course of pegylated interferon alfa or consensus interferon is considered experimental and investigational because of a lack of evidence on the effectiveness of standard interferon in these persons. Note: Upon medical review, extended treatment with interferon alfa beyond these limits may be considered medially necessary for persons with cryoglobulinemia and for liver transplant recipients with recurrent hepatitis C infection;

10. Hyper-eosinophilic syndrome that is not adequately responsive to glucocorticoids;
11. Kasabach-Merritt syndrome;
12. Leptomeningeal metastases of CNS tumors, intracerebrospinal fluid treatment;
13. Life-threatening hemangioma of infancy (intralesional) when member is intolerant of, or the hemangioma is resistant to, corticosteroid therapy;
14. Melanoma;
15. Meningioma, recurrent, surgically inaccesible;
16. Mycosis fungoides/Sezary syndrome
17. Myelofibrosis - Treatment of symptomatic low-risk myelofibrosis;
18. Neuroendocrine tumors of the GI tract, lung and thymus;
19. Ocular herpes simplex (interferon alfa eye drops);
20. Ocular surface neoplasia (interferon alfa 2b only);
21. Persons with chronic hepatitis B who meet all of the following criteria:

    a. Member has compensated liver disease (Child-Pugh score less than or equal to 6 [class A]); *and*
    b. Serum aminotransferase (AST) greater than double the upper limit of normal range (AST normal range 0 to 35 u/l).

A course of standard interferon alfa in persons with hepatitis B who have failed an adequate course of pegylated interferon alfa is considered experimental and investigational because of a lack of evidence on the effectiveness of standard interferon in these persons.

(The use of interferon alfa is considered contraindicated in the following persons with hepatitis B: those who are HIV positive; hepatitis B surface antigen (HBs Ag) positive persons undergoing liver transplantation; and those with a history of or currently active autoimmune hepatitis);

Additional Information

Clinical Policy Bulletin Notes

22. Polycythemia vera (PV) when phlebotomy is not effective, not tolerated or contraindicated.

    Note: Failure of phlebotomy may be defined as any of the following:

    - Lack of hematological control (e.g., hematocrit greater than 45 or platelet count greater than 600 x 10(9)/L);
    - Occurrence of intractable symptoms (e.g., headaches, pruritis);
    - Occurrence of symptoms related to hepatosplenomegaly;
    - Occurrence of thrombotic or hemorrhagic complications; *or*
    - Phlebotomy required more often than once every 2 months

23. Renal cell carcinoma;
24. Respiratory papillomatosis;
25. Vulvar vestibulitis

Aetna considers interferon alfa 2a and 2b experimental and investigational for all other indications because it has not been shown to be effective for them:

1. Acute hepatitis B;
2. Age-related macular degeneration;
3. AIDS-related complex;
4. AIDS in combination with AZT;
5. Basal cell carcinoma;
6. Behçet's uveitis;
7. Breast cancer;
8. Cervical cancer;
9. Chickenpox;
10. Cholangiocarcinoma;
11. Chronic delta hepatitis;
12. Chronic myelogenous leukemia;
13. Colorectal cancer;
14. Cutaneous squamous cell carcinoma
15. Cutaneous warts;
16. Cytomegalovirus (CMV);
17. Familial Mediterranean fever;
18. Gardner syndrome;
19. Hepatocellular carcinoma;

20. Hepatitis D;
21. Hereditary hemorrhagic telangiectasia;
22. Herpes keratoconjunctivitis;
23. Islet cell tumors;
24. Keloids;
25. Mesothelioma;
26. Multiple myeloma;
27. Multiple sclerosis;
28. Osteosarcoma;
29. Ovarian cancer;
30. Pancreatic cancer;
31. Pelvic fibromatosis;
32. Peyronie's disease;
33. Plexiform neurofibroma;
34. Primary cutaneous anaplastic large cell lymphoma with multifocal lesions;
35. Primitive neuroectodermal tumor (PNET);
36. Prostate cancer;
37. Retinal vasculitis;
38. Rhinoviruses;
39. Sjogren's syndrome-associated dry eye;
40. Solitary plasmacytoma;
41. Sudden hearing loss;
42. Systemic light-chain amyloidosis;
43. Systemic lupus erythematosus:
44. Vaccinia;
45. Varicella zoster virus (VZV); *and*
46. Waldenstrom's macroglobulinemia.

Pegylated interferon alfa

I. Hepatitis C

A. Aetna considers the following pegylated interferon alfa (pegylated interferon alfa-2a (Pegasys), pegylated interferon alfa-2b (PegIntron)) regimens for hepatitis C medically necessary for the following indications:

1. Aetna considers pegylated interferon alfa, either as monotherapy or in combination with ribavirin (Rebetol) medically necessary for the treatment of chronic hepatitis C in persons who are interferon naïve or who have relapsed or failed to respond to

prior non-pegylated interferon alfa therapy.

2. Continued treatment with pegylated interferon alfa is considered not medically necessary for persons with HCV genotypes 1 and 4 through 6 who have failed to attain an early virologic response after 12 weeks of therapy. Early virologic response is indicated by achievement of at least a 100-fold (2 log10) decrease in serum HCV RNA from pretreatment baseline.
3. For persons infected with HCV genotype 1 and genotypes 4 through 6 who have attained an early virologic response by 12 weeks of therapy, up to 48 weeks of treatment with pegylated interferon alfa is considered medically necessary.
4. Up to 72 weeks of treatment with pegylated interferon alfa is considered medically necessary for persons with HCV genotype 1 infection who have delayed virus clearance. Delayed virus clearance is indicated by an HCV RNA test becoming negative between weeks 12 and 24.
5. For persons with other HCV genotypes (i.e., genotypes 2 and 3) up to 24 weeks of treatment with pegylated interferon alfa is considered medically necessary.
6. Repeat treatment with pegylated interferon alfa with or without ribavirin without oral antiretrovirals for hepatitis C is considered experimental and investigational for persons who have completed or failed to respond to a therapeutic course of pegylated interferon alfa.
7. Chronic maintenance treatment with pegylated interferon alfa is considered experimental and investigational.
8. Up to 48 weeks of pegylated interferon alfa is considered medically necessary for persons coinfected with HIV and HCV, regardless of HCV genotype, are on stable anti-retroviral therapy, and (for HCV genotypes 1 and 4 through 6 only) have achieved an early virologic response after 12 weeks of therapy.

B. Upon medical review, extended treatment with pegylated interferon alfa beyond these limits may be considered medically necessary for persons with cryglobulinemia and for liver transplant recipients with recurrent hepatitis C infections.
C. See Pharmacy CPB on Hepatitis C for medical necessity criteria for oral and combination oral/pegylated interferon regimens.

Note: See also Aetna Pharmacy Clinical Policy Bulletin (PCPB) on *Hepatitis C for* Daklinza (daclatasvir), Eclusa (sofosbuvir, velpatasvir), Harvoni (sofosbuvir/ ledipasvir), Olysio (simeprevir), Sovaldi (sofosbuvir), Technivie (ombitasvir, paritaprevir, ritonavir), Victrelis (boceprevir), Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir), and Viekira XR (ombitasvir, paritaprevir, ritonavir, dasabuvir).

II. Hepatitis B

A. Peginterferon alfa-2a (Pegasys) is considered medically necessary for the treatment of adult persons with HBeAg positive or HBeAg negative chronic hepatitis B who have compensated liver disease (Child-Pugh score less than or equal to 6 [Class A]) and evidence of viral replication (HBV greater than 500,000 copies per ml for HBeAg positive and HBV greater than 100,000 copies per ml for HBeAg negative) and liver inflammation (serum aminotransferase (AST) greater than the upper limit of normal range (AST normal range 0 to 35 u/l)), and who are interferon naïve or who have relapsed or failed to respond to prior non-pegylated interferon therapy.

B. Treatment of chronic hepatitis B with peginterferon alfa-2a for more than 48 weeks is considered experimental and investigational.

C. Repeat or chronic maintenance treatment with peginterferon alfa-2a is considered experimental and investigational for persons who have completed a therapeutic course of pegylated interferon and ribavirin.

D. Note: Upon medical review, extended treatment with peginterferon alfa-2a beyond these limits may be considered medically necessary for liver transplant recipients with recurrent hepatitis B infections.

III. Essential thrombocythemia

IV. Melanoma (Sylatron-pegylated interferon alfa 2b only)

V. Myelofibrosis - treatment of symptomatic low-risk myelofibrosis

VI. Polycythemia vera (PV) when phlebotomy is not effective, not tolerated, or contraindicated.

Note: Failure of phlebotomy may be defined as any of the following:

- Lack of hematological control (e.g., hematocrit greater than 45 or platelet count greater than 600 x 10(9)/L);
- Occurrence of intractable symptoms (e.g., headaches, pruritis);
- Occurrence of symptoms related to hepatosplenomegaly;
- Occurrence of thrombotic or hemorrhagic complications; *or*
- Phlebotomy required more often than once every 2 months

Aetna considers pegylated interferon alfa experimental and investigational for the following

indications (not an all-inclusive list) because of insufficient evidence of effectiveness:

- Chronic myelogenous leukemia
- Desmoid tumor
- Eosinophilia/hyper-eosinophilic syndrome
- Human papilloma virus
- Osteosarcoma
- Plexiform neurofibroma
- Progressive multi-focal leukoencephalopathy
- Squamous cell carcinoma
- Systemic lupus erythematosus
- Warts

Note: Pegylated interferons are self-administered subcutaneously once-weekly.

Consensus Interferon (Interferon alfacon-1)*

* Note: Infergen (interferon alfacon-1) was discontinued in September 2013.

1. Consensus interferon (Infergen interferon alfacon-1) is considered medically necessary for initial treatment of persons with chronic hepatitis C.
2. Consensus interferon is considered medically necessary for retreatment of chronic hepatitis C who have failed to respond to a complete therapeutic course of pegylated interferon, defined as less than a 2 log decline in viral load after undergoing at least 12 weeks of previous pegylated interferon plus ribavirin therapy with greater than 80 % adherence, or a detectable viral load at end-of-treatment after completing at least 24 weeks of therapy. Up to 48 weeks of treatment with consensus interferon is considered medically necessary for retreatment. Continued treatment with consensus interferon is considered not medically necessary for persons with a poor response to re-treatment at week 12 (defined as less than 2 log10 reduction in viral load from baseline) or persons who have detectable virus at week 24.
3. Use of consensus interferon for persons with hepatitis C who have failed to respond or relapsed after an adequate course of standard alfa interferon is considered experimental and investigational. Although there is limited evidence regarding the use of consensus interferon in persons with hepatitis C who have relapsed or failed to respond to standard alfa interferon therapy, current guidelines indicate pegylated interferons as the treatment of choice for persons with hepatitis C, including those who relapsed or failed to respond to standard alfa interferon therapy. There is insufficient evidence in the peer-reviewed published medical literature comparing

consensus interferon to pegylated interferons in persons with hepatitis C who have failed standard interferon therapy.

4. Repeat or chronic (more than 48 weeks) maintenance treatment with consensus interferon is considered experimental and investigational because there is insufficient evidence to show that repeat or prolonged therapy has a clinically significant impact on long term outcomes.
5. Consensus interferon is considered experimental and investigational for all other indications.

Interferon beta

Aetna considers Rebif (interferon beta-1a) monotherapy medically necessary for the treatment of relapsing/remitting multiple sclerosis (MS) in members who meet all of the conditions described below.

Aetna considers Avonex (interferon beta-1a), Plegridy (peginterferon beta-1a), Betaseron or Extavia (interferon beta-1b) monotherapy medically necessary for the treatment of relapsing/remitting MS in members who meet all of the conditions described below, and who have a contraindication, allergy, intolerance, or failure of a 1-month trial of glatiramer acetate, plus have a contraindiction, allergy, intolerance or failure of 1-month trials of both Rebif and fingolimod (Gilenya).

Member meets either of the following criteria for clinically definite or laboratory supported definite MS:

1. Clinically definite MS is defined as either:

   - Two attacks and clinical evidence of 2 separate lesions; *or*
   - Two attacks; clinical evidence of 1 lesion and para-clinical evidence of another, separate lesion

2. Laboratory-supported definite MS consists of demonstration of any of the following:

   - Two attacks; either clinical or para-clinical evidence of 1 lesion; and cerebro-spinal fluid (CSF) OB/IgG*; *or*
   - One attack; clinical evidence of 2 separate lesions; and CSF OB/IgG*; *or*
   - One attack; clinical evidence of 1 lesion and para-clinical evidence of another separate lesion; and CSF OB/IgG*

*CSF OB/IgG is defined as either:

- IgG oligoclonal band (OB) in the CSF; *or*
- Increased CNS synthesis of IgG (IgG is higher in CSF than in serum, and is increased in the CSF in the presence of a normal concentration of total protein).

Limits: Oligoclonal bands must not be present in the member's serum and the serum IgG level must be normal.

Aetna considers interferon beta medically necessary for treatment of persons with clinically isolated syndromes who are at high-risk of developing MS.

Aetna considers use of interferon beta in combination with other disease modifying treatments (Tysabri, Copaxone, Glatopa, Gilenya, Aubagio, or Tecfidera) experimental and investigational because there is a lack of reliable evidence that interferon beta in combination with other disease modifying treatment is more effective than interferon beta alone.

Aetna considers interferon beta experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established (not an all-inclusive list):

- Chronic inflammatory demyelinating polyradiculoneuropathy
- Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)
- Guillain Barre syndrome
- Pancreatic cancer
- Systemic lupus erythematosus

Aetna considers testing for neutralizing antibodies to interferon beta experimental and investigational (see CPB 0264 - Multiple Sclerosis (../200_299/0264.html)).

Notes: Interferon beta, fingolimod (Gilenya) and glatiramir acetate (Copaxone, Glatopa) are first-line treatments for multiple sclerosis. There are several brands of interferon beta on the market. There is a lack of reliable evidence that any one brand of interferon beta is superior to other brands for relapsing-remitting multiple sclerosis. Rebif (interferon beta-1a) brand of interferon beta ("least cost brand of interferon beta") is less costly to Aetna. Consequently, because other brands (Avonex (interferon beta-1a), Plegridy (peginterferon beta-1a), Betaseron (interferon beta-1b), and Extavia (interferon beta-1b)) are more costly than the least

cost brand of interferon beta, and the least cost brand of interferon beta is at least as likely to produce equivalent therapeutic results, no other brands of interferon beta will be considered medically necessary unless the member has a contraindication, allergy, intolerance or failure of an adequate trial of the least cost brand of interferon beta plus an adequate trial of glatiramer acetate and fingolimod.

Glatopa brand of glatiramer acetate is less costly to Aetna than Copaxone brand of glatiramer acetate, and is likely to produce equivalent therapeutic results. Therefore, Copaxone will be considered medically necessary only if the member has a contraindication, allergy, intolerance, or failure of an adequate trial of Glatopa.

For purpose of this policy, failure of an adequate trial of multiple sclerosis treatment is defined as follows:

- The member has increasing relapses (defined as two or more relapses in a year, or one severe relapse associated with either poor recovery or MRI lesion progression); or
- The member has lesion progression by MRI (increased number or volume of gadolinium-enhancing lesions, T2 hyperintense lesions or T1 hypointense lesions); or
- The member has worsening disability (sustained worsening of Expanded Disability Status Scale (EDSS) score or neurological examination findings).

Intolerance is defined as intolerable side effects despite optimized management strategies.

Because interferon beta is administered subcutaneously or intramuscularly, it is appropriate for administration by the member in the home setting.

The Biojector 2000 (Bioject, Inc.) is a needle-free injection system that uses CO2 as the power source and disposable needle-free syringes to deliver medication in a fraction of a second through a tiny orifice. Biojector 2000 is considered a medically necessary acceptable alternative to conventional needle and syringes for members with exacerbating-remitting MS who can not safely use needles for self-injection due to tremors and decreased coordination.

See also CPB 0264 - Multiple Sclerosis (../200_299/0264.html).

Interferon alfa-N3 (Alferon)

Aetna considers interferon alfa-N3 (Alferon N) medically necessary for intralesional treatment of refractory or recurring external condylomata acuminata (venereal/genital warts). Aetna considers interferon alfa-N3 experimental and investigational for all other indications.

Interferon gamma

Aetna considers interferon gamma medically necessary for the following indications:

1. Chronic granulomatous disease, to reduce the frequency and severity of infections; *or*
2. Chronic recalcitrant atopic dermatitis; *or*
3. Mycosis fungoides and Sezary syndrome; *or*
4. Severe, malignant osteopetrosis, to delay time to disease progression.

Aetna considers interferon gamma experimental and investigational for the treatment of the following (not an all-inclusive list) because its effectiveness for indications other than the ones listed above has not been established:

- Brain tumors
- Idiopathic pulmonary fibrosis
- Juvenile idiopathic arthritis
- Macrophage activation syndrome
- Malignant neoplasm of peritoneum
- Pancreatic cancer
- Pulmonary tuberculosis
- Systemic lupus erythematosus
- Waldenstrom's macroglobulinemia.

Background

Interferons are biological response modifiers that are indicated in the treatment of numerous malignant and infectious disease conditions. Interferons are proteins secreted in response to viral infection through binding at specific membrane receptors on the cell surface. Binding results in induction of certain enzymes, suppression of cell proliferation, enhancement of the phagocytic activity of macrophages, augmentation of specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

Interferons bind to specific cell surface receptors and initiate a sequence of intracellular events that lead to the transcription of interferon-stimulated genes. The three major groups of interferons (alfa, beta, and gamma) have partially overlapping biological activities that include immunoregulation such as increased resistance to microbial pathogens and inhibition of cell proliferation. Type 1 interferons (alfa and beta) bind to the alfa/beta receptor. Interferon-gamma binds to a different cell surface receptor and is classified as Type 2 interferon. Specific effects

of interferon-gamma include the enhancement of oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity (ADCC), activation of natural killer (C+NK) cells, and the expression of Fc receptors and major histocompatibility antigens.

Interferon alfa products (Roferon; Intron-A; Alferon; Infergen) have been granted orphan-drug status by the Food and Drug Administration (FDA) for several types of malignancies and viral infections and have unlabeled uses for several others. Although the efficacy of all alfa interferons (e.g., interferon alfa 2a, alfa 2b, alfa-n3, and alfacon-1) for various indications appear to be similar, differences in relative efficacy for a particular indication may exist. Interferon alfa should be used with caution in patients with pre-existing psychiatric conditions or a history of severe psychiatric disorders. According to the product labeling, depression, confusion, and other alterations of mental status have been observed in some patients and suicidal ideation and attempted suicide have been observed rarely.

A Cochrane evidence review of treatments for herpes simplex eye disease (Wilhelmus, 2007) found that the combination of interferon-alfa eye drops and either trifluridine or acyclovir resulted in faster healing of dendritic keratitis than treatment with trifluridine or acyclovir alone; 90 % of eyes healed within 1 week with combined interferon-antiviral therapy.

Intron-A

Intron A (interferon alfa-2b) is a recombinant alfa interferon (IFN).

The NCCN Drug and Biologics Compendium (2017) recommends Intron A for the following indications:

- Therapy of giant cell tumor of the bone as a
  - single agent or combined with denosumab or radiation therapy for localized disease
  - single agent for metastatic disease
- Intracerebrospinal fluid (CSF) treatment for leptomeningeal metastases
  - as induction therapy for primary treatment of good-risk patients with normal CSF flow
  - as maintenance therapy for patients with negative CSF cytology or for clinically stable patients with persistently positive CSF cytology
  - as postinduction therapy for patients with positive CSF cytology
- Treatment for surgically inaccessible recurrent or progressive meningiomas when

further radiation is not possible

- Kidney cancer - First-line therapy in combination with bevacizumab for relapse or stage IV disease with predominant clear cell histology
- Melanoma
  - Intralesional therapy for primary and/or second-line treatment of
    - unresectable stage III disease with clinical satellite or in-transit metastases
    - unresectable local, satellite and/or in-transit recurrence
  - Adjuvant treatment in combination with interleukin-2, dacarbazine, cisplatin, and vinblastine following
    - wide excision of primary tumor and a complete therapeutic lymph node dissection for stage III disease with clinically positive node(s)
    - complete lymph node dissection and/or complete resection of nodal recurrence
  - Adjuvant treatment as a single agent
    - for stage IIB or C disease following wide excision
    - for stage III sentinel node positive disease following lymph node dissection
    - for stage III disease with clinically positive node(s) following wide excision of primary tumor and a complete therapeutic lymph node dissection
    - for stage III disease with clinical satellite or in-transit metastases if no evidence of disease post-surgery
    - for local, satellite and/or in-transit recurrence if no evidence of disease post-surgery
    - following complete lymph node dissection and/or complete resection of nodal recurrence
  - Therapy for metastatic or unresectable disease in combination with interleukin-2, and dacarbazine or temozolomide, and cisplatin or carboplatin, with or without vinblastine or a nitrosourea (carmustine or lomustine) as second-line or subsequent therapy for disease progression or after maximum clinical benefit from BRAF targeted therapy for patients with performance status 0-2
- Myeloproliferative Neoplasms - Primary Myelofibrosis and Post-PV or Post-ET MF - Treatment of symptomatic low-risk myelofibrosis
- Neuroendocrine Tumors of the GI Tract, Lung, and Thymus - Management of clinically significant locoregional unresectable or metastatic progressive disease
- Adult T-Cell Leukemia/Lymphoma -

- Used in combination with zidovudine for chronic, smoldering, or acute disease as
  - first-line therapy
  - additional therapy following response to first-line therapy
  - additional therapy for acute disease in nonresponders if not previously received
- Second-line therapy in combination with arsenic trioxide for nonresponders to first-line therapy for acute disease or lymphoma or as subsequent therapy after high dose therapy/autologous stem cell rescue (HDT/ASCR)

- Hairy Cell Leukemia - Single-agent therapy in patients with indication for treatment for
  - refractory disease
  - relapse within one year of complete response

- Mycosis Fungoides (MF)/Sezary Syndrome (SS)
  - Systemic biologic therapy as a
    - single agent or in combination with skin-directed therapy for stage I-IIA and stage III MF with blood involvement
    - single agent or in combination with skin-directed therapies for stage IB-IIA MF with histologic evidence of folliculotropic or large cell transformation or stage IIB MF with limited tumor lesions
    - single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids) for stage IB-IIB MF with histologic evidence of folliculotropic or large cell transformation, or stage IIB MF with generalized tumor lesions, with or without skin-directed therapy
    - as a single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids) for SS
  - May be used as adjuvant systemic biologic therapy after total skin electron beam therapy for stage IIB MF generalized tumor lesions, or after chemotherapy for stage IV non-Sezary or visceral disease
  - Systemic biologic therapy as a single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids), with or without skin-directed therapy for stage I-III MF which has progressed or is refractory to multiple previous therapies

- Desmoid Tumors (Aggressive Fibromatosis) - Low-dose single agent for primary,

recurrent, or progressive disease as

- initial treatment for resectable disease
- adjuvant treatment for gross residual disease
- initial treatment for unresectable disease or for disease for which surgery would be unacceptably morbid.

The NCCN Drug and Biologics Compendium also has a Category 3 recommendation for use of Intron A as single-agent therapy for primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions or cutaneous ALCL with regional nodes (excludes systemic ALCL) as

- primary treatment
- therapy for relapsed or refractory disease.

Extensive study of alfa interferons in combination with 5-fluorouracil (5-FU) for the treatment of colorectal cancer has shown no benefit over 5-FU therapy alone. In 1986, the FDA approved interferon alfa-2b for the treatment of hairy cell leukemia. An extended release formulation of interferon alfa-2b (PEG-Intron) has been approved by the FDA. Use of peginterferon alfa with ribavirin is recommended in consensus guidelines for the treatment of chronic hepatitis C.

Alfa interferons, including Intron A, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.

Safety and efficacy in pediatric members < 3 years of age have not been established other than for chronic hepatitis B or hepatitis C.

In an interventional, comparative case series, Lane and colleagues (2009) examined if interferon (IFN)-alfa-2a treatment after radiation or enucleation reduces death rates in patients with uveal melanoma. Patients were identified through the ocular oncology clinic of the Massachusetts Eye and Ear Infirmary. Subjects eligible for the study were at increased risk of metastasis because of the presence of at least 1 of the following characteristics: (i) age greater than or equal to 65 years, (ii) largest tumor diameter (LTD) greater than or equal to 15 mm, (iii) ciliary body involvement of the tumor, or (iv) extra-scleral tumor extension. A total of 121 patients with choroidal or ciliary body melanoma began a 2-year course of therapy (3 million inernational units [MIU] IFN-alfa-2a subcutaneously 3 times per week), initiated within 3 years of primary therapy. All patients underwent regular monitoring for drug toxicity. To evaluate IFN-alfa-2a efficacy, these researchers selected a series of historical controls frequency-matched (2:1) to IFN-alfa-2a-treated patients on age (+/- 5 years), LTD (+/- 3 mm), gender, and survival time between primary therapy and initiation of IFN therapy. Survival status was

ascertained for all patients. Main outcome measures were melanoma-related mortality, metastasis, IFN-related toxicities. A total of 55 patients (45 %) completed therapy; the median dose for IFN-alfa-2a-treated patients was 792 MIU (85 % of the theoretic dose). The median follow-up time in the IFN-alfa-2a-treated group was approximately 9 years. Treatment and control groups were similar with respect to age (p = 0.78), LTD (p = 0.38), and gender (p = 1.0). Of 363 patients, 108 developed metastasis under observation; 42 of these were IFN-alfa-2a-treated patients. Cumulative 5-year melanoma-related death rates were 17 % in the radiation or enucleation-only group, 15 % in those who completed the entire IFN-alfa-2a course, and 35 % in those who discontinued IFN-alfa-2a therapy. In multi-variate Cox regression, IFN-alfa-2a had no significant influence on melanoma-related mortality (rate ratio = 1.02, 95 % confidence interval [CI]: 0.68 to 1.5, p = 0.91) or all-cause mortality (rate ratio = 0.84, 95 % CI: 0.58 to 1.2, p = 0.34). The authors concluded that interferon-alfa-2a has no material influence on survival in patients with choroidal melanoma.

Alferon N (interferon alfa-n3)

Alferon N (interferon alfa-n3) is a formulation of purified, natural, human interferon (IFN) alfa proteins derived from human leukocytes.

Interferon alfa-n3 acts similarly to native interferon alfa. Endogenous alfainterferons (IFNs) are secreted by leukocytes (e.g., macrophages, B lymphocytes, and non-B non-T lymphocytes) in response to viral infection or various synthetic and biological inducers. All alfa-IFNs share common biologic activities generated by the binding of interferon to the cell-surface receptor. Although the exact mechanism of action is not fully understood, interferon binding to the cell surface receptor is followed by activation of tyrosine kinases, which leads to the production of several IFN-stimulated enzymes such as 2'-5'-oligoadenylate synthetase (2'-5'-OAS) and beta2-microglobulin. These and possibly other IFN-stimulated enzymes are thought to be responsible for the pleiotropic biologic effects of alfa-IFNs, which include antiviral, antiproliferative and immunomodulatory effects, cellular differentiation, regulation of cell surface major histocompatibility antigen expression (HLA class I), and cytokine induction.

Alferon N (interferon alfa-n3) is indicated for the intralesional treatment of refractory or recurring external condylomata acuminata in patients 18 years of age or older.

Genital warts usually begin to disappear after several weeks of treatment with Alferon N. Treatment should continue for a maximum of 8 weeks. In clinical trials with Alferon N, many patients who had partial resolution of warts during treatment experienced further resolution of their warts after cessation of treatment. Of the patients who had complete resolution of warts due to treatment, half the patients had complete resolution of warts by the end of the treatment

and half had complete resolution of warts during the 3 months after cessation of treatment.

Alferon N is contraindicated in patients with known hypersensitivity to human interferon proteins or any component of the product, anaphylactic hypersensitivity to mouse immunoglobulin, egg protein, or neomycin.

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

Alferon N 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. However, if such reactions develop, drug administration should be discontinued immediately and appropriate medical therapy should be instituted.

The American Association for the Study of Liver Diseases (AASLD) recommends a peginterferon alfa product as the preferred interferon therapy for chronic hepatitis C infection.

PegIntron

PegIntron, peginterferon alfa-2b powder for injection, either alone or in combination with ribavirin (Rebetol), is an alternative to standard interferon alfa plus ribavirin for treatment of chronic hepatitis C. PegIntron is a covalent conjugate of recombinant alfa interferon with monomethoxy polyethylene glycol (PEG). It offers an alternative to patients in whom combination therapy may be a contraindication or who are intolerant of this therapy. The drug is self-administered subcutaneously once-weekly by patients and, therefore, is more convenient to use than the standard interferon alfa, which is injected 3 times weekly. Studies of combination therapy with weekly PegIntron and daily ribavirin (Rebetol) reported that this combination was somewhat more effective than alfa interferon (Intron A) with Rebetol. Twenty-four weeks after treatment ended, 52 % of patients who received the PegIntron combination had undetectable HCV virus levels in the blood compared to 46 % for the Intron A combination. In patients with genotype 1 virus (a particularly difficult to treat variant of the HCV virus), the difference in sustained responses was 41 % compared to 33 %. PegIntron from Schering-Plough is the first pegylated interferon to have FDA approval in the United States.

PegIntron, as part of a combination regimen, is indicated for the treatment of Chronic Hepatitis C in patients with compensated liver disease. PegIntron in combination with Rebetol (ribavirin) and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor is indicated in adult patients (18 years of age and older) with HCV genotype 1 infection. PegIntron in combination with Rebetol is indicated in patients with genotypes other than 1, pediatric patients (3-17 years of age), or in patients with genotype 1 infection where use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications or other clinical factors.

The American Association for the Study of Liver Disease (AASLD) indicates that an interferon-based treatment for genotype 1, chronic HCV infection in adults 18 years of age and older is the use of an NS3/4A serine protease inhibitor in combination with peginterferon alfa and ribavirin.

PegIntron is contraindicated in: hepatic decompensation (Child-Pugh class B or C) in cirrhotic members before or during treatment; hepatic decompensation (Child-Pugh class B or C) in cirrhotic members co-infected with HIV before or during treatment; autoimmune hepatitis; and kidney, liver, heart, or other solid-organ transplant.

The NCCN Drug and Biologics Compendium (2017) recommends the use of peginterferon alfa-2b (PegIntron) for the following indications:

- Melanoma - Adjuvant treatment as a single agent
  - for stage III sentinel node positive disease following lymph node dissection
  - for stage III disease with clinically positive node(s) following wide excision of primary tumor and a complete therapeutic lymph node dissection
  - for stage III disease with clinical satellite or in-transit metastases if no evidence of disease post-surgery
  - for local, satellite and/or in-transit recurrence if no evidence of disease post-surgery
  - following complete lymph node dissection and/or complete resection of nodal recurrence
- Myeloproliferative Neoplasms - Primary Myelofibrosis and Post-PV or Post-ET MF - Treatment of symptomatic low-risk myelofibrosis.

Use with Ribavirin may cause birth defects and death of the unborn child.

Alfa interferons, including PegIntron, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.

The safety and efficacy in pediatric patients less than 3 years of age has not been established.

Sylatron

Sylatron (peginterferon alfa-2b) is a member of the interferon drug class. It is a covalent conjugate of recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). Although the exact mechanism of Sylatron (peginterferon alfa-2b) effects in melanoma is unknown, interferon-stimulated genes modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation and immunomodulation.

Sylatron (peginterferon alfa-2b) is indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.

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  - for stage III disease with clinical satellite or in-transit metastases if no evidence of disease post-surgery
  - for local, satellite and/or in-transit recurrence if no evidence of disease post-surgery
  - following complete lymph node dissection and/or complete resection of nodal recurrence
- Myeloproliferative Neoplasms - Primary Myelofibrosis and Post-PV or Post-ET MF - Treatment of symptomatic low-risk myelofibrosis.

Sylatron (peginterferon alfa-2b) therapy is not recommended for persons with hepatic decompensation (Child-Pugh score >6 [class B and C]).

The risk of serious depression, with suicidal ideation and completed suicides, and other serious neuropsychiatric disorders are increased with alfa interferons, including Sylatron (peginterferon alfa-2b). Permanently discontinue Sylatron (peginterferon alfa-2b) in patients with persistently severe or worsening signs or symptoms of depression, psychosis, or encephalopathy. These

disorders may not resolve after stopping Sylatron (peginterferon alfa-2b).

Sylatron (peginterferon alfa-2b) should not be used in the following:

- Pediatric patients < 18 years of age because safety and efficacy have not been established.
- Women who are pregnant or lactating and have not been apprised of the potential hazard to the fetus.
- Patients with a history of anaphylaxis to peginterferon alfa-2b or interferon alfa-2.

The NCCN Drugs and Biologics Compendium (2018) lists Sylatron (pegylated interferon alfa-2b) as the only pegylated interferon alfa drug for treatment of melanoma.

Pegasys

Pegasys (peginterferon alfa-2a) is in the interferon alfa therapeutic class. Pegasys (peginterferon alfa-2a) is a covalent conjugate of recombinant alfa-2a interferon with a single branched bis-monomethoxy polyethylene glycol (PEG) chain. Pegasys (peginterferon alfa-2a) is indicated for the treatment of chronic hepatitis C and chronic hepatitis B.

Roche Pharmaceutical's Pegasys (pegylated interferon alfa-2a) has been approved by the FDA for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alfa. Patients in whom efficacy was demonstrated included patients with compensated cirrhosis. Pegasys was granted approval based on the results of 3 phase III clinical trials that demonstrated it is an effective treatment for patients with chronic hepatitis C, including cirrhotic patients with compensated liver disease, versus treatment with Roferon-A (interferon alfa-2a). The sustained virological response rate in the patients treated with pegylated interferon alfa-2a was as high as 38 % in the overall population versus 19 % in the interferon alfa-2a group. The sustained virological response in patients with cirrhosis treated with pegylated interferon alfa-2a was as high as 30 % versus 8 % in the interferon alfa-2a group. Higher sustained virological response results were also found in patients with genotype 1, on pegylated interferon alfa-2a treatment (23 %) versus interferon alfa-2a (6 %), the most common type in the U.S. and most difficult to treat. Sustained virological response was defined as undetectable serum hepatitis C RNA levels post-treatment (on or after study week 68). Pegylated interferon alfa-2a is dosed at 180 µg as a subcutaneous injection once-weekly for a recommended duration of 48 weeks.

Peginterferon alfa-2a (Pegasys) has also been approved by the FDA for treatment of hepatitis C in HIV coinfected persons, whose HIV disease is clinically stable (e.g., anti-retroviral therapy

not required or receiving stable antiretroviral therapy). In studies submitted to the FDA, 868 HCV/HIV coinfected patients were randomized to receive peginterferon alfa-2a plus placebo, peginterferon alfa-2a plus ribavirin, or interferon alfa-2a plus ribavirin (Roche, 2005). All subjects received 48 weeks of therapy, and sustained virologic response was assessed at 24-weeks of treatment free follow-up. All subjects included in the study had compensated liver disease, a CD4+ cell count greater than or equal to 200 cells/μL or CD4+ cell count greater than or equal to 100 cells/μL but less than 200 cells/μL and HIV-1 RNA less than 5,000 copies/ml, and stable status of HIV. Approximately 15 % of patients in the study had cirrhosis. Sustained virologic response was noted in 40 % of subjects treated with peginterferon alfa-2a plus ribavirin, 20 % of patients treated with peginterferon alfa-2a plus placebo ($p < 0.0001$), and 11 % of subjects treated with interferon alfa-2a plus ribavirin ($p < 0.0001$). Of patients who did not demonstrate either either undetectable HCV RNA or at least a 2 log 10 reduceion from baseline in HCV RNA titer by 12 weeks of peginterferon alfa-2a and ribavirin combination therapy, 2 % achieved a sustained virologic response.

There is inadequate evidence for the effectiveness of use of pegylated interferons as maintenance therapy. According to the FDA-approved labeling for pegylated interferons, there are no safety and efficacy data on treatment with pegylated interferons for more than one year.

The NCCN Drug and Biologics Compendium (2017) recommends use of peginterferon alfa-2a (Pegasys) for treatment of low-risk myelofibrosis.

Pegasys is contraindicated in: autoimmune hepatitis; hepatic decompensation (Child-Pugh score >6 [class B or C]) in cirrhotic patients before or during treatment; hepatic decompensation (Child-Pugh score >6) in cirrhotic patients co-infected with HIV before or during treatment.

Pegasys has a boxed warning that it may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.

Use with Ribavirin: May cause birth defects and/or death of the fetus; causes hemolytic anemia and may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

Factors to consider before prescribing Pegasys and during treatment:

The patient must not display any signs or symptoms of jaundice, ascites, active gastrointestinal bleeding, and encephalopathy.

The HCV RNA level must have decreased by at least two log10 units for continuation of therapy for Hepatitis C.

Pegasys is not recommended in patients with known cases of hypersensitivity to peginterferon or any of its components.

The most important pediatric-specific safety issue related to Pegasys/Copegus was growth delay. Pediatric subjects treated with Pegasys/Copegus combination therapy experienced a delay in gaining weight and height after 48 weeks of therapy compared with baseline.

There is a lack of evidence of safety and efficacy of Pegasys in children less than 5 years of age.

Laboratory Tests:

Eye exam: Pre-treatment. If pre-existing ophthalmologic disorder-periodic exams during therapy.

Hematological tests (Hemoglobin or hematocrit levels): Pre-treatment and at Week 2 and 4 of therapy, or more frequently if clinically indicated.

Renal function: Monitor periodically with elderly population (>65 years of age). If creatinine clearance <50 mL/min—discontinue ribavirin.

Hepatitis C

Hepatitis C is an inflammation of the liver caused by the hepatitis C virus (HCV). Hepatitis C is one of the most common causes of chronic liver disease in the U.S. Hepatitis is a single stranded RNA virus. HCV is classified into six major genotypes, numbered 1 to 6. In the United States the most common genotypes are 1a and 1b. Hepatitis C is one of the top causes for liver transplantation. The goal of treating hepatitis C is to prevent complications associated with this infection, which is principally achieved by eradication of infection.

Although HCV has 6 genotypes labeled 1 through 6, there are also subtypes labeled with letters (e.g., 1a and 1b). People infected with HCV usually have a single, dominant genotype; however, it is possible to have more than one at the same time, called mixed infection (e.g., 1a and 2). All HCV genotypes cause the same amount of liver damage. However, people infected with genotype 1, particularly subtype 1b, may have a greater chance of developing cirrhosis. Genotypes 1b and 3 may increase the risk of liver cancer (AASLD and IDSA, 2017; TAG,

2017).

Clinical trials of pegylated interferon alfa-2a have shown that patients with HCV genotypes 1 and 4 can determine at 12 weeks if they are unlikely to attain an early virological response with pegylated interferon alfa-2a. According to an NIH Consensus Statement on Hepatitis C (1997; 2002), 12 weeks after beginning an initial course of therapy, patients who are unlikely to respond to that dosage and frequency can be identified by persistent elevation of serum ALT levels and presence of HCV RNA in the serum. In this situation, therapy should be discontinued because the likelihood of future response is extremely low. If HCV RNA is below the detection level of the assay or if there is at least a 2 log10 reduction in the HCV RNA titer from baseline, therapy should be continued for an additional 36 weeks. Non-responders should be encouraged to participate in clinical trials directed toward this difficult-to-treat group.

According to guidelines from the National Institute for Health and Clinical Excellence (NICE, 2004), people infected with HCV of genotype 1, 4, 5 or 6, should initially be treated for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1 % of its level at the start of treatment (at least a 2-log reduction) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1 % of its level at the start of treatment, treatment should be discontinued. These guidelines note that people infected with more than one genotype that includes one or more of genotypes 1, 4, 5, or 6 should be treated as for genotype 1 (NICE, 2004; see also Hadziyannis et al, 2004; NIH, 2002). These guidelines are based upon the observation that the SVRs for patients infected with HCV genotype 1 are much lower than those for genotypes 2 and 3, whereas SVRs for genotypes 4, 5 and 6 appear to be between those of the more prevalent genotypes.

Guidelines from the American Association for the Study of Liver Diseases (Ghany et al, 2009) state that "for patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks (Class IIa, Level B)." The strategy of extending therapy in naive subjects with delayed virological responses, defined as clearance of HCV RNA between weeks 12 and 24, was evaluated in two studies (Berg et al, 2006; Sanchez-Tapias et al, 2006). One study randomized subjects to either 48 or 72 weeks of treatment at week 12 if HCV RNA remained detectable (Pearlman et al, 2007), and the other was a post-hoc analysis of a study in which randomization of treatment duration occurred at baseline (Berg et al, 2006). The study populations were not homogeneous, differing in their baseline characteristics and the regimens utilized were different. Nevertheless, the results showed a trend toward a higher SVR rate by extending therapy from 48 to 72 weeks. The SVR rate increased from 18 % for 48 weeks treatment to 38 % for 72 weeks of treatment in one study (Pearlman et al, 2007) and 17 % to 29 % in the other study (Berg et al, 2006). The increased SVR was primarily due a lower

relapse rate in the patients treated for 72 weeks. An additional study demonstrated that patients who failed to achieve an RVR (HCV RNA detectable at treatment week 4) also seemed to benefit from extending therapy from 48 to 72 weeks (Sanchez-Tapias et al, 2006). The SVR rates were significantly higher in patients who received treatment for 72 (45 %) compared to those treated for 48 weeks (32 %). It is clear that not all patients will benefit from extended therapy judging from the results of the trial in which randomization to 48 or 72 weeks of therapy occurred at baseline (Berg et al, 2006). No difference in SVR rates was observed between those treated for 48 compared to 72 weeks (53 % versus 54 %, respectively). Thus, prolonging therapy can be considered in patients who are slow to respond (clearance of HCV RNA between weeks 12 and 24) (Ghany et al, 2009). Further studies are needed to determine whether extended therapy would be beneficial to patients who fail to clear virus between weeks 4 and 12.

For persons with other HCV genotypes (i.e., genotypes 2 and 3), there is no proven benefit to extending therapy beyond 24 weeks (Hadziyannis et al, 2004; NIH, 2002; NICE, 2004).

Infection with hepatitis C virus (HCV) genotype 6 is common in patients from parts of China and Southeast Asia. There is limited evidence regarding the appropriate duration of therapy for persons with genotype 6. Fung et al (2008) evaluated the effectiveness of pegylated interferon plus ribavirin for the treatment of chronic infection with hepatitis C virus (HCV) genotype 6 compared to genotype 1. Forty-two patients chronically infected with HCV were treated with pegylated interferon combined with oral ribavirin for 48 weeks. The investigators found no difference between genotypes 1 and 6 in the rates of early virological response (76 % versus 81 %) and end-of-treatment response (71 % versus 81 %). Patients infected with genotype 6 had a higher SVR than did patients infected with genotype 1 (86 % versus 52 %). The overall adverse-effects profile was similar in both genotype groups. The investigators concluded that treatment with pegylated interferon and ribavirin for 48 weeks resulted in a significantly higher rate of SVR in patients infected with genotype 6 than in those infected with genotype 1. This suggests that the response of HCV genotype 6 to pegylated interferon is more similar to that for genotypes 2 and 3 than for genotypes 1 and 4. The investigators stated that further studies are required to determine whether lower dosages and 24 weeks of therapy may be sufficient for the treatment of genotype 6 infection. The findings of a higher SVR with interferon treatment in persons infected with genotype 6 versus genotype 1 was also found in an earlier study of standard interferon plus ribavirin (Yuen and Lai, 2006).

Nguyen et al (2004) reported on a retrospective study of 190 consecutive Asian-American patients who were diagnosed with HCV genotype 6 at a gastroenterology clinic in northern California between 2001 and 2004, 66 of whom were treatment-naïve and subsequently completed 24 weeks of interferon plus ribavirin or pegylated interferon plus ribavirin, or 48

weeks of pegylated interferon plus ribavirin therapy. These investigators found no statistical difference in SVR of 31 patients treated with 24 weeks of interferon plus ribavirin and in 23 patients treated with 24 weeks of pegylated interferon plus ribavirin (51.6 % versus 39 %, p = 0.363). The SVR in 12 patients treated with 48 weeks of pegylated interferon plus ribavirin was significantly higher than that in those treated for only 24 weeks (75 % versus 39 %, p = 0.044). The investigators concluded that treatment-eligible patients with HCV genotype 6 should be treated with a full course of 48 weeks as tolerated. The investigators noted that larger prospective studies of patients with HCV genotype 6 are needed to confirm the optimal treatment duration with pegylated interferon plus ribavirin.

Data are scarce on patients infected with hepatitis C virus of genotype 5, due to the low prevalence of this genotype around the world. Antaki et al (2008) reported on a retrospective study of treatment outcomes of 26 HCV genotype 5 patients who had completed a course of therapy and a 6-month follow-up. Treatment consisted of ribavirin plus standard or pegylated interferon. Patients were treated for 24 or 48 weeks. The investigators reported that an SVR was achieved in 54 % (47 % with standard interferon and 67 % with pegylated interferon, p = 0.43). A trend towards better results was observed for younger patients, low viremia and mild fibrosis. The investigators reported that SVR was similar for treatment course of 24 or 48 weeks. The investigators concluded that treatment of HCV genotype 5 with combination therapy resulted in SVR in 54 % of patients. The investigators stated that 24 weeks of treatment might be adequate, and that further research should evaluate the ideal duration of treatment.

The NIH Consensus Conference on Hepatitis C (2002) stated: “Failure to respond to optimal therapy with pegylated interferon and ribavirin presents a significant problem, particularly in the presence of advanced fibrosis or cirrhosis. Currently, several large-scale, multi-center U.S. trials are evaluating the role of maintenance therapy with pegylated interferon alone in preventing further progression of cirrhosis, clinical decompensation, or development of HCC. Until the results of these studies are available, the role of long-term, continuous therapy with pegylated interferon (or ribavirin or both) for non-responders should be considered experimental.”

Patients without initial responses to peginterferon and ribavirin did not benefit from long-term low-dose peginterferon therapy in the HALT-C trial.

The HALT-C trial found that patients without initial responses to peginterferon and ribavirin did not benefit from long-term low-dose peginterferon therapy (Di Bisceglie et al, 2008). In this multi-center study, 1,050 patients with chronic hepatitis C and advanced fibrosis who had not responded to previous treatment were randomized to receive maintenance therapy with weekly

peginterferon alfa-2a or no therapy for 3.5 years. Patients were seen every 3 months and underwent liver biopsies at baseline and 1.5 and 3.5 years after randomization. The criteria for the primary outcome -- progression of liver disease -- varied according to whether patients had cirrhosis or noncirrhotic fibrosis at baseline. Maintenance therapy was associated with significant decreases in aminotransferase and hepatitis C virus RNA levels, but it did not influence the likelihood of disease progression, which was about 34 % in each group (hazard ratio, 1.01). Serious adverse events occurred in 39 % of peginterferon recipients versus 32 % of untreated patients (p = 0.07). Commenting on this study, Baddour (2008) said that long-term low-dose peginterferon does not reduce the rate of disease progression and may increase the risk for serious adverse events in patients with failure on initial regimens. "Based on these data, the continued use of peginterferon in this setting cannot be recommended."

The impact of interferon (IFN) treatment on the occurrence of complications related to HCV-related cirrhosis is controversial since the majority of studies are retrospective. In a randomized controlled trial, Fartoux et al (2007) compared the effectiveness of prolonged IFN alfa-2a treatment versus non-treatment on complication-free survival in patients with compensated HCV cirrhosis. A total of 102 patients (mean age of 60.5 +/- 9.5 years; male/female ratio, 0.82) with biopsy examination-proven HCV cirrhosis, Child-Pugh score A, who were hepato-cellular carcinoma (HCC) free, and had at least 1 risk factor of complications, were randomized to receive IFN or no therapy for 24 months. During the follow-up evaluation, the complication rate was 24.5 %: HCC occurred in 12 and decompensation unrelated to HCC occurred in 13 patients. The number of HCC patients was similar in both groups. The probability of complication-free survival was not significantly different between treated and untreated patients (98 % and 72.3 % versus 90 % and 70.7 % at 12 and 24 months, respectively, p = 0.59). The median time until complication occurrence was 17.1 months in the treated group versus 13.6 months in the untreated group (p = 0.2). The authors concluded that this randomized controlled trial showed that a 2-year course of IFN has little or no impact on complication-free survival in patients with high-risk compensated HCV cirrhosis.

A technology assessment of ribavirin and pegylated interferon in hepatitis C for the Wessex Institute for Health Research and Development (Shepherd et al, 2004) noted that cryoglobulinemia and vasculiitis occurs in a minority of patients with hepatitis C, and these conditions are not likely to be the subject of clinical trials because of the relatively small number of patients affected. The report noted, however, that clinicians point out that in some patients with vasculitis due to viral/antibody complexes the vasculitis can resolve after long-term treatment. The report stated that appropriate treatment of such patients needs to be addressed.

HCV-related liver cirrhosis is the most common indication for liver transplantation in most

transplant centers. However, recurrence of hepatitis C-infection after liver transplant in HCV positive patients is almost universal (Neumann and Neuhaus, 2004). Severity of graft hepatitis increases during the long term follow-up and up to 30 % of patients develop severe graft hepatitis and cirrhosis. This led to decreased patient and graft survival in HCV positive patients. Prophylactic or therapeutic regimens which alter the course of disease in HCV positive patients are not established yet. Anti-viral treatment with ribavarin in combination with pegylated interferon is being investigated to reduce the complications of HCV recurrence in the future (Triantos et al, 2005). Treatment of recurrent hepatitis C virus after liver transplantation with either interferon or interferon and ribavirin has yielded only limited success (Shiffman et al, 2003; Triantos et al, 2005). Regardless of this, treatment is instituted. Pegylated interferon is more effective than standard interferon for treatment of chronic hepatitis C virus infection in the non-transplantation setting when used either alone or with ribavirin. The effectiveness of peginterferon, both with and without ribavirin in the posttransplantation setting, is currently being explored.

Triantos et al (2005) reported on the results of a systematic evidence review of anti-viral therapy for HCV in liver transplant recipients. The authors concluded that anti-viral therapy for recurrent HCV infection and disease after liver transplantation has only been evaluated in 16 randomized studies (534 patients) and thus robust data to evaluate efficacy is scanty. However it is clear from both randomized and the 74 non-randomized (2,061 patients) that treatment is far less effective and with more side effects than for chronic HCV hepatitis pre-transplant. Moreover, the data concerning combinations of either interferon or pegylated interferon with ribavirin mainly reflect on treatment virologic response (OTVR) (maximum 36 %) or end of treatment virologic response (ETVR) (maximum 32 %) with very little data on sustained virologic response (SVR). Thus, the authors concluded, currently there is no easily applicable, nor reasonably effective, anti-viral therapy for HCV recurrence after liver transplantation, considering the frequency of side effects and need to reduce doses or to discontinue therapy. The most applicable strategy is to treat established disease with pegylated interferon and ribavirin but only future results of ongoing randomized studies will define the cost-effectiveness and applicability of this regimen. The authors noted that the number of patients who have already failed antiviral therapy pretransplant may well further limit the likelihood of sustained viral clearance. Most importantly data on stopping the progression of fibrosis or slowing it down significantly, are not available and unfortunately initial results are not promising.

Consensus guidelines from the from the International Liver Transplantation Society Expert Panel on Liver Transplantation and HCV (Wiesner et al, 2003) state that “[a]lthough no firm recommendations can be made based on data, there are enough anecdotal and single center reports that suggest that a patient with recurrent HCV disease who has grade II fibrosis or

higher should be given a trial of combination therapy with interferon." Regarding maintenance therapy in liver transplant recipients with recurrent HCV diseases, the Expert panel agreed that there were no data to recommend maintenance therapy as an approach. Regarding the role of preemptive therapy in liver transplant recipients prior to HCV recurrence, the Expert panel stated that preemptive therapy should be considered in patients who undergo retransplantation for rapidly progressive recurrent hepatitis C and HCV-negative transplant recipients who receive organs from HCV-positive donors because of great clinical need. The Expert panel noted, however, that "demonstration of efficacy is lacking at this time."

Hepatitis B

Hepatitis B can cause both acute and chronic infection. Hepatitis B is one of the world's most common infectious pathogens. HbeAG-positive chronic hepatitis is characterized by high levels of viremia and persistently or intermittently increased ALT levels. If untreated, the majority of patients will maintain high HBV replication and active liver inflammation.

HbeAG-negative chronic hepatitis is characterized by persistent HVB replication, lower viermia and progressive inflammation and fibrosis of the liver. A spontaneous remission of HbeAG-negative hepatitis is rare and this type of hepatitis B is associated with poor response to therapy.

The goals of treating hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. There are three key guidelines used for the treatment of hepatitis B. The European Association for the study of liver (EASL) recommends the use of IFNα as first line drug therapy. The American Association for the Study of Liver Diseases (AASLD) recommends lamivudine and adefovir as first line drug therapy. The Asia-Pacific Association for Study of the Liver (APASL) another European guidelines, list lamivudine, adefovir, IFNα, and Peg IFNα, all as first line therapy drug therapy options.

The safety and effectiveness of peginterferon alfa-2a (Pegasys) for the treatment of chronic hepatitis B was assessed in 2 phase III controlled clinical trials in HBeAg positive and HBeAg negative patients with hepatitis B. In each study, patients were randomized to peginterferon alfa-2a 180 µg subcutanelusly once-weekly, lamivudine 100 mg once-daily, or both peginterferon alfa-2a plus lamivudine. All patients received 48 weeks of their assigned therapy followed by 24 weeks of treatment-free follow-up. These 2 clinical trials demonstrated that 24 weeks after a defined 48 week period of therapy, more patients achieved a sustained response with peginterferon alfa-2a than with lamivudine (Epivir). These studies demonstrated that the addition of lamivudine to peginterferon alfa-2a did not improve response rates over peginterferon alfa-2a alone.

All patients included in these studies of peginterferon alfa-2a for chronic hepatitis B virus (HBV) infection were adults with compensated liver disease and evidence of HBV replication (serum HBV greater than 500,000 copies/ml for the study of HBeAg positive patients and serum HBV greater than 100,000 copies/ml for the study of HBeAg negative patients). All patients had serum alanine aminiotransferase (ALT) between 1 and 10 times the upper limit of normal and liver biopsy findings compatible with the diagnosis of chronic hepatitis.

In a study of HBeAg positive patients with chronic HBV infection, 32 % of 271 patients treated with peginterferon alfa-2a seroconverted by the end of follow-up versus 19 %sero-conversion among 272 patients treated with lamivudine. Subjects treated with peginterferon alfa-2a had a higher rate of DNA response (defined as less than 100,000 copies per ml) (32 %) by the end of follow-up than subjects treated with lamivudine (22 %). In a study of HBeAg negative patients with chronic HBV infection, 43 % of 177 patients treated with peginterferon alfa-2a exhibited a HBV DNA response (defined as less than 20,000 copies per mL) by the end of follow-up versus 29 % of 181 patients treated with lamivudine. Subjects treated with peginterferon alfa-2a had a higher rate of ALT normalization (59 %) by the end of follow-up than subjects treated with lamivudine (44 %). Conclusions regarding comparative efficacy of peginterferon alfa-2a and lamivudine treatment based upon the end of follow-up results are limited by the different mechanisms of action of the two compounds. Most treatment effects of lamivudine are unlikely to persist 24 weeks after therapy is withdrawn.

The effectiveness of repeat or maintenance pegylated interferon treatment of chronic HBV infection is unknown. According to guidelines from the American Gastroenterological Association (Dienstag and McHutchison, 2006), re-treatment is indicated for persons who have relapsed (with relapse defined as where HBV RNA is undetectable during and at the end of therapy but re-appears after completion of therapy) after having completed a course of less-effective therapy. For example, it may be appropriate to re-treat a person with pegylated interferon plus ribavirin who have relapsed after a course of standard interferon plus ribavirin. However, relapsers are likely to experience a response only to subsequently relapse again with a subsequent course of the same therapy (e.g., re-treatment of a person with pegylated interferon plus ribavirin who had relapsed following previous treatment with this same regimen).

Interferon Beta

The American Academy of Neurology (AAN) has concluded that, on the basis of several consistent Class I studies, interferon-beta has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with multiple sclerosis (MS) or with clinically isolated syndromes who are at high-risk for developing MS (Type A recommendation). The

AAN has stated that treatment of MS with interferon beta produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression (Type B recommendation).

There currently are two types of interferon beta (recombinant) commercially available in the United States, interferon beta-1a and interferon beta-1b. Important differences in beneficial effects (clinical, MRI measures of response) between these different types of interferon beta in the management of multiple sclerosis have not been reported and the existence of such differences is as yet unknown (Luzzio, 2013). Clinical interpretation of head-to-head comparative studies involving various interferon beta preparations is limited by methodologic problems (e.g., short duration, open-label studies, nonstandardized dosages and/or routes of administration). In addition, the comparative efficacy of interferon beta preparations and other disease-modifying agents (e.g., glatiramer acetate, mitoxantrone) has not been evaluated in well-designed, controlled studies (Luzzio, 2013).

The efficacy of interferon beta-1a (Avonex, Rebif) and interferon beta-1b (Betaseron, Extavia) appear similar for reducing the frequency and severity of exacerbations in relapsing, remitting MS. A randomized clinical study comparing Avonex to Rebif in 677 patients with primary relapsing/remitting MS found a statistically significant difference in favor of Rebif in the proportion of patients who were relapse free at 24 weeks. The investigators found that 75 % of patients treated with Rebif were relapse-free, compared to 63 % of patients treated with Avonex. However, the design of the study did not support any conclusion regarding effects on accumulation of disability.

However, the effectiveness of interferon beta in slowing disease progression and lessening accumulation of disability in secondary progressive MS is still being studied. Furthermore, the FDA has not approved interferon beta for the additional indication of chronic progressive MS.

The Therapeutics and Technology Assessment Subcommittee of the AAN (Goodinc et al, 2007) evaluated the clinical and radiological impact of developing neutralizing antibodies (NAbs) to interferon beta (IFN-beta) while on this therapy for MS. On the basis of Class II and III evidence, it is concluded that treatment of patients with MS with IFN-beta is associated with the production of NAbs (Level A). NAbs in the serum are probably associated with a reduction in the radiographical and clinical effectiveness of IFN-beta treatment (Level B). In addition, the rate of NAb production is probably less with IFN-beta-1a treatment than with IFN-beta-1b treatment, although the magnitude and persistence of this difference is difficult to determine (Level B). Finally, it is probable that there is a difference in sero-prevalence due to variability in the dose of IFN-beta injected or in the frequency or route of its administration (Level B). Regardless of the explanation, it seems clear that IFN-beta-1a (as it is currently formulated for

IM injection) is less immunogenic than the current IFN-beta preparations (either IFN-beta-1a or IFN-beta-1b) given multiple times per week subcutaneously (Level A). However, because NAbs disappear in some patients even with continued IFN-beta treatment (especially in patients with low titers), the persistence of this difference is difficult to determine (Level B). Although the finding of sustained high-titer NAbs (greater than 100 to 200 NU/ml) is associated with a reduction in the therapeutic effects of IFN-beta on radiographical and clinical measures of MS disease activity, there is insufficient information on the utilization of NAb testing to provide specific recommendations regarding when to test, which test to use, how many tests are necessary, or which cutoff titer to apply.

Hughes et al (2010) carried out a dose-ranging efficacy study of IFN-beta-1a in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Adults with intravenous immunoglobulin (IVIG)-dependent CIDP (n = 67) were enrolled in this 32-week double-blind trial and randomized to intramuscular (IM) IFN-beta-1a. Patients received 30 microg once-weekly plus placebo (n = 12), IM IFN-beta-1a 60 microg once-weekly plus placebo (n = 11), IM IFN-beta-1a 30 microg twice-weekly (n = 11), IM IFN-beta-1a 60 microg twice-weekly (n = 11), or placebo twice-weekly (n = 22). Participants were maintained on IVIG through week 16, when IVIG was discontinued. Patients who worsened were re-started on IVIG. The primary outcome was total IVIG dose (g/kg) administered from week 16 to 32. There was no difference in total IVIG dose administered after week 16 for patients treated with IFN-beta-1a (1.20 g/kg) compared with placebo (1.34 g/kg; p = 0.75). However, exploratory analyses suggested IFN-beta-1a significantly reduced total dose of IVIG compared with placebo for participants who required either high-dose IVIG (greater than 0.95 g/kg per month) or had greater weakness at baseline (Medical Research Council sum score less than 51). Adverse events included flu-like symptoms, headache, and fatigue in the IFN-beta-1a groups. The authors concluded that IFN-beta-1a therapy did not provide significant benefit over IVIG therapy alone for patients with CIDP. However, IFN-beta-1a might be beneficial for patients with more severe disability or those needing high doses of IVIG. This study was designed to provide Class I evidence for the safety and efficacy of IM IFN-beta-1a in the treatment of CIDP but has been subsequently classified as Class II due to a greater than 20 % patient drop-out rate. Thus, this randomized controlled trial (RCT) provided Class II evidence of no effect on primary and secondary endpoints of 4 dosage regimens of IM IFN-beta-1a added to IVIG in persons with CIDP.

Actimmune

Actimmune (interferon gamma-1b) is a synthesized version of interferon gamma, a naturally occurring protein believed to stimulate the immune system.

Currently, the only FDA-approved indications for interferon gamma (Actimmune) is for

treatment of chronic granulomatous disease, and for delaying time to disease progression in patients with severe, malignant osteopetrosis. Interferon gamma has also been shown to be effective for the treatment of atopic dermatitis and Waldenstrom's macroglobulinemia.

Chronic Granulomatous Disease (CGD) is an inherited disorder of the leukocyte function caused by defects in the enzyme complex responsible for phagocyte superoxide generation. Gamma interferon enhances phagocytic function, resulting in an increase in superoxide anion production by granulocytes and monocytes. Gamma interferon also enhances the oxygen-independent antimicrobial activity of monocytes from patients with classic X-linked CGD.

Severe Malignant Osteopetrosis is an inherited disorder characterized by an osteoclast defect, leading to bone overgrowth, and by deficient phagocyte oxidative metabolisms. Gamma interferon enhances superoxide production by phagocytes in situ and enhances osteoclast function in vitro.

Contraindications to interferon gamma-1b therapy include patients who develop or have known hypersensitivity to interferon gamma, E. coli derived products, or any component of the product. Patients undergoing interferon gamma-1b treatment should be monitored for changes in pre-existing cardiac conditions (ischemia, congestive heart failure or arrhythmia), neurologic disorders (seizure disorders or compromised central nervous system function), bone marrow toxicity, hepatic toxicity and hypersensitivity reactions, and renal toxicity.

In addition to those tests normally required for monitoring patients with chronic granulomatous disease and osteopetrosis; hematologic tests (including complete blood count, differential and platelets counts), blood chemistries (renal and hepatic function tests), and urinalysis are recommended for all patients on interferon gamma -1b therapy prior to the beginning and at three month interval during treatment. In patients less than one year of age, hepatic function test should be measured monthly.

Patients undergoing interferon gamma-1b treatment should not be vaccinated with a live vaccine due to increase risk of infection.

Interferon gamma was not better than placebo in improving progression-free survival, pulmonary function, or the quality of life in patients with idiopathic pulmonary fibrosis (Raghu et al, 2004). Idiopathic pulmonary fibrosis (IPF) is a condition that has a poor prognosis, with a median survival of 4 to 5 years. Preliminary data from a phase III trial of interferon (IFN) gamma-1b injection for the treatment of IPF failed to show a significant difference between IFN gamma-1b-treated patients and control group patients in progression free survival time, the primary endpoint of the study. The double-blind, placebo-controlled trial at 58 U.S. and

European centers randomized 300 patients to receive either placebo or 200 mcg of IFN gamma-1b injected subcutaneously 3 times a week. However, there was non-significant 10 % difference in progression-free survival time in favor of IFN gamma-1b treated patients, where progression free survival time is defined as either a decrease in forced vital capacity of greater than 10 %, or an increase in A-a gradient of 5 mmHg, or death. There was also a positive trend in increased survival in IFN gamma-1b treated patients versus the control group; this survival benefit was statistically significant in IFN gamma-1b-treated patients with mild-to-moderate disease. The overall mortality in the IFN gamma-1b-treated patients was 9.9 % versus 16.7 % in the control population. Of the 254 patients with mild-to-moderate disease, mortality was 4.8 % in the IFN gamma-1b-treated patients and 16.4 % in the control group. Trends were also observed later in the course of the study in favor of IFN gamma-1b in terms of improved breathing and reduced need for supplemental oxygen. All remaining phase III trial patients in the active and control groups are being transitioned into an open-label clinical trial in which all patients receive IFN gamma-1b to track longer-term outcomes with IFN gamma-1b for a minimum of 1 year.

In a randomized prospective multi-center clinical trial, Antoniou et al (2006) examined the clinical effects of IFNgamma-1b administered subcutaneously thrice weekly versus colchicine for 2 years. This study had no pre-specified end-points. Fifty consecutive IPF patients were randomized. Patients with mild-to-moderate IPF were eligible for the study if they had histologically proven IPF, or, in the absence of surgical biopsy, fulfilled the European Respiratory Society/American Thoracic Society criteria. In the intent-to-treat population, 5 out of 32 (15.6 %) IFN gamma-1b patients and 7 out of 18 (38.8 %) colchicine patients died after a median follow-up period of 25 months. Patients treated with IFN gamma-1b showed a better outcome after 2 years of therapy, and fewer symptoms, as assessed using the St George's Respiratory Questionnaire, after 12 months of therapy. Also, the IFN gamma-1b group exhibited a higher forced vital capacity (percentage of the predicted value) after 24 months of treatment. No significant differences were detected in resting arterial oxygen tension, total lung capacity (% pred), transfer factor of the lung for carbon monoxide (% pred) and high-resolution computed tomographic scoring between the 2 treatment groups. These data suggest that long-term treatment with IFN gamma-1b may improve survival and outcome in patients with mild-to-moderate IPF. The authors stated that further studies are needed to verify these results. Additionally, the effect of IFN gamma-1b on progressive cases needs to be evaluated.

Walter et al (2006) noted that the clinical course of IPF is variable; however, the long-term survival in IPF is poor. Prednisone has been the mainstay of therapy since its release for clinical use in 1948. Recently, prednisone combined with azathioprine or cyclophosphamide has been used. A number of other drug combinations have been tried with prednisone (e.g., methotrexate, colchicine, penicillamine, or cyclosporine) but have failed or are not well-

tolerated by the patient. Few high quality, prospective, controlled clinical trials have been performed. Thus, there is no good evidence to support the routine use of any specific therapy in the management of IPF. Additional large clinical trials are needed to confirm the potential usefulness of the newer agents (e.g., IFN gamma-1b, pirfenidone, N-acetylcysteine, coumadin, bosentan, or etanercept).

It should be noted that in March 2007, InterMune abandoned efforts to develop Actimmune (IFN gamma-1b) as a treatment for IPF because results from a late-stage clinical trial showed the drug did not prolong lives. The phase 3 INSPIRE clinical trial evaluating Actimmune (IFN gamma-1b) in IPF patients with with mild-to-moderate impairment in lung function was discontinued based upon the recommendation of the study's independent data monitoring committee (DMC). In a planned interim analysis that included a total of 115 deaths, the DMC found the overall survival result crossed a pre-defined stopping boundary for lack of benefit of Actimmune relative to placebo. Among the 826 randomized patients, there was not a statistically significant difference between treatment groups in overall mortality (14.5 % in the Actimmune group as compared to 12.7 % in the placebo group). Based on a preliminary review of the interim safety data, the adverse events associated with Actimmune appear generally consistent with prior clinical experience, including constitutional symptoms, neutropenia and possibly pneumonia.

In a multi-center, randomized, placebo-controlled study, King et al (2009) evaluated if treatment with IFN gamma-1b improved survival compared with placebo in patients with IPF and mild-to-moderate impairment of pulmonary function. A total of 826 patients with IPF were enrolled from 81 centers in 7 European countries, the USA, and Canada. Patients were randomly assigned (double-blind) in a 2:1 ratio to receive 200 microg IFN gamma-1b (n = 551) or equivalent placebo (n = 275) subcutaneously, 3 times per week. Eligible patients were aged 40 to 79 years, had been diagnosed in the past 48 months, had a forced vital capacity of 55 to 90 % of the predicted value, and a hemoglobin-corrected carbon monoxide diffusing capacity of 35 to 90 % of the predicted value. The primary endpoint was overall survival time from randomization measured at the second interim analysis, when the proportion of deaths had reached 75 % of those expected by the study conclusion. At the second interim analysis, the hazard ratio for mortality in patients on IFN gamma-1b showed absence of minimum benefit compared with placebo (1.15, 95 % CI: 0.77 to 1.71, p = 0.497), and indicated that the study should be stopped. After a median duration of 64 weeks (IQR 41 to 84) on treatment, 80 (15 %) patients on IFN gamma-1b and 35 (13 %) on placebo had died. Almost all patients reported at least 1 adverse event, and more patients on IFN gamma-1b group had constitutional signs and symptoms (influenza-like illness, fatigue, fever, and chills) than did those on placebo. Occurrence of serious adverse events (e.g., pneumonia, respiratory failure) was similar for both treatment groups. Treatment adherence was good and few patients

discontinued treatment prematurely in either group. The authors concluded that they can not recommend treatment with IFN gamma-1b since the drug did not improve survival for patients with IPF, which refutes previous findings from subgroup analyses of survival in studies of patients with mild-to-moderate physiological impairment of pulmonary function.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2017) recommend the use of interferon gamma-1b in selected persons with mycosis fungoides (MF) and Sezary syndrome (SS). NCCN guidelines recommend use of IFN gamma-1b as systemic biologic therapy as a

- single agent or in combination with skin-directed therapy for stage I-IIA and stage III MF with blood involvement
- single agent or in combination with skin-directed therapies for stage IB-IIA MF with histologic evidence of folliculotropic or large cell transformation or stage IIB MF with limited tumor lesions
- single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids) for stage IB-IIB MF with histologic evidence of folliculotropic or large cell transformation or stage IIB MF with generalized tumor lesions, with or without skin-directed therapy
- as a single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids) for SS.

According to NCCN (2017) Drug and Biologics Compendium, interferon gamma-1B may be used as adjuvant systemic biologic therapy after total skin electron beam therapy for stage IIB MF generalized tumor lesions, or after chemotherapy for stage IV non-Sezary or visceral disease. NCCN guidelines also indicate interferon gamma-1B as systemic biologic therapy as a single agent or in combination with systemic retinoids, phototherapy, or photopheresis (with or without systemic retinoids), with or without skin-directed therapy for stage I-III MF which has progressed or is refractory to multiple previous therapies.

There is a lack of published evidence of the effectiveness of interferon gamma for Waldenstrom's macroglobulinemia. National Comprehensive Cancer Network guidelines on Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma did not include a recommendation for use of interferon gamma (NCCN, 2012).

Consensus interferon

Consensus interferon (interferon alfacon-1; Infergen) is a non-naturally occurring recombinant type 1 alfa interferon. It has been approved by the FDA for use in the treatment of chronic

hepatitis C in person 18 years of age or older with compensated liver disease who have anti-hepatitic C virus serum antibodies and/or the presence of hepatitis C virus RNA. Although there are studies comparing standard alfa interferon to consensus interferon, and limited evidence regarding the use of consensus interferon in persons with hepatitis C who fail to respond to standard alfa interferon therapy, current guidelines indicate pegylated interferons as the treatment of choice for persons with hepatitis C, including those who fail to respond to standard alfa interferon therapy. There are insufficient published studies comparing consensus interferon to pegylated interferons in persons with hepatitis C who have failed standard interferon therapy.

An open-label multicenter controlled clinical trial evaluated the effectiveness of consensus interferon plus ribavirin in persons with hepatitis C who were non-responsive to previous pegylated interferon and ribavirin. This study, the DIRECT (Daily-Dose Consensus Interferon and Ribavrin: Efficacy of Combined Therapy) trial compared the effectiveness of ribavirin plus 2 different doses of consensus interferon versus no treatment in subjects with hepatitis C who were nonresponsive to pegylated interferon and ribavirin therapy (Bacon et al, 2006; Bacon et al, 2009; Three Rivers Pharmaceuticals, 2010). This study compared 2 doses of consensus interferon (9 mcg or 15 mcg) administered daily plus ribavirin (1,000 mg or 1,200 mg weight-based dosed) administered daily for 48 weeks to subjects who were non-responders to previous pegylated interferon plus ribavirin therapy. Prior non-response was defined as a less than 2 log decline in viral load while undergoing at least 12 weeks of previous pegylated interferon/ribavirin therapy with greater than or equal to 80 % adherence or a detectable viral load at end-of-treatment after completing at least 24 weeks of therapy. Ninety-five percent of study subjects were infected with genotype 1. Approximately 80 % of subects were null responders (less than 2 log drop in viral load during their previous pegylated interferon/ribavirin therapy). In study IRHC-001, 515 subjects were randomized to consensus interferon 9 mcg plus ribavirin, consensus interferon 15 mcg plus ribavirin, or no treatment. In study IRHC-002, 144 subjects in the no treatment arm of IRHC-001 were re-randomized to either consensus interferon 9 mcg plus ribavirin or consensus interferon 15 mcg plus ribavirin. Subjects were treated for up to 48 weeks. The primary endpont was sustained virologic response, defined as undetectable HCV RNA 24 weeks after the end of treatment. None of the subjects in the no-treatment arm of IRHC-001 achieved a sustained virologic response. The overall rate of sustained virologic response in subjects treated with consensus interferon 9 mcg plus ribavirin was 5 %, and 9 % for subjects treated with consensus interferon 15 mcg plus ribavirin. Persons with genotype 1 had less benefit from retreatment. The sustained virologic response rates for persons infected with genotype 1 was 4 % for persons assigned to consensus interferon 9 mcg and 6 % for persons assigned to consensus interferon 15 mcg. The sustained virologic response rates for other genotypes was 21 % for consensus interferon 9 mcg and 67 % for consensus interferon 15 mcg. Persons with high viral load were less likely

to benefit from re-treatment. The sustained virologic response rate for persons with HCV RNA less than 850,000 IU/ml was 13 % and 14 % for persons assigned to 9 mcg and 15 mcg of consensus interferon, respectively. The sustained virologic response rate for persons with HCV RNA greater than or equal to 850,000 IU/ml was 2 % and 6 %for persons assigned to 9 mcg and 15 mcg of consensus interferon, respectively.

The recommended dose of consensus interferon for monotherapy is 9 mcg 3 times weekly for 24 weeks (as initial treatment) or 15 mcg 3 times weekly for up to 48 weeks (as retreatment). The recommended dose of combination treatment is 15 mcg consensus interferon daily with 1,000 mg or 1,200 mg ribavirin (for body weight less than 75 kg and greater than or equal to 75 kg) daily for up to 48 weeks (as re-treatment). According to the product labeling, persons who fail to achieve at least a 2 log drop at 12 weeks or undetectable HCV-RNA at week 24 are highly unlikely to achieve a sustained virologic response and discontinuation of therapy should be considered.

Hepatocellular Carcinoma (HCC)

Recurrence is common following hepatic resection for HCC. Interferon possesses anti-angiogenic, anti-proliferative, anti-viral, and immunomodulatoryeffects; and may be an effective form of adjuvant therapy. Small randomized controlled clinical trials suggest a benefit from prolonged interferon therapy following resection of hepatocellular carcinoma in persons with hepatitis C (Shiratori et al, 2003; Nishiguchi et al, 2005; Mazzaferro et al, 2006).

Chen et al (2012) examined the clinical efficacy of adjuvant interferon alfa-2b (IFNα-2b) therapy on recurrence-free survival (RFS) of patients with post-operative viral hepatitis-related hepatocellular carcinoma (HCC). Patients with curative resection of viral hepatitis-related HCC were eligible, and were stratified by underlying viral etiology and randomly allocated to receive either 53 weeks of adjuvant IFNα-2b treatment or observation alone. The primary endpoint of this study was RFS. A total of 268 patients were enrolled with 133 in the IFNα-2b arm and 135 in the control arm. Eighty percent of them were hepatitis B surface antigen sero-positive. At a median follow-up of 63.8 months, 154 (57.5 %) patients had tumor recurrence and 84 (31.3 %) were deceased. The cumulative 5-year recurrence-free and overall survival rates of intent-to-treat cohort were 44.2 % and 73.9 %, respectively. The median RFS in the IFNα-2b and control arms were 42.2 (95 % confidence interval [CI]: 28.1 to 87.1) and 48.6 (95 % CI: 25.5 to infinity) months, respectively (p = 0.828, log-rank test). Adjuvant IFNα-2b treatment was associated with a significantly higher incidence of leucopenia and thrombocytopenia. Thirty-four (24.8 %) of treated patients required dose reduction, and 5 (3.8 %) of these patients subsequently withdrew from therapy because of excessive toxicity. Adjuvant IFNα-2b only temporarily suppressed viral replication during treatment period. The authors concluded that in

this study, adjuvant IFNα-2b did not reduce the post-operative recurrence of viral hepatitis-related HCC. They stated that more potent anti-viral therapy deserves to be explored for this patient population.

Guidelines from the NCCN (2012) no longer recommend use of interferon in hepatocellular carcinoma for treatment of hepatitis C patients with completely resected tumors.

Interferon is also being evaluated for use following resection of hepatocellular carcinoma in persons with hepatitis B. Lo et al (2007) performed a randomized controlled trial of adjuvant interferon therapy in patients with predominantly hepatitis B-related HCC to examine if the prognosis after hepatic resection could be improved. Patients with no residual disease after hepatic resection for HCC were randomly assigned with stratification by pathologic tumour-node-metastasis (pTNM) stage to receive no treatment (control group), interferon alfa-2b 10 MIU/m (IFN-I group) or 30 MIU/m (IFN-II group) thrice-weekly for 16 weeks. Enrollment to the IFN-II group was terminated because adverse effects resulted in treatment discontinuation in the first 6 patients. A total of 40 patients each had been enrolled into the control group and IFN-I group. The baseline clinical, laboratory, and tumor characteristics of both groups were comparable. The 1- and 5-year survival rates were 85 % and 61 %, respectively, for the control group and 97 % and 79 %, respectively, for the IFN-I group ($p = 0.137$). After adjusting for the confounding prognostic factors in a Cox model, the relative risk of death for interferon treatment was 0.42 (95 % CI: 0.17 to 1.05; $p = 0.063$). Exploratory subset analysis showed that adjuvant interferon had no survival benefit for pTNM stage I/II tumor (5-year survival 90 % in both groups; $p = 0.917$) but prevented early recurrence and improved the 5-year survival of patients with stage III/IVA tumor from 24 % to 68 % ($p = 0.038$). The authors concluded that in a group of patients with predominantly hepatitis B-related HCC, adjuvant interferon therapy showed a trend for survival benefit, primarily in those with pTNM stage III/IVA tumors. They stated that further larger RCTs stratified for stage are needed. An editorial that accompanied the afore-mentioned article stated that any new strategy to prevent HCC recurrence following resection must still be tested in randomized controlled studies, including a control group without treatment (Clavien, 2007).

Desmoid Tumors

Guidelines from the NCCN (2008) recommend use of interferon alfa in desmoid tumors, as a low-dose single agent for gross residual disease following surgery or for unresectable disease either as an initial treatment or for recurrence. NCCN guidelines cite for support the results of a non-randomized, retrospective study of 13 patients with extra-abdominal desmoid tumors, which found encouraging response rates with interferon alfa treatment. Seven of the patients included in the study also received tretinoin. After a mean of 27 months of treatment, local

control was seen in 11 of 13 patients (85 %). Seven patients had no evidence of disease at a mean disease-free interval of 22 months; in 2 patients progressive disease occurred after only 7 and 9 months, respectively, of observation. In another 4 patients, progression of the desmoid tumor was stabilized. The investigators concluded that these data suggest that treatment with interferon may be effective in prolonging the disease-free interval of patients with desmoid tumors after intralesional or marginal surgery.

Hypereosinophilic Syndrome (HES)

Hypereosinophilic syndromes (HES) constitute a rare and heterogeneous group of disorders, defined as persistent and marked blood eosinophilia (greater than 1.5 x 10(9)/L for more than 6 consecutive months) associated with evidence of eosinophil-induced organ damage, where other causes of hypereosinophilia such as allergic, parasitic, and malignant disorders have been excluded (Roufosse et al, 2007). Target-organ damage mediated by eosinophils is highly variable among patients, with involvement of skin, heart, lungs, and central and peripheral nervous systems in more than 50 % of cases. Other frequently observed complications include hepato- and/or splenomegaly, eosinophilic gastroenteritis, and coagulation disorders. Diagnosis of HES relies on observation of persistent and marked hypereosinophilia responsible for target-organ damage, and exclusion of underlying causes of hypereosinophilia, including allergic and parasitic disorders, solid and hematological malignancies, Churg-Strauss disease, and HTLV infection (Roufosse et al, 2007). Therapeutic management should be adjusted to disease severity and eventual detection of pathogenic variants. For patients with the FIP1L1-PDGFRA fusion gene (F/P+) variant, imatinib is first line therapy. For others, corticosteroids are generally administered initially. Interferon alfa is the drug of choice for patients with hypereosinophilic syndromes who do not respond to corticosteroids, or as a corticosteroid-sparing agent in those who require higher doses of corticosteroids (Roufosse et al, 2008). Other second line options for corticosteroid-resistant cases include hydroxycarbamide and imatinib (Roufosse et al, 2007).

Familial Mediterranian Fever (FMF)

In a double-blind, placebo-controlled trial, Tunca et al (2004) examined the effect of INF-alfa on acute attacks of familial Mediterranean fever (FMF). These investigators treated 34 acute abdominal attacks with IFN-alfa 5 MIU or placebo subcutaneously in the early phase of the attack. Leucocytes, thrombocytes, the erythrocyte sedimentation rate, fibrinogen, C-reactive protein (CRP), serum amyloid A protein (SAA), haptoglobin, transferrin, IL-1beta and TNF-alfa were measured at hours 0, 6, 12, 24 and 48. The median time to recovery in those treated with IFN-alfa and placebo was not significantly different, while the leucocytosis and high levels of fibrinogen were significantly more prolonged in placebo-treated patients; CRP and SAA were

extremely elevated and peaked at 24 hours, remaining less marked in the patients treated with IFN-alfa, but the difference was not statisticaly significant. Observations regarding the other parameters were unremarkable. The authors concluded that although there were some clues indicating a depressed inflammatory response with IFN-alfa, they could not demonstrate a definitive effect of this agent in this double-blind trial. The drug may suppress the acute inflammation of FMF only if administered at the earliest phase.

Pancreatic Cancer

Schmidt and associates (2007) stated that data from a phase II clinical trial combining chemoradiotherapy with IFN-alfa (CapRI scheme) for adjuvant treatment of pancreatic carcinoma are very encouraging. Thus, a phase III trial comparing chemotherapy with the chemoradiotherapy with IFN-alfa scheme has been initiated in August 2004. Translational research with a focus on immunomodulation is performed in parallel to the study. Blood and serum samples were taken at various time points. Patients in arm A (chemo-radioimmunotherapy) receive a single low-dose interferon injection before therapy to investigate the direct effect of IFN-alfa. So far, samples from 44 patients have been investigated for surface molecule expression, cytokine levels, natural killer cell cytotoxicity, and antigen-specific Granzyme B release. Patients in arm A showed 1 day after IFN-alfa injection a significant increase in spontaneous cytotoxicity; this effect was fading after repeated injections. Furthermore, cells releasing Granzyme B after stimulation with CA 19.9 and MUC-1 protein increased under therapy. Five days after the first IFN-alfa injection, interleukin-12 and tumor necrosis factor-alfa serum levels peak. These researchers observed significant increases of monocytes, peripheral dendritic cells, CD40 cells, central and effector memory T cells, and CD8 cells, CD4 cells decreased during therapy. All these effects were only observed in arm A patients and none of them in arm B patients. The authors concluded that in a translational research project accompanying a challenging multi-modality treatment trial including IFN-alfa, they observed an immediate activation of antigen-presenting cells and natural killer cells followed later on by antigen-specific activation. It will be most interesting if the immunologic data will show a correlation with the clinical course of the patients.

In a feasibility study, Nitsche and colleagues (2008) noted that recent studies give rise to the hypothesis, that adjuvant chemor-adioimmunotherapy with 5-fluorouracil (5-FU), cisplatin and IFN-alfa might be a possible new treatment of pancreatic cancer in resected patients. These researchers reported the up-to-now experience at their institution. A total of 11 patients with histological diagnosis of localized carcinoma of the pancreas (n = 7) or peri-ampullary (n = 4) were prospectively analyzed. Four patients were deemed unresectable because of local invasion of adjacent organs (neoadjuvant setting) and 7 patients underwent curative resection (adjuvant setting). Eight patients were classified as T3 carcinomas and 3 T4 carcinomas. Six

of the 11 (55 %) patients presented with positive lymph node involvement. One histological grade I, 6 grade II and 3 grade III were detected. External conformal irradiation to a total dose of 50.4 Gy with 1.8 Gy per day was delivered. All patients received a concomitant chemotherapy with continuous 5-FU 200 mg/m2 per day on 28 treatment days and intravenous bolus cisplatin 30 mg/m2 per week (day 2, 9, 16, 23, 30). A recombinant r-IFN-alfa was administered on 3 days weekly during week 1 to 5 of the radiotherapy course as subcutanous injections with 3*3 Mio. I.U. weekly. The 4-year overall survival rate for all patients was 55 %. In the neoadjuvant group, 3 of 4 patients died due to progressive disease; in the adjuvant group, combined chemo-radioimmunotherapy lead to controlled disease in 5 of 7 patients. The overall toxicity was well-managed. The authors concluded that these findings strengthened the hypothesis of concomitant chemo-radioimmunotherapy with 5-FU, IFN-alfa and cisplatin as a possible new treatment of pancreatic cancer in resected patients.

Booy et al (2015) stated that pancreatic cancer is a highly aggressive malignancy with limited treatment options. To improve survival for patients with pancreatic cancer, research has focused on other treatment modalities like adding biological modulators such as type-I interferons (IFNs). Type I IFNs (i.e., IFN-alpha/IFN-beta [IFN-α/IFN-β]) have anti-proliferative, anti-viral as well as immunoregulatory activities. Furthermore, they are able to induce apoptosis, exert cell cycle blocking, and sensitize tumor cells for chemo- and radiotherapy. A few years ago, in-vitro, in-vivo, and several clinical trials have been described regarding adjuvant IFN-α therapy in the treatment of pancreatic cancer. Some studies reported a remarkable increase in the 2- and 5-year survival. Unfortunately, the only RCT did not show a significant increase in overall survival, although the increased median survival implicated that some patients in the experimental group benefited from the adjuvant IFN-α therapy. Furthermore, encouraging in-vitro and in-vivo data pointed to a possible role for adjuvant IFN therapy. However, up till now, the use of IFNs in the treatment of pancreatic cancer remains controversial.

An UpToDate review on “Adjuvant therapy for resected exocrine pancreatic cancer” (Ryan and Mamon, 2015) does not mention interferon as a therapeutic option.

National Comprehensive Cancer Network’s Drugs & Biologics Compendium (2015) does not list pancreatic cancer as a recommended indication of interferon gamma-1B or interferon alfa.

Behcet's Syndrome

In an open, non-randomized, uncontrolled, interventional, prospective study, Sobaci et al (2010) evaluated the intermediate-term safety and effectiveness of interferon alfa-2a (IFN-alfa2a) in patients with Behcet's uveitis (BU) refractory to corticosteroids and

immunosuppressive agents. A total of 53 patients (106 eyes) with active, vision-threatening BU who failed to respond to conventional treatments were included in this study. In 53 patients, acute inflammation was suppressed with effective prednisolone dosage (1 to 2 mg/kg/day, tapered to 10 mg within 4 to 6 weeks). The patients were treated with IFN-alfa2a 4.5 MIU 3 times per week for the first 3 months followed by IFN-alfa2a 3 MIU 3 times per week for the next 3 months. Observation or other treatment methods were performed according to the decision tree developed for this study. Primary outcome measures were remission and complete response; secondary outcome measures were frequency of uveitis attacks, visual acuity (VA), and adverse effects. During 2 years of follow-up (median of 65 months, range of 12 to 130 months), compliance with the therapy was excellent. At the end of 1-year follow-up, treatment response was obtained in 45 of 53 patients (84.9 %). The mean attack rate of 3.6 +/- 1.1 per year (range of 2 to 8) decreased to 0.56 +/- 0.75 (range of 0 to 4) per year (p = 0.001). Visual acuity improved (greater than or equal to 0.2 logarithm of the minimum angle of resolution units from initial VA) in 30 eyes (28.3 %) and worsened in 12 eyes (11.3 %). Five patients (9.4 %) did not respond to the initial treatment, and 3 patients (5.6 %) developed severe adverse effects, including psoriasis, epileptic seizure, and extreme tiredness. Fifteen patients (28.3 %) were off treatment for all the medications and disease free for 28 +/- 13.1 months (range of 12 to 50 months). The authors concluded that these findings suggested that IFN-alfa2a may be a valuable treatment option in BU that is refractory to corticosteroids and conventional immunosuppressive agents. The possible role of IFN-alfa2a as a first-line agent in BU should be validated in RCTs against newly described biologic agents.

In a Cochrane review, Nava et al (2014) evaluated the benefit and harms of available treatments for neuro-Behcet's syndrome (NBS), including biologics, colchicine, corticosteroids, immunosuppressants and IFN-alfa. The authors concluded that there is no evidence to support or refute the benefit of biologics, colchicine, corticosteroids, immunosuppressants and IFN-alfa for the treatment of patients with NBS. They stated that well-designed multi-center RCTs are needed in order to inform and guide clinical practice.

Plexiform Neurofibromas

In a phase I clinical trial, Jakacki et al (2011) evaluated preliminary effectiveness and determined the recommended phase II dose (RP2D) for pegylated interferon-α-2b (PI) in patients with unresectable progressive or symptomatic plexiform neurofibromas (PN). Pegylated interferon-α-2b was administered weekly in cohorts of 3 to 6 patients during the dose-finding phase and continued for up to 2 years. A total of 12 patients were treated at the RP2D to further evaluate toxicity and activity. Thirty patients (median age of 9.3 years, range of 1.9 to 34.7 years) were enrolled in this study. No dose-limiting toxicity (DLT) was seen in patients treated at the 3 µg/kg dose level (DL) during the first 4 weeks. All 5 patients treated at

the 4.5 µg/kg DL came off study or required dose reductions for behavioral toxicity or fatigue. Similar DLT on the 3 µg/kg DL became apparent over time. There was 1 DLT (myoclonus) in 12 patients enrolled at the 1.0 µg/kg DL. Eleven of 16 patients with pain showed improvement and 13 of 14 patients with a palpable mass had a decrease in size. Five of 17 patients (29 %) who underwent volumetric analysis had a 15 % to 22 % decrease in volume. Three of 4 patients with documented radiographical progression before enrollment showed stabilization or shrinkage. The authors concluded that the RP2D of PI for pediatric patients with PN is 1 µg/kg/wk. Clinical and radiographical improvement and cessation of growth can occur. The authors acknowledged the limitations of using subjective assessments to determine clinical response and more stringent, validated criteria have been incorporated into an ongoing phase II clinical study.

Guillain Barre Syndrome

In a Cochrane review, Hughes et al (2011) reviewed systematically the evidence from RCTs for pharmacological agents other than plasma exchange, intravenous immunoglobulin and corticosteroids for the treatment of Guillain Barré syndrome. Only very low quality evidence was found for 4 different interventions. One RCT with 13 participants showed no significant difference in any outcome between IFN beta-1a and placebo. Another with 10 participants showed no significant difference in any outcome between brain-derived neurotrophic factor and placebo. A third with 37 participants showed no significant difference in any outcome between cerebrospinal fluid filtration and plasma exchange. In a fourth with 20 subjecs, the risk ratio of improving by 1 or more disability grades after 8 weeks was significantly greater with the Chinese herbal medicine tripterygium polyglycoside than with corticosteroids (risk ratio 1.47; 95 % CI: 1.02 to 2.11). The authors concluded that the quality of the evidence was very low. Three small RCTs, of IFN beta-1a, brain-derived neurotrophic factor and cerebrospinal fluid filtration, showed no significant benefit or harm. A fourth small trial showed that the Chinese herbal medicine tripterygium polyglycoside hastened recovery significantly more than corticosteroids but this result needs confirmation. It was not possible to draw useful conclusions from the few observational studies.

Boceprevir

Boceprevir capsules (Victrelis, Merck) is a protease inhibitor that has been FDA approved to treat adults with chronic hepatitis C genotype 1 with compensated liver disease, and who either have not been previously treated with interferon therapy for their hepatitis C or who have failed such treatment. Boceprevir is approved for use in combination with peginterferon alfa and ribavirin. The safety and effectiveness of boceprevir was evaluated in 2 phase 3 clinical trials with 1,500 adult patients. In both trials, 2/3 of patients receiving boceprevir in combination with

pegylated interferon and ribavirin experienced a significantly increased sustained virologic response (i.e., the hepatitis C virus was no longer detected in the blood 24 weeks after stopping treatment), compared to pegylated interferon and ribavirin alone. Boceprevir is taken 3 times a day with food. The most commonly reported side effects in patients receiving boceprevir in combination with pegylated interferon and ribavirin include fatigue, anemia, nausea, headache and dysgeusia. According to the FDA-approved labeling, 800 mg of boceprevir is administered orally 3 times daily in combination with peginterferon alfa and ribavirin. Duration of therapy is determined by Response-Guided Therapy (RGT) guidelines based upon the patient's HCV-RNA levels at treatment weeks 8, 12 and 24.

Telaprevir

Telaprevir tablets (Incivek, Vertex) are protease inhibotors that have received FDA approval to treat chronic hepatitis C genotype 1 infection in adults who have either not received interferon-based drug therapy for their infection or who have not responded adequately to prior therapies. Telaprevir is approved for use with peginterferon alfa and ribavirin. The safety and effectiveness of telaprevir was evaluated in 3 phase 3 clinical trials with about 2,250 adult patients who were previously untreated, or who had received prior therapy. In all studies patients also received the drug with standard of care. In previously untreated patients, 79 % of those receiving telaprevir experienced a sustained virologic response. The sustained virologic response for patients treated with telaprevir across all studies, and across all patient groups, was between 20 and 45 % higher than current standard of care. Studies indicate that treatment with telaprevir can be shortened from 48 weeks to 24 weeks in most patients; 60 % of previously untreated patients achieved an early response and received only 24 weeks of treatment (compared to the standard of care of 48 weeks). The sustained virologic response for these patients was 90 %. According to the FDA-approved labeling, 750 mg of telaprevir is taken 3 times a day (7 to 9 hours apart) with food (not low fat). The labeling states that telaprevir must be administered with both peginterferon alfa and ribavirin for all patients for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on viral response and prior response status. The most commonly reported side effects in patients receiving telaprevir in combination with peginterferon alfa and ribavirin include rash, low red blood cell count, nausea, fatigue, headache, diarrhea, pruritus, and anal or rectal irritation and pain. Rash can be serious and can require stopping telaprevir or all 3 drugs in the treatment regimen.

Commenting on the data from randomized trials of protease inhibitors in genotype 1 hepatitis C, Rosen (2011) stated that a reasonable initial regimen would be telaprevir with peginterferon and ribavirin for 12 weeks. If tests for HCV RNA were negative at weeks 4 through 12 (indicating an extended rapid virologic response), only 12 additional weeks of peginterferon

and ribavirin would be recommended, whereas if an extended rapid virologic response were not achieved, peginterferon and ribavirin would be continued for an additional 36 weeks. If boceprevir were used, according to FDA guidelines, a 4-week lead-in phase of peginterferon and ribavirin would be followed by peginterferon and ribavirin and boceprevir for 24 weeks (a total of 28 weeks) if tests for HCV RNA were negative at weeks 8 through 24 of treatment. If the tests were positive between weeks 8 and 24 but negative at week 24, peginterferon and ribavirin and boceprevir would be continued for an additional 8 weeks, followed by an additional 12 weeks of peginterferon-ribavirin (a total of 48 weeks).

Primitive Neuroectodermal Tumor (PNET)

Primitive neuroectodermal tumor (PNET) is a neural crest tumor. It is a rare tumor, usually occurring in children and young adults under 25 years of age. After successful chemotherapy or radiotherapy, the 5-year survival rate is only 8 %. Primitive neuroectodermal tumor belongs to the Ewing family of tumors; ependymoblastoma is a synonym for PNET. Based on location in the body, PNET is classified into 2 types: (i) peripheral PNET and (ii) central nervous system (CNS) PNET. It is also possible to add a third category, involving tumors of the autonomic nervous system, such as neuroblastoma. The peripheral PNET (pPNET) is now thought to be virtually identical to Ewing sarcoma. Primitive neuroectodermal tumor of the CNS are grossly divided into supra-tentorial PNET and infra-tentorial PNET, the latter being more common. An example of infra-tentorial PNET includes medulloblastoma, which occurs in the cerebellum. An example of supra-tentorial PNET includes pinealoblastoma, which occurs in the pineal region. National Comprehensive Cancer Network's guidelines on Ewing sarcoma make no recommendation for use of interferon alfa. Furthermore, NCCN guidelines on CNS cancers only recommend interferon alfa for meningiomas, making no recommendation for use of interferon alfa for medulloblastoma or supratentorial PNET.

Sjogren Syndrome

Akpek et al (2011) reviewed treatment options for patients with dry eye secondary to Sjogren's syndrome (SS). A search strategy was developed to identify prospective, interventional studies of treatments for SS-associated dry eye from electronic databases. Eligible references were restricted to English-language articles published after 1975. These sources were augmented by hand searches of reference lists from accessed articles. Study selection, data extraction, and grading of evidence were completed independently by 4 or more review authors. The searches identified 3,559 references as of August 10, 2010. After duplicate review of the titles and abstracts, 245 full-text papers were assessed, 62 of which were relevant for inclusion in the review. The authors concluded that in the current literature on SS-associated dry eye, there is a paucity of rigorous clinical trials to support therapy

recommendations. Nonetheless, the recommended treatments include topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies. The efficacy of oral secretagogues seems greater in the treatment of oral dryness than ocular dryness. Although oral hydroxychloroquine is commonly prescribed to patients with SS to alleviate fatigue and arthralgias, the literature lacks strong evidence for the efficacy of this treatment for dry eye. Intrferon-alfa was dicussed in this review ; but it was not recommended as a therapeutic option.

Pulmonary Tuberculosis

Gao et al (2011) evaluated the safety and effectiveness of adjunctive therapy using interferon-gamma (IFN-γ) for the treatment of pulmonary tuberculosis (TB). These investigators conducted a systematic review of controlled clinical trials that compared anti-TB drugs in combination with IFN-γ with the same anti-TB drugs alone for the treatment of pulmonary TB. A total of 9 trials were identified, with IFN-γ being aerosolized or administered subcutaneously in 1 trial, aerosolized only in 5 trials, and administered intramuscularly in 3 trials. The methodology quality of all trials was rated "C". Meta-analysis of the trials with aerosolized IFN-γ showed statistical benefits on sputum negative conversion and chest radiograph: the pooled relative risk (RR) for conversion was 1.97 (95 % CI: 1.20 to 3.24, p = 0.008) after 1 month of treatment, 1.74 (95 % CI: 1.30 to 2.34, p = 0.0002) after 2 months of treatment, 1.53 (95 % CI: 1.16 to 2.01, p = 0.003) after 3 months of treatment, 1.57 (95 % CI: 1.20 to 2.06, p = 0.001) after 6 months of treatment, and 1.55 (95 % CI: 1.17 to 2.05, p = 0.002) at the end of treatment; the pooled RR for the chest radiograph was 1.38 (95 % CI: 1.10 to 1.17, p = 0.006) at the end of treatment. For intramuscularly administered IFN-γ, meta-analysis of 3 trials showed its significant improvement on sputum negative conversion after 2 months of treatment. A RCT with aerosolized and subcutaneously administered IFN-γ reported significant reductions in the symptoms of fever, wheeze, and night sweats in the IFN-γ-treated groups compared with the control group after 1 month of treatment. No patients discontinued treatment because of adverse effects caused by IFN-γ. The authors concluded that adjuvant therapy using IFN-γ, especially by aerosol, might be beneficial to TB patients, but large RCTs are needed for further evaluation of its safety and effectiveness considering the quality of the trials analyzed.

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL)

Kanemaru et al (1997) employed IFN-alfa in the treatment of severe idiopathic sudden sensorineural hearing loss (ISSHL). A total of 42 patients were studied and had an average hearing ability of greater than or equal to 70 dB before treatment. These researchers also examined 2'-5' oligoadenylate synthetase (2,5A-S) activity, one of the parameters indicating anti-viral activity of IFN, to investigate the relationship between the suppression of viral

proliferation and prognosis and explain the pathogenesis of ISSHL. Complete recovery was found in 27 patients (64.3 %) after IFN therapy. Increased 2,5A-S activity was observed on the 3rd day of IFN therapy in 24 of the 27 patients who completely recovered. No severe adverse events were reported after IFN therapy. The authors concluded that these findings suggested that IFN therapy may be effective and safe in the treatment of ISSHL and calls for further investigation.

The American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF)'s clinical practice guideline on "Sudden hearing loss" (Stachler et al, 2012) noted that "[t]he panel made a recommendation against clinicians routinely prescribing anti-virals, thrombolytics, vasodilators, vasoactive substances, or anti-oxidants to patients with ISSNHL .... In addition to the therapies discussed above, a host of other therapies have been used to treat SSNHL (i.e., vitamins, minerals, interferon, nitroglycerin, and other complementary and alternative medications). The evidence base for these therapies was insufficient to review in this guideline and no comment is made on their use".

Pelvic Fibromatosis:

Arien et al (2015) stated that fibromatosis is a rare, non-invasive but aggressive tumor. The tumor displaces tissue by "pushing" the normal structures aside. Optimal treatment should be individualized. These researchers reported the case of a 35-year old woman who presented with a recurrent fibromatosis, which filled the vagina and extended into the pelvis. The classical surgical removal would have had a high morbidity. Therefore, it was decided, after shared decision-making, to opt for treatment with alfa IFN. The side effects of the therapy were tolerable, and a complete regression of the fibromatosis was achieved. At present, 13 years after the diagnosis and 7 years after discontinuation of the therapy, the patient is well with no signs of disease. The authors concluded that IFN may be considered as primary treatment for extensive pelvic fibromatosis. Moreover, they stated that more research is needed to elucidate its working mechanism.

Retinal Vasculitis:

Rosenbaum et al (2016) noted that ophthalmologists and rheumatologists frequently have a miscommunication among themselves, and as a result differ in their opinion for patients consulting them with retinal vasculitis. These investigators sought to establish a common understanding of the term, retinal vasculitis, and reviewed recent studies on this diagnosis. The genetic basis of some rare forms of retinal vascular disease has recently been described. Identified genes include CAPN5, TREX1, and TNFAIP3; Behcet's disease is a systemic illness that is very commonly associated with occlusive retinal vasculitis; retinal imaging, including

fluorescein angiography and other newer imaging modalities, has proven crucial to the identification and characterization of retinal vasculitis and its complications; although monoclonal antibodies to interleukin-17A or interleukin-1 beta failed in trials for Behcet's disease, antibodies to TNF-alfa, either infliximab or adalimumab, have demonstrated consistent benefit in managing this disease. These researchers stated that IFN treatment and B-cell depletion therapy via rituximab may be beneficial in certain types of retinal vasculitis. The authors concluded that retinal vasculitis is an important entity for rheumatologists to understand. Retinal vasculitis associated with Behcet's disease responds to monoclonal antibodies that neutralize TNF, but the many other forms of non-infectious retinal vasculitis may require alternate therapeutic management.

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS):

Rico and colleagues (2016) noted that chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described inflammatory disease of the CNS, distinguished by brainstem- and spinal cord-centered lesions with a characteristic contrast enhancement on MRI, a lymphocytic perivascular infiltrate on pathological examination, and a dramatic response to and dependence on steroids therapy. Since its initial description in 2010, different glucocorticoid-sparing agents, mostly immunosuppressant drugs, have been used to minimize the dosage, but these therapies also carry the risk of important secondary effects. These researchers presented the first reported case of CLIPPERS treated with IFN-beta-1a as add-on therapy. The case entailed a previously healthy 31-year old man presented with gait ataxia and dysarthria; MRI showed pons-centered hyper-intense patchy lesions on T2-weighted images. Additional tests ruled out other possible diagnoses and symptoms reversed with intravenous methylprednisolone. Over the years the patient presented with several episodes of deterioration each year, which were partly reversed with glucocorticoid therapy, but leaving him with growing sequelae. Four years after the initial event, treatment with IFN-beta-1a was initiated, achieving reduced frequency of the relapses to 1 every 4 years, which were no longer associated to increasing disability. This allowed reducing glucocorticoids to 30 mg of Deflazacort every other day. The authors concluded that IFN-beta-1a could be an alternative to corticosteroid-combined therapy in CLIPPERS and its more benign profile of secondary effects compared to immune-suppressants could make it an attractive choice. These preliminary findings need to be validated by well-designed studies.

Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome:

Avau and Matthys (2015) noted that IFN-gamma (IFN-γ) affects immune responses in a

complex fashion. Its immune-stimulatory actions (e.g., macrophage activation and induction of T helper 1-type responsiveness), are widely acknowledged, however, as documented by a large body of literature, IFN-γ has also the potential to temper inflammatory processes via other pathways. In autoimmune and auto-inflammatory disorders, IFN-γ can either play a disease-enforcing role or act as protective agent, depending on the nature of the disease. In animal models of any particular autoimmune disease, certain changes in the induction procedure can reverse the net outcome of introduction or ablation of IFN-γ. These investigators reviewed the role of endogenous IFN-γ in inflammatory disorders and related murine models, with a focus on systemic juvenile idiopathic arthritis (sJIA) and macrophage activation syndrome (MAS). In particular, these researchers discussed their recent findings in a mouse model of sJIA, in which endogenous IFN-γ acted as a regulatory agent, and compared with results from mouse models of MAS. Furthermore, the authors elaborated on the complexity in the activity of IFN-γ and the resulting difficulty of predicting its value or that of its antagonists as therapeutic option.

Squamous Cell Carcinoma:

Cranmer et al (2010) stated that cutaneous squamous cell carcinoma (SCC) is an already common disorder with a rapidly increasing incidence. Treatment of early disease depends primarily on surgery or destructive techniques. In contrast to the frequency of early SCC, unresectable or metastatic SCC is relatively rare, but potentially life-threatening without clearly proven therapeutic options. Few rigorous studies of the treatment of advanced SCC have been undertaken. In the past, various agents have been explored in a limited fashion, including chemotherapy (cisplatin, fluoropyrimidines, bleomycin, doxorubicin), 13-cis-retinoic acid, and interferon-α2a. Clinical activity has been suggested by these trials, but their small sizes, heterogeneous patient populations, and lack of randomization have hindered the use of their results in defining treatment paradigms. Only 1 rigorous randomized trial has focused on cutaneous SCC. Enrolling 66 patients, that trial randomized patients at high recurrence risk to either observation or post-operative interferon-α2a and 13-cis-retinoic acid. This treatment did not improve time to recurrence or prevent secondary cutaneous SCC from developing. Though not in the metastatic setting, this study casts doubt on the ability of this regimen to control metastatic disease. Recently, agents targeting the human epidermal growth factor receptor (erlotinib, gefitinib, cetuximab) have displayed preliminary evidence of activity in phase II clinical trials and case series reports. Expression of this receptor is frequent in cutaneous SCC and appears to be prognostically adverse. Only the conduct of rigorous trials, with well-defined endpoints, adequate patient numbers, and preferably randomization, can prove the clinical efficacy of this promising treatment approach and define better therapy for this vexing clinical problem.

Kim et al (2004) noted that intra-lesional interferon (IFN) alpha-2b has been shown to be a safe and effective mode of treatment for basal cell carcinoma and squamous cell carcinoma. Multiple studies published in the 1980s through the early 1990s have demonstrated the efficacy of intra-lesional interferon in the treatment of these malignancies. Unfortunately, this modality appears to be under-used. These investigators reminded dermatologists that in addition to cryotherapy, electro-desiccation, and surgical excision, intra-lesional IFN-alpha is an important part of the armamentarium in the treatment of non-melanoma skin cancers. In addition to a review of the literature, these researchers presented 8 cases in 7 patients successfully treated with intra-lesional IFN for basal cell carcinoma and squamous cell carcinoma. The authors concluded that its non-surgical approach and excellent cosmetic results made IFN alpha-2b an attractive option for patients and an important alternative when other treatment modalities are impractical or contraindicated. They stated that further, more extensive, controlled clinical trials are needed to confirm this assessment.

Furthermore, National Comprehensive Cancer Network's Drugs & Biologics Compendium (2017) does not list cutaneous squamous cell carcinoma as a recommended indication of interferon alfa-2b, recombinant.

In a pilot study, Karp et al (2010) examined the effectiveness of pegylated interferon alpha 2b (PEGIFNalpha2b) for treatment of ocular surface squamous neoplasia (OSSN). A total of 3 patients with histologically proven OSSN were studied prospectively. Patients were given subconjunctival/perilesional injections of 1 ug/kg of PEGIFNalpha2b (PEG Intron, Schering-Plough, Kenilworth, NJ) until the tumor resolved. Patients were followed clinically and photographically for evidence of tumor resolution and recurrence. All patients had clinical resolution of the tumor. The mean time to resolution was 47 days. During the follow-up time after resolution of the lesion (mean of 41 months), 1 patient had disease recurrence 7 months after clinical resolution. This was successfully treated with 1 further injection. The authors concluded that PEGIFNalpha2b may be a viable medical alternative for the treatment of OSSN. They stated that more studies are needed to examine if PEGIFNalpha2b is as effective as recombinant interferon alpha 2b.

Furthermore, National Comprehensive Cancer Network's Drugs & Biologics Compendium (2017) does not list squamous cell carcinoma as a recommended indication of peginterferon alfa-2b.

Ocular Surface Neoplasia:

Lee and colleagues (2018) stated that the use of topical interferon alpha-2b is a well-established treatment for ocular surface squamous neoplasia. There have been numerous

reports on its efficacy and high safety profile. Benign reactive lymphoid hyperplasia in ocular tissues has not been previously documented by histopathology after interferon treatment. This case report described a 55-year old man who had successful resolution of his ocular surface squamous neoplasia after topical treatment, but developed forniceal tissue deposits. The appearance of the lesions was unexpected and alerted the clinician to the possibility of further neoplastic extension. The authors noted that excisional biopsy of the lesions confirmed benign reactive lymphoid hyperplasia and resolved with no recurrence.

The American Academy of Ophthalmology's webpage on "Ocular surface squamous neoplasia" (AAO, 2017) stated that "The use of topical chemotherapeutic agents, including interferon-α2b, mitomycin C, and 5- fluorouracil, has the advantage of treating the entire ocular surface and avoiding surgical complications such as positive margins, scarring, and limbal stem cell deficiency".

Systemic Lupus Erythematosus:

Chasset and Arnaud (2018) noted that significant advances in the understanding of the molecular basis of innate immunity have led to the identification of IFNs, particularly IFN-α, as central mediators in the pathogenesis of systemic lupus erythematosus (SLE). Thus, targeting of IFNs and of their down-stream pathways has emerged as important developments for novel drug research in SLE. Based on this, several specific interferon blocking strategies using anti-IFN-α antibodies, anti-type I interferon receptor antibodies, Interferon-α-kinoid, or anti-IFN-γ antibodies have all been assessed in recent clinical trials. Alternative strategies targeting the plasmacytoid dendritic cells (pDCs), Toll-like receptors (TLRs)-7/9 or their down-stream pathways such as the myeloid differentiation primary-response protein 88 (MYD88), spleen tyrosine kinase (Syk), Janus-kinases (JAKs), interleukin-1 receptor-associated kinase 4 (IRAK4), or the tyrosine kinase 2 (TYK2) are also investigated actively in SLE, at more preliminary clinical development stages, except for JAK inhibitors that have reached phase_ II clinical trials. The authors concluded that in the near future, in-depth and personalized functional characterization of IFN pathways may provide further guidance for the selection of the most relevant therapeutic strategy in SLE, tailored at the patient-level.

Miscellaneous:

The following are recommendations from the NCCN Drugs and Biologics Compendium (2018):

- Pegylated interferon alfa for essential thrombocythemia (Category 2A) for:
  - symptomatic very low-risk, low-risk, or intermediate-risk essential thrombocythemia with potential indications for cytoreductive therapy

- high-risk essential thrombocythemia
- inadequate response or loss of response to hydroxyurea, interferon therapy, or anagrelide, if peginterferon alfa-2a or peginterferon alfa-2b not previously used.

- Interferon alfa and pegylated interferon alfa may be used as an alternative for hydroxyurea when phlebotomy is not effective, not tolerated, or contraindicated. (Category 2A) for:
  - symptomatic low-risk polycythemia vera with potential indications for cytoreductive therapy
  - high-risk polycythemia vera
  - inadequate response or loss of response to hydroxyurea or interferon therapy, if interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b not previously used.
- Interferon alfa-2b is the only interferon alfa drug indicated for Giant cell tumor of the bone.

Appendix

Table 1: Child-Pugh Score

Measure	1 point	2 points	3 points	units
Bilirubin (total)	< 34 (<2)	34-50 (2-3)	> 50 (>3)	µmol/l (mg/dl)
Serum albumin	> 3.5	2.8-3.5	< 2.8	g/dl
INR	< 1.7	1.71-2.20	> 2.20	no unit
Ascites	None	Mild	Severe	no unit
Hepatic encephalopathy	None	Grade 1-2 (or suppressed with medication)	Grade 3-4 (or refractory)	no unit

Child-Pugh Grade: Class A (5 to 6 points); Class B (7 to 9 points); Class C (10 to 15 points).

Table 2: West Haven Criteria for Grading Hepatic Encephalopathy:

- *Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction*
- *Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle*

personality change; inappropriate behavior

- *Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation*
- *Grade 4 - Coma (unresponsive to verbal or noxious stimuli)*

Table 3: Expanded Disability Status Scale (EDSS)

The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist.

1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transfering. Can wheel self but can not carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms

8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

Table 4: Dosing of Interferons

Intron A: Interferon alfa-2b is available as Intron A in:

- Powder for injection: 10, 18 and 50 million IU/vial
- Solution for injection in vials: 18 and 25 million IU multidose vial
- Injectable solution in multidose Pens: 6 doses of 3 million IU (18 million IU), 5 million IU (30 million IU), and 10 million IU (60 million IU).

Dosing of Intron A for hepatitis C:

- Member weight ≤ 61 kg: The recommended dose is three million IU/m2 three times a week administered subcutaneously.
- Member weight > 61 kg: The recommended dose is three million IU three times a week administered subcutaneously or intramuscularly.

If Intron A is tolerated with normalization of ALT at 16 weeks of treatment, therapy should be extended to 18 to 24 months (72-96 weeks) to improve sustained response rate.

Rebetol (ribavirin) capsules are administered orally at a dose of 1000mg or 1200mg daily (weight-based) in two divided doses (morning and evening), in combination with Intron A.

- Members weight <75kg should receive 1000mg daily as two 200mg capsules in the morning and three 200mg capsules in the evening.
- As for members weighing >75kg should receive 1200mg daily as three 200mg capsules in the morning and three 200mg capsules in the evening.

Dosing of Intron A for hepatitis B:

- Adult: The recommended dose is 30-35 million IU per week administered subcutaneously or intramuscularly, either as five million IU daily or as 10 million IU

three times a week for 16 weeks.

- Pediatric: The recommended dose is three million IU/m2 administered three times a week for the first week of therapy followed by dose escalation to six million IU/m2 three times a week (maximum of 10 million IU TIW) administered subcutaneously for a total duration of 16 to 24 weeks.

Dosing of Intron A for hairy cell leukemia:

The recommended dose is two million IU/m2 administered intramuscularly or subcutaneously three times a week for up to six months.

Dosing of Intron A for malignant melanoma:

The adjuvant treatment is given in two phases, induction and maintenance:

- Induction dose is 20 million IU/m2 as an intravenous infusion, over 20 minutes, five consecutive days per week, for four weeks.
- Maintenance dose is 10 million IU/m2 as a subcutaneous injection three times per week for 48 weeks.

Dosing of Intron A for follicular non-Hodgkin's lymphoma:

The recommended dose is five million IU subcutaneously three times per week.

Dosing of Intron A for condylomata accuminata:

The recommended dose is one million IU intralesionally in a maximum of five lesions in a single course. The lesions should be injected three times weekly on alternate days for three weeks. An additional course may be administered at 12 to 16 weeks.

Dosing of Intron A for AIDS-related Kaposi's sarcoma:

The recommended dose is 30 million IU/m2/dose administered subcutaneously or intramuscularly three times a week until disease progression or maximal response has been achieved after 16 weeks of treatment.

Alferon N:

Interferon alfa-n3 is available as Alferon N as a 5,000,000 U/ml solution for injection in 1 ml

vials.

The recommended dose of Alferon N (interferon alfa-n3) for the treatment of condylomata acuminata is 0.05 ml (250,000 IU) per wart administered twice weekly for up to 8 weeks. The maximum dose per treatment session is 0.5ml (2.5 million IU). Therapy should not be repeated for at least 3 months after the initial 8 week course of therapy.

Actimmune:

Interferon gamma-1b is available as Actimmune, a sterile solution filled in a single-use vial for subcutaneous injection containing 100mcg/ 0.5mL (2 million IU).

The recommended dose for the treatment of members with Chronic Granulomatous Disease and severe Malignant Osteopetrosis is 50 mcg/m2 (1 million IU/m2) for members whose body surface area is greater than 0.5 m2 and 1.5 mcg/kg/dose for members whose body surface areas is equal to or less than 0.5 m2. Injections should be administered subcutaneously three times weekly. The optimum sites of injection are the right and left deltoid and anterior thigh.

Higher doses are not recommended. Safety and efficacy has not been established for doses greater or less than the recommended dose of 50 mcg/m2.

PegIntron:

PegIntron is available in:

- PegIntron REDIPEN Package: One-50mcg, 80mcg, 120mcg, or 150mcg per 0.5mL REDIPEN
- PegIntron REDIPEN PAK 4: Four-50mcg, 80mcg, 120mcg, or 150mcg per 0.5mL REDIPEN Units
- PegIntron Package: One-50mcg, 80mcg, 120mcg, or 150 mcg per 0.5 mL vial of PegIntron Powder and one 1.25mL vial of Diluent.

Dosing of PegIntron:

- ADULT: 1.5mcg/kg/week subcutaneously
- PEDIATRIC (3 - 17 years of age): 60mcg/m2 /week subcutaneously

Pegasys:

Pegasys (peginterferon alfa-2a) is available as an injectable solution in vials (180 µg/1.0 mL), pre-filled syringes (180 µg/0.5 mL), and pen autoinjectors (135 µg/0.5 mL, 180 µg/0.5 mL).

Dosing of Pegasys for hepatitis C:

- Adults ≥ 18 years of age: 180 µg subcutaneously once weekly
- Pediatrics 5 to 17 years of age: BSA X 180 µg/1.732 m2 subcutaneously once weekly

Dosing of Pegasys for hepatitis B:

180 µg once a week subcutaneously for 48 weeks.

- For HBeAG Positive members: ALT must >2x the upper limit of normal and have HBV DNA >20,000 IU/ml.
- For HBeAG Negative members: ALT must be greater than 1x the upper limit of normal and have HBV DNA >2,000 IU/ml.

Sylatron:

Peginterferon alfa-2b is available as Sylatron lyophilized powder per single-use vial: 200 MCG, 300 MCG, 600 MCG.

Dosing of Syaltron for melanoma:

- 6 MCG/KG/week Subcutaneously for 8 doses, followed by 3 MCG/KG/week Subcutaneously for up to 5 years. Premedicate with acetaminophen 500 to 1000 MG Orally 30 minutes prior to the first dose and as needed for subsequent doses.
- For dosing recommendations in moderate or severe renal impairment, please consult Full Prescribing Information.

Interferon Beta (Avonex, Betaseron, Extavia, Rebif, Plegridy):

For dosing of beta interferons, see CPB 0264 - Multiple Sclerosis (../200_299/0264.html).

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description

Code	Code Description
Interferon Alpha:	
Other CPT codes related to the CPB:	
11900	Injection, intralesional; up to and including 7 lesions
11901	more than 7 lesions
87520 - 87522	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique, amplified probe technique, or quantification
96401 - 96402	Chemotherapy administration, subcutaneous or intramuscular
HCPCS codes covered if selection criteria are met:	
J9212	Injection, interferon alfacon-1, recombinant, 1 mcg
J9213	Injection, interferon, alfa-2A, recombinant, 3 million units
J9214	Injection, interferon, alfa-2B, recombinant, 1 million units
J9215	Injection, interferon, alfa-N3, (human leukocyte derived), 250,000 IU
Other HCPCS codes related to the CPB:	
S9559	Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem
ICD-10 codes covered if selection criteria are met:	
A63.0	Anogenital (venereal) warts [genital warts (intralesional only)]
B17.10 - B17.11	Acute hepatitis C
B18.0 - B18.1	Chronic viral hepatitis B
B18.2	Chronic viral hepatitis C
B19.20 - B19.21	Unspecified viral hepatitis C
C18.0 - C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal
C22.0 - C22.9	Malignant neoplasm of liver, primary and intrahepatic bile ducts [cholangiocarcinoma] [hepatocellular carcinoma]
C43.0 - C43.9	Malignant melanoma of skin [only Sylatron brand is considered medically necessary]
C46.0 - C46.9	Kaposi's sarcoma [AIDS-associated]
C64.1 - C65.9	Malignant neoplasm of kidney and of renal pelvis [renal cell carcinoma]
C67.0 - C67.9	Malignant neoplasm of bladder
C69.00 - C69.92	Malignant neoplasm of eye and adnexa [ocular surface neoplasia]

Code	Code Description
C7A.010 - C7A.029	Malignant carcinoid tumors of the small intestine, appendix, large intestine and rectum
C7A.090 - C7A.092	Malignant carcinoid tumors of the bronchus and lung, thymus and stomach
C7A.094 - C7A.096	Malignant carcinoid tumors of the foregut, midgut and hindgut NOS
C79.00 - C79.02	Secondary malignant neoplasm of other parts of nervous system [leptomeningeal metastases of central nervous system tumors][code is being added to be consistent with NCCN guidelines]
C82.00 - C82.99	Follicular lymphoma
C83.00 - C83.99	Non-follicular lymphoma
C84.00 - C84.99	Mature T/NK-cell lymphomas
C85.10 - C85.99	Other specified and unspecified types of non-Hodgkin lymphoma
C86.0 - C86.6	Other specified types of T/NK-cell lymphoma
C88.0	Waldenstrom macroglobulinemia
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C91.10 - C91.12	Chronic lymphocytic leukemia of B-cell type [chronic myelogenous leukemia (not in accelerated phase)]
C91.40 - C91.42	Hairy cell leukemia
C94.40 - C94.42	Acute panmyelosis with myelofibrosis [symptomatic low-risk myelofibrosis]
C96.0 - C96.4, C96.a - C96.9	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
D01.0	Carcinoma in situ of colon
D04.0 - D04.9	Carcinoma of skin in situ
D06.0 - D06.9	Carcinoma in situ of cervix uteri
D09.0	Carcinoma in situ of bladder
D14.1	Benign neoplasm of larynx [respiratory papillomatosis]
D18.00 - D18.09	Hemangioma [intralesional] [life-threatening hemangioma of infancy when member is intolerant/resistant to corticosteroids]
D31.00 - D31.92	Benign neoplasm of eye and adnexa. [ocular surface neoplasia]
D32.0, D32.9	Benign neoplasm of meninges [recurrent, surgically inaccessible meningioma]

Code	Code Description
D3A.010 - D3A.029	Benign carcinoid tumors of the small intestine, appendix, large intestine and rectum
D3A.090 - D3A.092	Benign carcinoid tumors of the bronchus and lung, thymus and stomach
D3A.094 - D3A.096	Benign carcinoid tumors of the foregut, midgut and hindgut NOS
D45	Polycythemia vera
D47.1	Chronic myeloproliferative disease [symptomatic low-risk myelofibrosis]
D47.3	Essential (hemorrhagic) thrombocythemia
D47.4	Osteomyelofibrosis [symptomatic low-risk myelofibrosis]
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage [giant cell tumor]
D69.3 - D69.49	Immune thrombocytopenic purpura and other primary thrombocytopenia
D72.1	Eosinophilia [Hypereosinophilic syndrome]
D75.1	Secondary polycythemia
D75.81	Myelofibrosis [symptomatic low-risk myelofibrosis]
E34.0	Carcinoid syndrome
N94.810	Vulvar vestibulitis
P61.1	Polycythemia neonatorum
Z22.51	Carrier of viral hepatitis B
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
B00.1, B00.3, B00.50 - B00.9	Herpesviral [herpes simplex] infections
B01.0 - B01.9	Varicella [chickenpox]
B02.33	Zoster keratitis
B07.9	Viral wart, unspecified [cutaneous]
B08.011	Vaccinia not from vaccine
B16.0 - B16.9	Acute hepatitis B
B17.0	Acute delta-(super) infection of hepatitis B carrier
B19.10 - B19.11	Unspecified viral hepatitis B
B20	Human immunodeficiency virus [HIV] disease [AIDS-related complex] [AIDS in combination with AZT]

Code	Code Description
B25.0 - B25.9	Cytomegaloviral disease [CMV]
B34.8	Other viral infections of unspecified site [rhinovirus infection]
C22.0 - C22.8	Malignant neoplasm of liver and intrahepatic bile ducts [cholangiocarcinoma] [hepatocellular carcinoma]
C25.0 - C25.9	Malignant neoplasm of pancreas
C25.4	Malignant neoplasm of endocrine pancreas
C38.4	Malignant neoplasm of pleura [mesothelioma]
C40.00 - C41.9	Malignant neoplasm of bone and articular cartilage [osteosarcoma]
C44.01 C44.111 - C44.119 C44.211 - C44.219 C44.310 - C44.319 C44.41 C44.510 - C44.519 C44.611 - C44.619 C44.711 - C44.719 C44.81 C44.91	Basal cell carcinoma
C44.02, C44.121 - C44.129, C44.221 - C44.229, C44.320 - C44.329, C44.42, C44.520 - C44.529, C44.621 - C44.629, C44.721 - C44.729, C44.82, C44.92	Squamous cell carcinoma
C50.011 - C50.929	Malignant neoplasm of breast
C53.0 - C53.9	Malignant neoplasm of cervix uteri
C56.1 - C57.4	Malignant neoplasm of ovary and other female genital organs
C61	Malignant neoplasm of prostate
C70.0 - C70.9	Malignant neoplasm of meninges

Code	Code Description
C71.0 - C71.9	Malignant neoplasm of brain [for primitive neuroectodermal tumor (PNET)]
C72.0 - C72.9	Malignant neoplasm of other and unspecified parts of nervous system [for primitive neuroectodermal tumor (PNET)]
C78.5	Secondary malignant neoplasm of large intestine and rectum
C79.49	Secondary malignant neoplasm of other parts of nervous system [leptomeningeal metastases of central nervous system tumors][code is being added to be consistent with NCCN guidelines]
C79.81	Secondary malignant neoplasm of breast
C86.6	Primary cutaneous CD30-positive T-cell proliferations [primary cutaneous anaplastic large cell lymphoma with multifocal lesions]
C90.00 - C90.02	Multiple myeloma
C90.30 - C90.32	Solitary plasmacytoma
C92.10 - C92.12	Chronic myeloid leukemia, BCR/ABL positive [chronic myelogenous leukemia]
D05.00 - D05.92	Carcinoma in situ of breast
D12.0 - D12.6	Benign neoplasm of colon [Gardner's syndrome]
D13.7	Benign neoplasm of endocrine pancreas
D21.0 - D21.9	Other benign neoplasms of connective and other soft tissue
D36.10 - D36.17	Benign neoplasm of peripheral nerves and automatic nervous system [plexiform neurofibroma]
E85.0	Non-neuropathic heredofamilial amyloidosis
E85.81 - E85.89	Other amyloidosis [systemic light chain amyloidosis]
G35	Multiple sclerosis
H04.121- H04.129	Dry eye syndrome
H04.561 - H04.569	Stenosis of lacrimal punctum
H11.141 - H11.149	Conjunctival xerosis, unspecified
H35.061 - H35.069	Retinal vasculitis
H35.30 - H35.3293	Degeneration of macula [age-related]
H91.20 - H91.23	Sudden idiopathic hearing loss

Code	Code Description
I78.0	Hereditary hemorrhagic telangiectasia
K63.5	Polyp of colon
K73.0 - K73.9, K75.4	Chronic hepatitis
L91.0	Hypertrophic scar
M32.0 - M32.9	Systemic lupus erythematosus
M35.00 - M35.09	Sicca syndrome [Sjögren]
M35.2	Behcet's disease
N48.6	Induration penis plastica
R18.0 - R18.8	Ascites
T88.1xxA - T88.1xxS	Other complications following immunization, not elsewhere classified
Pegylated Interferon Alpha:	
Other CPT codes related to the CPB:	
87520 - 87522	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique, amplified probe technique, or quantification
HCPCS codes covered if selection criteria are met:	
S0145	Injection, pegylated interferon alfa-2a, 180 mcg per ml
S0148	Injection, pegylated interferon alfa-2b, 10 mcg
Other HCPCS codes related to the CPB:	
S9559	Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem
ICD-10 codes covered if selection criteria are met:	
B18.0 - B18.1	Chronic viral hepatitis B [see criteria]
B18.2	Chronic viral hepatitis C [see criteria]
C43.0 - C43.9	Malignant melanoma of skin [only Sylatron brand is considered medically necessary]
C94.40 - C94.42	Acute panmyelosis with myelofibrosis
D45	Polycythemia vera
D47.1	Chronic myeloproliferative disease
D47.3	Essential (hemorrhagic) thrombocythemia

Code	Code Description
D47.8	Osteomyelofibrosis
D75.81	Myelofibrosis
ICD-10 codes not covered for indications listed in the CPB:	
A81.2	Progressive multifocal leukoencephalopathy
B07.0 - B07.9	Viral warts
B97.7	Papillomavirus as the cause of diseases classified elsewhere
C40.00 - C41.9	Malignant neoplasm of bone and articular cartilage [osteosarcoma]
C44.02, C44.121 - C44.129, C44.221 - C44.229, C44.320 - C44.329, C44.42, C44.520 - C44.529, C44.621 - C44.629, C44.721 - C44.729, C44.82, C44.92	Squamous cell carcinoma
C92.10 - C92.12	Chronic myeloid leukemia, BCR/ABL-positive
D21.0 - D21.9	Other benign neoplasms of connective and other soft tissue
D36.10 - D36.17	Benign neoplasm of peripheral nerves and automatic nervous system [plexiform neurofibroma]
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage [giant cell tumor]
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue
D48.2	Neoplasm of uncertain behavior of peripheral nerves and autonomic nervous system
D72.1	Eosinophilia [eosinophilia/hyper-eosinophilic syndrome]
R85.618	Other abnormal cytological findings on specimens from anus
R85.81	Anal high risk human papillomavirus (HPV) DNA test positive
R87.628	Other abnormal cytological findings on specimens from vagina
R87.810 - R87.811	High risk human papillomavirus [HPV] DNA test positive from female genital organs
R87.820	Cervical low risk human papillomavirus (HPV) DNA test positive

Code	Code Description
Interferon beta:	
HCPCS codes covered if selection criteria are met:	
J1595	Injection, glatiramer acetate, 20 mg [medically necessary only if the member has a contraindication, allergy, intolerance, or failure of an adequate trial of Glatopa]
J1826	Injection, interferon beta-1a, 30 mcg
J1830	Injection interferon beta-1b, 0.25 mg (code may be used for Medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered) [covered for relapsing, remitting multiple sclerosis in persons with a contraindication, allergy, intolerance or failure of a 1-month trial of Copaxone plus have a contraindication, allergy, intolerance or failure of a 1-month trial of Avonex or Rebif]
Q3027	Injection, interferon beta-1a, 1 mcg for intramuscular use
Other HCPCS codes related to the CPB:	
S9559	Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem
ICD-10 codes covered if selection criteria are met:	
G35	Multiple sclerosis [relapsing/remitting]
ICD-10 codes not covered for indications listed in the CPB:	
G04.81	Other encephalitis and encephalomyelitis [chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)]
G61.0	Guillain-Barre syndrome
G61.81	Chronic inflammatory demyelinating polyneuritis
Interferon gamma:	
HCPCS codes covered if selection criteria are met:	
J9216	Injection, interferon, gamma-1B, 3 million units
ICD-10 codes covered if selection criteria are met:	
C84.00 - C84.09	Mycosis fungoides
C84.10 - C84.19	Sezary disease
D71	Functional disorders of polymorphonuclear neutrophils [chronic granulomatous disease, to reduce frequency and severity of infections]
L20.0 - L20.82, L20.84 - L20.9	Atopic dermatitis [chronic recalcitrant]
Q78.2	Osteopetrosis

Code	Code Description
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
A15.0	Tuberculosis of lung
C25.0 - C25.9	Malignant neoplasm of pancreas
C45.1	Mesothelioma of peritoneum
C48.0 - C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C71.0 - C71.9	Malignant neoplasm of brain
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C88.0	Waldenstrom macroglobulinemia
D33.0 - D33.2	Benign neoplasm of brain
D76.1 - D76.3	Other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue [macrophage activation syndrome]
J84.112	Idiopathic pulmonary fibrosis
M04.1 - M04.9	Autoinflammatory syndromes
M08.80 - M08.9	Other juvenile arthritis
Sovaldi (sofosbuvir) in combination with Pegylated Interferon Alpha:	
Other CPT codes related to the CPB:	
87520 - 87522	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique, amplified probe technique, or quantification
HCPCS codes covered if selection criteria are met:	
Sovaldi (sofosbuvir):	
No specific code	
Other HCPCS codes related to the CPB:	
S0145	Injection, pegylated interferon alfa-2a, 180 mcg per ml
S0148	Injection, pegylated interferon alfa-2b, 10 mcg
S9559	Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem
ICD-10 codes covered if selection criteria are met:	
B18.2	Chronic viral hepatitis C

The above policy is based on the following references:

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