



PLEASE READ FIRST

The International Society for Interferon and Cytokine Research (ISICR) provides information on interferons as a public service. To the best of our knowledge the information is accurate but it is not meant to and must not substitute for the advice of your personnel physician.

Interferon is considered a **black box** drug by the FDA because the use of interferon may be accompanied by serious side effects. If you are anticipating beginning treatment with interferon, read the information provided by the pharmaceutical company from which your interferon was obtained carefully. If you experience any side effects upon receiving interferon, including depression, discuss these effects with your physician immediately. The ISICR does not recommend any particular form of interferon and cannot be held liable for any consequences that may result due to the use of interferon in any clinical situation.

Interferons: A primer for the non-scientist

What are they, what do they do and how are they used?

What are interferons? Interferons are natural proteins made and released by cells of the body in response to viruses and other disease-causing microorganisms. They were first discovered by scientists in England in 1957 although a few years earlier, scientists in Japan had evidence of some type of substance produced by the body that blocked viruses from reproducing. Interferons help protect you against infection and help in the recovery from infections. They can also affect how cancer cells grow. Interferons are critical to maintaining a healthy immune system.

What are the types of interferons? Interferons can be grouped into two general categories, the Type I and Type II interferons. Type I interferons include one beta interferon and over 20 different alpha interferons. While the alpha interferons are very similar in how they work, different members of the alpha interferon family can vary greatly in how effective they are in helping your body defend itself against infection and cancer. The only Type II interferon is known as gamma interferon.

How do interferons work? Much remains unknown about how interferons inhibit viruses and the growth of cancer cells. Interferons are known to interact with other proteins on the outside of cells that are called receptors. Through their interactions with receptors, interferons send signals to the inside of cells that result in temporary changes in the cells of your body. These changes can make your body much more resistant to the spread of infection. When you have a cold, there is lots of interferon in the circulation because your body has responded to infection by the cold virus. The benefit of interferons in cancer, and particularly melanoma, appears to be due to its effects on the immune system. Studies to better understand how interferons work are being performed in laboratories around the world. In the US, most of this research is funded by your tax dollars through the National Institutes of Health (NIH).

What is “natural” interferon? Natural interferons are those produced and purified from human cells. The benefit of using natural interferons, as with other products derived from human sources, is that they are like the proteins made in your body. However, these natural products also have the potential to carry their own viruses that may cause disease. The risk of carrying viruses as a result of the production of natural interferons is very low. Interferon alpha-n3, made from human blood, is carefully screened to prevent any contamination. There have been no known cases of infection with any viruses as a result of receiving interferon as a treatment.

What is “recombinant” interferon? Recombinant interferons are produced in bacteria or in animal cells by using DNA technology. This permits the production of highly purified interferon at a much cheaper cost. The production of recombinant interferons in animal cells results in modifications to the proteins that make them more like those isolated from humans but interferons made in bacteria are also effective when given to patients.

What types of interferons have been approved by the FDA for use in the treatment of clinical diseases in the US?

The FDA has approved eleven different interferons: interferon alpha-2a (Roferon A), Interferon alpha-2b (Intron A), Interferon alfacon-1 (Infergen), Interferon alfa-n3 (Alferon N Injection), Interferon beta-1a (Avonex and Rebif), Interferon beta-1b (Betaseron), Peginterferon alfa-2a (Pegasys), Peginterferon alfa-1a plus ribavirin (Peginterferon), Peginterferon alfa-2b (Peg-Intron), and Interferon gamma-1b (Actimmune).

For what diseases are interferons approved for treatment?

Interferon alpha-2a (Brand name Roferon-A) has been used to treat chronic hepatitis C, hairy cell leukemia, and some forms of chronic myelogenous leukemia (CML). Roferon-A has also been approved for use in combination with ribavirin. Roferon-A is produced by Hoffman- La Roche Inc.

Interferon alpha-2b (Brand name Intron A) has been used to treat hairy cell leukemia, AIDS-related Kaposi sarcoma, certain types of genital warts, chronic hepatitis C, follicular lymphoma in combination with chemotherapy, and malignant melanoma. Interferon alpha-2b may be used in combination with another drug called ribavirin (Brand name Rebetron) to treat chronic hepatitis C in those people who no longer are receiving any benefit from being treated with interferon alpha alone. Some patients may have been cured of these conditions when the combination of drugs was used. Intron A is produced by Schering Corporation.

Interferon alfacon-1 (Brand name Infergen) is used to treat chronic hepatitis C. This interferon is produced by recombinant DNA technology and expressed and purified from bacteria. Infergen is produced by Amgen.

Interferon alpha-n3 (Brand name Alferon N) is used to treat venereal or genital warts caused by human papilloma virus (HPV). It is isolated from human blood lymphocytes induced to produce alpha interferon. Alferon N is produced by Interferon Sciences.

Interferon beta-1a (Brand names: Avonex and Rebif) is used to treat relapsing forms of multiple sclerosis (MS) and is a recombinant interferon produced in cell cultures. Interferon beta-1a will not cure multiple sclerosis but has been found to decrease the number of flare-ups and slow the occurrence of physical disability. Avonex is produced by Biogen, Inc. and Rebif is produced by Serano, Inc.

Interferon beta-1b (Brand name Betaseron) is used to treat relapsing forms of multiple sclerosis (MS). Betaseron is a modified interferon beta. Betaseron is generated by recombinant DNA technology and is expressed and purified from bacteria. Betaseron does not cure multiple sclerosis but has been found to reduce the frequency of attacks. Betaseron is produced by Chiron Corporation and distributed by Berlex Laboratories.

Interferon gamma-1b (Brand name Actimmune) is used to delay the time to disease progression in patients with: (i) Chronic Granulomatous Disease (CGD) and (ii) severe malignant osteopetrosis. Chronic Granulomatous Disease is a very rare inherited condition characterized by reduced function of a specific type of white blood cells. Severe, malignant osteopetrosis is also an inherited disease but one characterized by a problem in normal generation of bones. This problem results in bone overgrowth and defective ability of white blood cells to destroy microorganisms. Treatment with Actimmune for both conditions greatly improves the ability of the patients to fight infectious disease. Actimmune is produced by InterMune.

Peginterferon alfa-2b (Brand name PEG-Intron) is a form of interferon alfa-2b produced in bacteria. It is then combined with a compound called monomethoxypolyethylene glycol (PEG). The addition of PEG allows the interferon to remain in the body longer, thereby reducing the number of injections. PEG-intron is used in the treatment of chronic hepatitis C in the absence of compensated liver disease and without previous interferon alpha treatment in combination with REBETOL (ribavirin). It may cure chronic hepatitis C in some patients and may be able to prevent liver failure or cure liver cancer that is caused by hepatitis C infection. PEG-Intron is produced by Schering Corporation.

Peginterferon alfa-2a (Brand name Pegasys) is another form of interferon alfa-2a produced in bacteria and then combined with bis-monomethoxy polyethylene glycol (another type of PEG). The addition of PEG to interferon alpha allows the interferon to remain in the body longer, thereby reducing the number of injections. Pegasys is used in combination with COPEGUS (ribavirin) to treat patients with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. In some patients, chronic hepatitis has been cured with the combination treatment. Pegasys and COPEGUS are produced by Roche Laboratories.

How is interferon administered? The dosage and administration schedule for interferons varies with the specific interferon type, formulation and the disease being treated. All interferons are administered by injection. The site of injections can vary with the disease and the specific interferon being used.

What conditions should be discussed with your physician before starting interferon therapy? Before taking recombinant interferons inform your physician if you have allergies to bacterial products. Do not use interferon alfa-n3 if you are allergic to rodents, eggs, or neomycin products. Some of the interferon products contain human serum albumin. Discuss with your physician if you are allergic to human albumin or have other illnesses that are may be affected by your receiving interferon.

Discuss with your physician if you are pregnant, as it is unknown whether interferons can be harmful to your unborn child. Although no birth defects or spontaneous abortions have been associated with interferons, tests performed in monkeys using much higher doses of interferon than used in people produced more spontaneous abortions. It is also unknown whether

interferons can be found in breast milk. Therefore it is recommended that precautions against pregnancy be taken during treatment.

Interferon alpha-2b when taken together with ribavirin has been shown to cause birth defects, possibly due to the ribavirin. This combination treatment should not be taken by pregnant women or by the male partners of pregnant women. Great care should be taken to prevent pregnancy during this treatment and for 6 months after treatment.

Discuss with your physician if it is advisable to take interferon alpha-2a if you have any of the following conditions: a history of depression or suicidal thoughts, anxiety, drug or alcohol abuse or mental illness; an active infection; diabetes; heart disease or a history of heart attack; a seizure disorder; an autoimmune disease, or psoriasis of the skin; a suppressed immune system or have received an organ transplant; have bone marrow suppression; kidney disease; or liver disease. For interferon alpha-2b or interferon-alfacon-1 consider the above conditions plus lung disease; a history of blot clots; low platelet counts; or thyroid problems. For the combination of interferon alpha-2b and ribavirin you should talk with your physician if you have blood conditions such as anemia, thalassemia, sickle-cell anemia; low red or white blood cells or platelets; high blood pressure, history of heart attack or heart disease; had an organ transplant or are taking drugs to prevent rejection medicine; lung or breathing problems; kidney problems; livers problems (except viral hepatitis); diabetes; thyroid problems; autoimmune disease; psoriasis; an infection; eye problems; a seizure disorder; or pancreatitis.

What are the side effects of interferon treatment? *FOR ANY SPECIFIC INTERFERON, IT IS IMPORTANT TO READ THE INFORMATION PAMPHLET PROVIDED WITH THE DRUG BY THE MANUFACTURER.* The following is a summary of the major side effects and is not meant to include all possible side effects. Whether or not you will experience any of these possible side effects cannot be determined before you receive interferon.

Interferons can cause serious mood or behavioral changes. These changes can be life threatening. At least one in four persons (25%) taking interferon experience some psychological changes, such as irritability, anxiety, nervousness, sadness, depression, or emotional mood swings. Patients should be monitored closely with periodic clinical and laboratory evaluations. Contact your physician immediately if you experience symptoms of depression or suicidal thoughts, if you become very irritable, nervous, or aggressive, or if you experience any other mood or behavioral changes. In about one in ten patients (10%) these symptoms are severe enough to require stopping interferon treatment early. While these symptoms usually go away within one to three weeks after interferon is stopped, in rare instances people complain that the anxiety or depression continued.

Flu-like symptoms usually occur following the first injection of interferon. These symptoms include fever, chills, weakness, fatigue, muscle aches, joint aches, and headaches, slight nausea, and poor appetite. Remember your body produces interferon when you get a cold, the flu or other infections. The flu-like symptoms usually appear 4 to 8 hours after injection and last for 6 to 12 hours. These symptoms most commonly occur at the start of therapy and may decrease in severity as therapy continues. Over-the-counter medications such as acetaminophen (Tylenol) or

a non-steroidal anti-inflammatory drug (NSAID, such as motrin) and plenty of fluids are recommended to lessen or eliminate some of the symptoms. Administering the interferon at bedtime may also help. Other flu-like symptoms can include: vomiting or loss of appetite, diarrhea, dizziness or drowsiness, nervousness or anxiety, insomnia, loss or thinning of hair, increased sweating, itching or rash, or pain, redness, or bruising at the injection site. If you experience these flu-like symptoms, notify your physician but continue taking the interferon. Because of these symptoms it is advised that you not plan to work or drive during this period.

Continued treatment with interferon commonly causes fatigue, weakness, muscle and joint aches, headaches, and an increased need to sleep. The amount of fatigue can vary greatly from day to day and may or may not be troublesome. Sometimes the fatigue is severe enough to require stopping interferon treatment early.

Interferon causes mild suppression of the bone marrow, which results in fewer red blood cells, white blood cells, and platelets. The red blood cells carry oxygen in the body and a decrease in red blood cells is called anemia. Anemia can cause weakness, shortness of breath and headaches. The white blood cells make up the immune system of the body and lowering their numbers may increase the chance of getting an infection. The platelets are responsible for blood clotting and decreasing the numbers of platelets can lead to a tendency to bleed. These effects should be closely watched during treatment. These decreases are usually not severe during treatment and go away when the interferon treatment is stopped. Immediately contact your physician if you develop a persistent fever, any symptoms of an infection, unusual bruising or bleeding.

About one-quarter of the patients taking interferon have hair loss. This loss is temporary and the hair grows back after the interferon is stopped.

Less common side effects of interferon treatment can include: Stomach upset, nausea, vomiting, poor appetite, weight loss, diarrhea, stomach cramps, muscle aches, and headaches. Some patients complain of difficulty concentrating, disturbed sleep, or memory loss. These side effects tend to be mild and go away when treatment stops.

Interferons can also cause or aggravate autoimmune diseases. Patients should be monitored closely with frequent clinical and laboratory evaluations. Interferons can worsen rheumatoid arthritis, autoimmune hepatitis, or ulcerative colitis. Some of the autoimmune conditions that have appeared during interferon therapy are thyroid problems, skin rashes, diabetes, anemia, low platelets, arthritis, and inflammation of the blood vessels (vasculitis). Interferon treatment can also cause the autoimmune disease sarcoidosis, which involves skin rashes but can also damage other organs. Usually the conditions go away when interferon treatment is stopped. Autoimmune conditions occur in about 1 of every 100 patients treated.

Side effects occurring in less than 1 person in each 100 patients treated with interferon include: temporary worsening of hepatitis, increased rate of infections, lung problems, pneumonia, heart attack, heart failure, kidney failure, decrease or partial loss of vision or hearing, dizziness or seizures.

Gamma interferon should be used with caution in patients with cardiac disease, known seizure disorders, compromised central nervous system function, or myelosuppression.

Use caution when driving or operating machinery while being treated with interferon alphas. Interferon alphas can cause drowsiness, dizziness, or decreased alertness. No restrictions in food, beverages, or activities are necessary with either beta interferons or gamma interferons.

Patients taking interferons alone or in combination with ribavirin have experienced problems with a variety of organs. Immediately contact your physician if you have shortness of breath, blurred vision, chest pain, or loss of vision.

Seek emergency treatment if you develop difficulty breathing, closure of the throat, swelling of the lips, tongue, or face, or develop hives. Stop use immediately. These can be signs of an allergy to interferon or to something in the interferon preparation.

Alpha interferon plus ribavirin treatment can induce or aggravate a variety of eye conditions resulting in decrease or loss of vision. Patients should have an eye exam prior to initiation of treatment and should be followed periodically with additional eye exams. Report any vision changes to your physician.

Severe liver injury has been reported in patients taking Rebif and Avonex. These injuries are very rare but have required liver transplant.

What are the side effects of ribavirin? Ribavirin has been given to over 100,000 patients along with interferons as treatment for hepatitis C.

The most common side effect of ribavirin treatment is anemia (described above). The anemia is usually mild but if it becomes too severe the treatment will be stopped. The red blood count is returned to normal when the ribavirin is stopped. The anemia caused by ribavirin can increase the amount of iron in the liver. Usually the increase in iron levels in the liver is not a problem but if the iron levels become high enough they can cause liver damage.

Ribavirin also causes a decrease in lymphocytes, white blood cells that fight infections. The reduction in lymphocytes is usually small and normally does not cause serious problems.

Ribavirin may increase the levels of uric acid in the blood and trigger gout. This is rare and normally only occurs in patients with previous history of gout.

About 1 in 10 patients on ribavirin report an itching of their skin. This is not usually troublesome enough to stop treatment. Ribavirin may also cause allergic skin rashes.

Ribavirin causes increased sun sensitivity. You should try to stay out of direct sun while taking ribavirin.

About 1 in 10 patients on ribavirin report nasal stuffiness, worsening of sinus problems, cough or earaches. These can be improved with antihistamines and are usually not severe.

Do other drugs interact with interferons? If you are taking theophylline, interferon alpha-2a may increase the levels of theophylline in your blood. Other drugs may also interact with interferons so be sure to make your physician aware of all prescription and nonprescription medications that you are taking. Interferon alphas may effect the way your liver metabolizes other drugs and this should be considered if you are taking other drugs that are metabolized by your liver. Not all drug interactions with interferons are known.

Do not drink alcohol while taking the combination of interferon alpha-2b and ribavirin because it may be harmful to your liver and may increase drowsiness or dizziness.

What does the future hold? A number of companies are working to develop new forms of interferons. They are trying to develop interferons that don't have the side effects seen with some of the interferons being used today, that may be more specific in killing cancer cells or that can be used at much lower doses. In addition, new ways to give interferon are being tested, including by nasal sprays and even in a pill or liquid form. Interferons are also being tested as treatment for other diseases alone or in combination with other drugs.

Information for this pamphlet was obtained from:

www.drugs.com, www.fda.gov

See individual US prescribing information for complete information on each of the FDA-approved interferons.

The International Society for Interferon and Cytokine Research (ISICR) is a non-profit professional scientific society devoted to basic and clinical research on interferons and cytokines. For more information on the society, please go to www.isicr.org. For other useful websites on Ribavirin or the use of interferon with Ribavirin, see:

<http://www.nlm.nih.gov/medlineplus/druginfo/uspid/500032.html>

<http://www.nlm.nih.gov/medlineplus/druginfo/uspid/202509.html>

<http://en.wikipedia.org/wiki/Ribavirin>

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If you think you may have a medical emergency, call your doctor or 911 immediately.

