SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Multiferon, 3 million IU, solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

A pre-filled syringe contains 3 million IU human leukocyte interferon-alpha (HuIFN-alpha-Le) per 0.5 ml (3 million IU/0.5 ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe
The solution is clear and colourless to pale yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Malignant melanoma:
Adjuvant treatment of high-risk patients with cutaneous melanoma, stages IIb-III, after 2 initial cycles of dacarbazine (DTIC).

Other indications:
Treatment of patients who initially respond to recombinant interferon-alpha, but for whom treatment subsequently fails, most likely as the result of neutralising antibodies.

4.2 Posology and method of administration

Multiferon is administered subcutaneously.

Adjuvant treatment of malignant melanoma:
3 million IU three times weekly for 6 months after 2 initial cycles of DTIC 850 mg/m^2 (intravenous). DTIC should be administered once every 3 weeks, as well as 3 weeks prior to starting on interferon-alpha.

Second-line treatment of viral and malignant diseases:
Clinical experience is limited, but the transition from recombinant interferon-alpha to Multiferon should not normally entail a change in dosage (IU). Adverse reactions similar to those upon introduction of interferon-alpha treatment can develop and justify a gradual dosage reduction.

If intolerance persists or recurs after suitable dosage adjustment, Multiferon treatment should be discontinued. For subcutaneous maintenance treatment, the patient may self-administer the dose at the discretion of the physician. The injection site should be varied during the course of treatment.

Safety and efficacy data on the use of Multiferon in children and adolescents are very limited

4.3 Contraindications

- Hypersensitivity to human interferon-alpha or any of the excipients of Multiferon listed in section 6.1.
- Severe cardiac disease
- Severely impaired renal or hepatic function, including that caused by metastases

- Severe myelosuppression
- Chronic hepatitis with decompensated cirrhosis of the liver
- Chronic hepatitis in patients who are being, or recently have been, treated with immunosuppressive agents, with the exception of short-term corticosteroid treatment
- Autoimmune hepatitis, or history of autoimmune disease, immunosuppression in transplant recipients
- Pre-existing thyroid disease unless controlled with conventional treatment
- Epilepsy and/or central nervous system (CNS) dysfunction, see section 4.4.

Children and adolescents:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during interferon-alpha therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with interferon-alpha be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions: If treatment with interferon alpha is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of interferon alpha in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated, see section 4.3.

More significant obtundation and coma have been observed in some patients, usually the elderly, who have been treated with high doses of interferon-alpha. Although these effects are ordinarily reversible, full resolution took up to three weeks in some patients. In very rare cases, seizures have occurred with high doses of interferon-alpha.

Acute hypersensitivity reactions (including urticaria, angioedema, bronchoconstriction and anaphylaxis) have been reported in rare cases during interferon-alpha treatment. If such a reaction develops, taking of the product should be discontinued and appropriate medical treatment begun immediately. Transient rashes do not call for interruption of treatment.

Moderate or severe adverse reactions may necessitate modification of the patient's dose regimen – or termination of Multiferon treatment in some cases. Any patient who develops abnormal liver function during treatment with Multiferon should be monitored closely, and treatment should be discontinued if signs and symptoms progress.

Hypotension that requires supportive treatment may develop during interferon-alpha treatment or up to two days after the injection.

Because hypotension related to fluid depletion has been reported in some patients, adequate hydration should be maintained in patients who undergo Multiferon treatment. Fluid replacement may be necessary.

Although fever may be associated with flu-like symptoms commonly reported during interferon-alpha treatment, other causes of fever should be ruled out.

Paracetamol has been successfully used to alleviate the symptoms of fever and headache that can occur during Multiferon treatment. The recommended paracetamol dosage is 500 mg to 1 g 30 minutes prior to administration of Multiferon. The maximum permissible dosage of paracetamol is 1 g four times daily.

Multiferon should be used cautiously in patients with debilitating medical conditions, such as patients with a history of pulmonary disease (e.g. chronic obstructive pulmonary disease) or patients with diabetes mellitus who are prone to ketoacidosis. Caution should also be exercised in patients with coagulation disorders (such as thrombosis or pulmonary embolism).

In rare cases, pulmonary infiltrates, pneumonitis and pneumonia – including fatalities – have been reported in patients who have been treated with interferon-alpha. The aetiology has not been identified. The symptoms have been reported more frequently when Sho-saiko-to, a Chinese and Japanese herbal medicine, was administered concomitantly with interferon-alpha. Any patient who develops fever, cough, dyspnoea or other respiratory symptoms should be given a chest X-ray. If the X-ray shows pulmonary infiltrates, or there is evidence of impaired pulmonary function, the patient should be monitored closely – and interferon-alpha treatment should be discontinued when deemed appropriate. Although these symptoms have been reported more often in patients with chronic hepatitis C who have been treated with interferon-alpha, they have also been reported in patients with oncological diseases who have been treated with interferon-alpha. Immediate discontinuation of interferon-alpha administration and treatment with corticosteroids appears to be associated with the resolution of adverse pulmonary events.

Ocular adverse reactions may occur after interferon-alpha has been used for several months, but they have also been reported after shorter treatment periods. Any patient who complains of changes in visual acuity or field of vision, or who reports other ophthalmological symptoms during treatment with interferon-alpha, should be given an eye examination. Because retinal effects may need to be distinguished from those observed in diabetic or hypertensive retinopathy, an eye examination is recommended before introducing interferon-alpha treatment in patients with diabetes mellitus or hypertensive disorders.

Patients with a history of chronic cardiac insufficiency, myocardial infarct and/or previous or current arrhythmic disorders who require interferon-alpha treatment should be monitored closely. Patients with heart disease or advanced cancer should be given ECGs before and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) ordinarily respond to conventional treatment but may call for discontinuation of interferon-alpha treatment.

Due to reports that pre-existing psoriatic diseases have been exacerbated, interferon-alpha should be used in patients with psoriasis only if the potential benefit justifies the potential risk.

Preliminary data indicate that interferon-alpha treatment may be associated with an increased rate of graft rejection in patients who have received liver or kidney transplants.

The development of various autoantibodies has been reported during treatment with interferon-alpha. Clinical manifestations of an autoimmune disorder during interferon-alpha treatment may occur more frequently in patients predisposed to the development of such disorders.

Treatment with interferon-alpha should be discontinued in patients with chronic hepatitis who develop prolonged effects on coagulation markers, which may be indicative of liver decompensation.

In rare cases, hyperglycaemia has been reported in patients who have been treated with interferon-alpha. The blood glucose levels of any patient who develops symptoms of hyperglycaemia should be monitored. The dosage of the diabetes treatment prescribed for patients with diabetes mellitus may need to be adjusted.

Mild or moderate impaired renal or hepatic function – or myelosuppression – requires careful monitoring.

Chronic hepatitis C: Development of thyroid disorders – either hypothyroidism or hyperthyroidism – has been infrequently reported in patients who have been treated with interferon-alpha. The mechanism by which interferon-alpha can alter thyroid status is unknown. Prior to introducing interferon-alpha treatment for chronic hepatitis C, the level of serum thyroid-stimulating hormone (TSH) should be examined. Any thyroid disorder detected at that point should be conventionally treated. Interferon-alpha treatment may begin if the medicinal product can keep TSH levels within normal limits. The TSH levels of any patient who develops symptoms during the course of interferon-alpha treatment that suggest possible thyroid dysfunction should be measured. Interferon-alpha treatment may be maintained in patients with pre-existing thyroid dysfunction if the medicinal product can keep TSH levels within normal limits. The discontinuation of interferon-alpha treatment has not led to resolution of thyroid dysfunction that had occurred during the course of treatment.

Concomitant chemotherapy: Administration of interferon-alpha in combination with other chemotherapeutic agents may increase the risk of toxicity (severity and duration), which may be life-threatening or fatal due to the concomitantly administered medicinal product. The most commonly reported adverse reactions that are potentially life-threatening or fatal include mucositis, diarrhoea, neutropaenia, impaired renal function and electrolyte disturbance. Owing to the risk of increased toxicity, dosages of both interferon-alpha and the concomitantly administered chemotherapeutic agents should be carefully adjusted.

AIDS-related Kaposi's sarcoma: Interferon-alpha should not be used in combination with protease inhibitors. No safety data is available for combining Multiferon with analogues of Nucleoside Reverse Transcriptase Inhibitors.

Laboratory tests:
Leukocyte and differential leukocyte count – as well as measurements of platelet, electrolyte, liver enzyme, serum protein, serum bilirubin and serum creatinine levels – should be performed on all patients before and at regular intervals during treatment with Multiferon.

In patients treated for hepatitis B or C, the recommended testing schedule is week 1, 2, 4, 8, 12 and 16, followed by once every other month during the course of treatment. If alanine aminotransferase (ALT) levels flares during Multiferon therapy to greater than or equal to 2 times baseline, Multiferon therapy may be continued unless signs and symptoms of hepatic failure are observed. While ALT levels are rising, prothrombin time – as well as alkaline phosphatase, albumin and bilirubin levels – should be monitored at two-week intervals.

In patients who are being treated for malignant melanoma, liver tests – as well as a full leukocyte and differential leukocyte count – should be performed during the induction phase and monthly during the maintenance phase.

Paediatric use: Clinical experience in treating children is limited. Expected benefits of treatment should be carefully weighed against the potential risks.

Effect on fertility: Interferon may impair fertility. In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed. Decreased serum oestradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon. As a result, women of fertile age should not receive Multiferon unless they are using effective contraception during the treatment period. Multiferon should be used with caution in men of fertile age.

Virological safety: Multiferon is a human leukocyte interferon that uses human blood (buffy coats) as the starting material in the manufacturing process. Standard measures preventing infections due to the use of medicinal products manufactured from plasma or human blood include selecting donors and testing individual donations for specific markers of infection, as well as the adoption of manufacturing steps that effectively inactivate or remove viruses. Nevertheless, the transmission of infectious agents cannot be ruled out when using medicinal products manufactured from plasma or human blood. That is also true of new, previously unknown viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and non-enveloped viruses such as HAV and Parovirus B19. The process has also been validated and found to be effective for the Sendai virus (a non-human pathogen) which is used in inducing the leukocytes to produce interferon.

4.5 Interaction with other medicinal products and other forms of interaction

Medical product/medical product interactions: Narcotics, hypnotics and sedatives should be administered with caution when used concomitantly with interferon-alpha.

Interactions between Multiferon and other medicinal products have not been assessed. Caution should be exercised when administering Multiferon in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. That should be taken into consideration during concomitant treatment with medicinal products, such as the xanthine derivatives theophylline and aminophylline that are metabolised by this route. During concomitant treatment with xanthine agents, serum theophylline levels should be monitored and the interferon dosage adjusted if necessary.

4.6 Fertility, pregnancy and lactation

The data on pregnant women are insufficient. Interferon-alpha should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Interferon-alpha has been shown to have abortifacient effects in *Macaca mulatta* (Rhesus monkeys) at 90 and 180 times the recommended subcutaneous or intramuscular dose of 2 million IU/m^2. For that reason, Multiferon is recommended for women of fertile age only if they will be using effective contraception during the treatment period.

It is unknown whether interferon alpha or metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Multiferon therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with Multiferon should avoid driving a car or operating machinery.

4.8 Undesirable effects

The most frequently reported adverse reactions are fever, chills, sweating, fatigue, arthralgia, myalgia, headache, anorexia and nausea. Fever and fatigue are dose-related and are reversible within 72 hours of interruption or cessation of treatment.

These acute adverse reactions can ordinarily be alleviated or eliminated by concomitantly administering paracetamol. They tend to subside with continued treatment or dosage adjustment, although ongoing treatment can cause lethargy, weakness and persistent fatigue.

Investigations:
Uncommon (≥1/1,000, <1/100): Increased alanine aminotransferase (ALT), alkaline phosphatase in the blood and transaminases, weight loss.

Rare (≥1/10,000, <1/1,000): Higher blood levels of LDH, bilirubin, creatinine, uric acid, and urea.

Cardiac disorders:
Uncommon (≥1/1,000, <1/100): Arrhythmias, including atrioventricular block, palpitations.
Rare (≥1/10 000, <1/1,000): Cardiac arrest, myocardial infarct, chronic heart failure, pulmonary oedema, and cyanosis.

Blood and lymphatic system disorders:
Very common (≥1/10): Leucopenia.
Common (≥1/100, <1/10): Thrombocytopenia, anaemia.
Rare (≥1/10,000, <1/1,000): Agranulocytosis, haemolytic anaemia.
Very rare (<1/10,000): Idiopathic thrombocytopenic purpura.

Nervous system disorders:
Very common (≥1/10): Headache.
Uncommon (≥1/1,000, <1/100): Neuropathy, dizziness, somnolence, dysgeusia, paraesthesia, hypoesthesia, and tremor.
Rare (≥1/10,000, <1/1 000): Coma, cerebrovascular accident, convulsions, temporary erectile dysfunction.

Eye disorders:
Uncommon (≥1/1,000, <1/100): Conjunctivitis, visual disturbances.
Rare (≥1/10,000, <1/1,000): Ischaemic retinopathy.
Very rare (<1/10,000): Optic neuropathy, obstruction of retinal artery or vein, retinopathy, retinal haemorrhage, papillary oedema, retinal exudates.

Ear and labyrinth disorders:
Uncommon (≥1/1,000, <1/100): Vertigo.

Respiratory, thoraic and mediastinal disorders:
Rare (≥1/10,000, <1/1,000): Dyspnoea, cough.

Gastrointestinal disorders:
Very common (≥1/10): Diarrhoea.
Common (≥1/100, <1/10): Nausea/vomit.
Uncommon (≥1/1,000, <1/100): Abdominal pain, dryness of the mouth.
Rare (≥1/10,000, <1/1,000): Hypermotility, constipation, dyspepsia, flatulence, pancreatitis.
Very rare (<1/10,000): Recurrence of gastric ulcer, non life-threatening gastrointestinal bleeding.

Renal and urinary disorders:
Uncommon (≥1/1,000, <1/100): Proteinuria and greater number of cells in the urine.
Rare (≥1/10,000, <1/1,000): Acute renal failure (primarily in cancer patients with kidney disease), impaired renal function.

Skin and subcutaneous tissue disorders:
Very common (≥1/10): Alopecia (reversible after treatment, increased hair loss may continue for several weeks after cessation of treatment), increased sweating.
Uncommon (≥1/1,000, <1/100): Exacerbation or provocation of psoriasis, pruritus.
Rare (≥1/10,000, <1/1,000): Rash, dry skin and mucous membranes, epistaxis, rhinorrhoea.

Musculoskeletal and connective tissue disorders:
Very common (≥1/10): Myalgia, arthralgia.
Rare (≥1/10,000, <1/1,000): Systemic lupus erythematosus, arthritis.
Not known: Rhabdomyolysis

Endocrine disorders:
Rare (≥1/10,000, <1/1,000): Hyperthyroidism, hypothyroidism, thyroid disorder.

Metabolism and nutrition disorders:
Very common (≥1/10): Anorexia, nausea, hypocalcaemia of no clinical significance.
Uncommon (≥1/1,000, <1/100): Electrolyte imbalance, dehydration.
Rare (≥1/10 000, <1/1 000): Hyperglycaemia.
Very rare (<1/10,000): Diabetes mellitus, hypertriglyceridaemia.

Infections and infestations:
Rare (>1/10,000, <1/1,000): Pneumonia, herpes simplex (including exacerbation of labial herpes).

Vascular disorders:
Uncommon (≥1/1,000, <1/100): Hypertension, hypotension.
Rare (≥1/10 000, <1/1 000): Vasculitis.

General disorders and administration site conditions:
Very common (≥1/10): Flu-like symptoms, fatigue, fever, stiffness, reduced appetite.
Uncommon (≥1/1,000, <1/100): Chest pain, oedema.
Very rare (<1/10,000): Necrotic reactions at the site of injection, reactions at the site of injection.

Immune system disorders:
Rare (>1/10,000, <1/1,000): Autoimmune disease, acute hypersensitivity reactions (such as urticaria, angio-oedema, bronchospasm and anaphylaxis).
Very rare (<1/10,000): Sarcoidosis.

Hepatobiliary disorders:
Rare (>1/10,000, <1/1,000): Liver failure, liver damage, impaired liver function.

Psychiatric disorders:
Uncommon (>1/1,000, <1/100): Depressive disorder, anxiety disorder, altered mental status, state of confusion, conduct disorders, nervousness, memory deterioration, sleep disorders.
Rare (>1/10,000, <1/1,000): Suicide, attempted suicide, suicidal ideation.

For safety with respect to transmissible agents, see section 4.4.

Dental and periodontal disorders (which may lead to loss of teeth) and hearing loss have been suggested as class effects of alpha interferon treatment.

4.9 Overdose

Overdose with Multiferon has not been reported but, as for any pharmacologically active substance, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB01

Multiferon is a human leukocyte interferon that consists of several naturally occurring interferon-alpha subtypes. The interferon-alpha subtypes are purified from the supernatant of a culture medium of primary human leukocytes (referred to as buffy coats) challenged with Sendai virus. The purification is based on the method described by Cantell, which has been modified by the inclusion of immunoaffinity chromatography and gel filtration steps in order to increase the specific activity.

Interferons are naturally occurring proteins with antiviral, antiproliferative and immunomodulating properties with molecular weights of approximately 19,000 to 27,000 Daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers.

Three major classes of interferons have been identified: alpha, beta and gamma. These three classes are not homogeneous in themselves and may contain several different molecular species of interferon. The human genome consists of 13 functional genes that code for interferon-alpha. Multiferon has been classified as natural interferon-alpha.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, such as Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once the interferon has bound to the cell membrane, a complex sequence of intracellular events – including the induction of certain enzymes – is initiated. This process is thought to be at least partially responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to the therapeutic effects of interferon.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters reported for interferon-alpha are characterised by extensive variability. Subcutaneous administration of 3 million IU results in maximal serum concentrations of about 15 IU/ml (range: 7-24). The pharmacokinetics of interferon-alpha are linear and time-independent in clinical doses. Interferon-alpha is most likely metabolised by the kidneys. Only very small amounts of intact interferon-alpha have been found in the urine. The serum concentration of interferon-alpha increased 3-4 fold in patients with metastatic renal cell carcinoma. No data on binding to proteins in plasma is available.

Neutralising anti-interferon-alpha antibodies have not been observed after treatment with Multiferon.

5.3 Preclinical safety data

Because interferon-alpha is species-specific in its actions, only a limited pre-clinical safety programme was performed with Multiferon. No toxicity was observed in single-dose toxicity studies in mice and rats.

Reproduction toxicity studies have not been performed with Multiferon, but interferon-alpha in high doses are known to cause abortion in monkeys.

Mutagenicity studies have not been conducted with Multiferon, but studies with recombinant interferon-alpha were reported negative in the Ames test and the micronucleus test.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
anhydrous sodium dihydrogen phosphate
anhydrous disodium phosphate
sodium chloride
water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

For single use. Any remaining material must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) in the original package in order to protect from light. Do not freeze.

For the purpose of transport or to facilitate use, the product may be kept at room temperature (25°C or below) for up to 2 months. If not used during the 2-month period, it must not be put back in the refrigerator for continued storage. It must be destroyed.

6.5 Nature and contents of container

Syringes 1 ml (borosilicate glass), plastic syringe plunger, stainless steel injection needle for subcutaneous injection, sealed with silicon, attached to the syringe with UV-hardened adhesive, plastic needle protector.

Each pre-filled syringe contains 3 million IU interferon-alpha per 0.5 ml as a solution for injection, ready for use.

Pack size*:* 6 x 0.5 ml (0.5 ml = 3 million IU)

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum International AB
112 76 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

25001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 December 2007
Date of latest renewal: 7 December 2012

10 DATE OF REVISION OF THE SPC

28 March 2013