LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report

# Scientific discussion

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

# SE/H/837/01/MR

**This module reflects the scientific discussion for the approval of Multiferon, 3 million IU, solution for injection in pre-filled. The procedure was finalised at 2009-04-07. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Swedish Orphan International AB has applied for a marketing authorisation for "Multiferon, 3 million IU, solution for injection in pre-filled syringe".

Multiferon 3 MIU/0.5ml is a highly purified human leukocyte interferon product of the alpha type (INN: Interferon alpha, laboratory code: HuIFN αLe). It is a solution for injection and contains a mixture of several proteins all with structural, serological and functional properties typical for natural interferon alpha (nIFN α). The IFN-α content is expressed in international units per ml and the drug product is formulated in isotonic phosphate buffer solution (pH 7.2) supplemented with human albumin, 1.5 mg/ml.

The product is indicated for:

*Malignant melanoma:*
Adjunctive 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.

# II. QUALITY ASPECTS

## II.1 Introduction

Multiferon is presented in the form of a solution for injection in pre-filled syringe containing 3 million IU of human leukocyte interferon-alpha in 0.5ml. The excipients are human albumin, sodium dihydrogen phosphate, disodium phosphate, sodium chloride and water for injection. The solution is filled in glass syringes.

## II.2 Drug Substance

Human leukocyte interferon-alpha does not have a monograph in the Ph Eur.

Human leukocyte interferon consists of several naturally occurring Interferon-alpha subtypes, formed by incubation of human leukocytes ("buffy coats") with Sendai virus (a non-human pathogen) and subsequently purified. The major Interferon-alpha subtypes have been adequately identified and their physico-chemical properties and biological activity are sufficiently characterised.

Although Multiferon is not extracted from blood components and is thus not classified as a plasma derived product, the buffy coats are considered a starting material according to the definitions of Directive 2003/63/EC. 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, in accordance with the Directive 2002/98/EC ("Blood Directive") and corresponding Commission Directives. Furthermore, the manufacturing process has been shown to inactivate or remove viruses. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and non-enveloped viruses such as HAV and Parvovirus B19. The process has also been validated and

found to be effective for the reduction of Sendai virus. In conclusion, as based on the control of starting and raw materials and of the validated capacity of the process to remove and inactivate viral agents, the viral safety is acceptably assured.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the specifications.

The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.

Data of stability studies are sufficient to confirm the established shelf life.

### II.3 Medicinal Product

Multiferon, 3 million IU, solution for injection in pre-filled syringe, is formulated using excipients described in the current Ph Eur. All raw materials used in the product have shown to be in compliance with Commission Directive 2003/63/EC. Furthermore, adequate measures to prevent any risk of transmitting Animal Spongiform Encephalopathy Agents are in place. The Human Serum Albumin used as excipient is approved as a medical product in several EU member states.

The product development has taken into consideration the characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored in a refrigerator (2°C – 8°C) in the original package in order to protect from light or when kept at room temperature (25 °C or below) for up to 2 months.

## III. NON-CLINICAL ASPECTS

### III.1 Pharmacology

The application contains virtually no non-clinical pharmacodynamic data for Multiferon, the reason being the extensive clinical use of the product and the knowledge accumulated for other interferon alpha products. Safety pharmacology (cardiovascular and respiratory parameters) was evaluated in rats. Interferon alpha is known to induce cardiac ischemia and arrhythmias of various types. Arrhythmias were noted, and warnings are included in the SPC.

### III.2 Pharmacokinetics

The pharmacokinetics of Multiferon has not been studied in animals.

### III.3 Toxicology

The file contains no toxicological studies with Multiferon, since the product has been used in the clinical setting since 1987 and since interferon alpha is known to be largely species specific in its actions. Toxicity studies using rodents are of limited value due to species specificity issues. The poor non-clinical information about Multiferon toxicity is compensated by the clinical experience and the experience from other interferon alpha preparations.

### III.4 Ecotoxicity/environmental risk assessment

Not applicable for proteins.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

### IV.2 Pharmacokinetics

The pharmacokinetic data on Multiferon are derived from two studies, one conducted in HIV infected patients (Study I-305/PK001) and one in patients with advanced renal cell carcinoma (RCC) (Study I-301). Concentrations of IFN-α in serum were assayed using a dissociation-enhanced lanthanide fluoroimmuno assay (DELFIA) method. The specificity of the analytical method for subtypes of HuIFN-αLe is unknown.

In the first PK study, 18 (16 evaluable) patients with human immunodeficiency virus type-1 (HIV-1) infection were treated with Multiferon 3 MIU subcutaneously daily. The data indicate that the pharmacokinetics of IFN-α is linear and independent of time after administration of Multiferon. Furthermore, there is no accumulation of IFN-α after repeated administration. The serum concentrations of IFN-α in these patients are similar to those reported after administration of less purified HuIFN-αLe (Cantell-type) and of rIFN-α2.

In the second PK study, 22 patients with RCC received a single dose of 2 million IU of Multiferon subcutaneously. Most patients had various degree of renal insufficiency (creatinine serum concentration ranged from 83-269 μmol/L – normal < 80-100). The dose adjusted median concentration of IFN-α in these patients is 3 to 4 times higher than that in subjects with normal kidney function treated with IFN-α. These data are in line with the published literature on the pharmacokinetics of interferons.
No pharmacokinetic drug-drug interaction studies have been conducted with Multiferon.

### IV.3 Pharmacodynamics

Multiferon contains as prevalent subtypes IFN-α1, -α2, -α8, -α10, -α14 and -α21 of which two, IFN-α2 and IFN-α14, are glycosylated. Experimental data support the notion that these subtypes vary in biological activity with respect to antiproliferative, anti-viral and immune modulating activity and that neutralising antibodies raised against rIFN alpha do not inhibit the activity of Multiferon.

### IV.4 Clinical efficacy

**Clinical efficacy**

*Adjuvant treatment of malignant melanoma:*

One pivotal study has been submitted in support of this indication. It was a randomised no-treatment controlled, German, multicenter study. The study enrolled patients with DDG stage IIa to IIIb (the currently used classification AJCC 2002 is with respect to IIb to IIIb similar to DDG). As a result of data reported by Kirkwood et al., the IRC, however, recommended that efficacy in stage IIb to IIIb should be specifically assessed.

Due to a high early attrition rate (withdrawal owing to patient wish, see table below) in the control arm, study results were not considered interpretable and the sponsor was requested to retrieve data on melanoma recurrence and survival post study. This was done under a supplementary protocol (R13-86b).

| | Experimental arm n=128 | | Control arm n=124 | |
|---|---|---|---|---|
| | Completed n=106 | Withdrawn n=22 | Completed n=100 | Withdrawn n=24 |
| Return of consent 1-2 mo. | | 4 | | 20 |
| Return of consent 3-8 mo. | | | | 1 |
| Return of consent 12-60 mo. | | | | 3 |
| AE, other reasons, | | 18 | | |

Altogether 253 patients were randomised and received either two monthly cycles of DTIC 850 mg/m$^2$ IV (once per month), followed by nIFN-α 3MIU three times weekly for 6 months or standard of care, i.e. observation only. The primary efficacy endpoint according to the protocol was time to recurrence or melanoma death.

Survival (secondary endpoint): Altogether 4 patients with stage IV melanoma (protocol violation) and two patients without malignant melanoma were enrolled. In the total study population, long term survival data were not retrieved for four patients in the experimental arm and one in the control arm. This resulted in a number of alternative survival analyses.

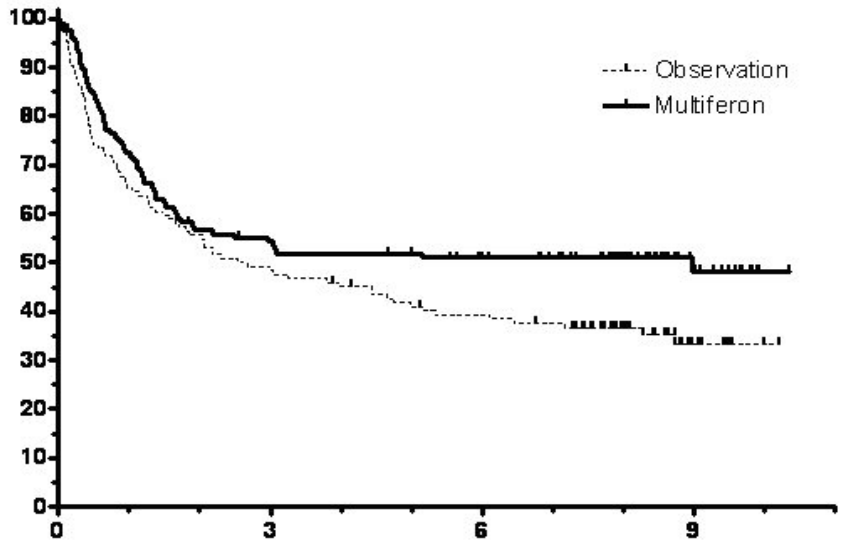
**Alternative analyses of all cause mortality**

| **Analysis** | **P-value/ 95% CI** |
|---|---|
| Log-rank test, all patients | 0.0520 |
| Log-rank test, wrong diagnoses excluded | 0.0619 |
| Event difference, all patients | -28.8%; -4.5% |
| Event difference, wrong diagnoses excluded | -28.2%; -3.8% |
| Event diff., non-retrievals counted as events, all patients | -26.6%; -2.1% |
| Event diff., non-retrievals counted as events, wrong diagnoses excluded | -25.9%; -1,4% |
| Event diff., non-retrievals/shorter follow-up counted as events, all patients | -24.2%; 0.2% |
| Event diff., non-retrievals/shorter follow-up counted as events, wrong diagnoses excluded | -23.5%; 1.0% |

A retrospective proportional hazard modelling for time to melanoma death was undertaken showing a hazard ratio of 0.5 at a p-value of 0.004. The retrospective nature and some missing base line co-variate data make this analysis supportive only. Altogether it is concluded that a survival effect is likely, but that the treatment effect is not sufficiently statistically robust to support a claim.

Time to progression defined as time to recurrence or melanoma death was the primary end point of the study.

**Time to progression after long-term follow-up**




Normally disease-free survival (DFS) is considered to be the preferred end point as it cannot be excluded that, e.g. cardiac deaths may be related to study therapy. This results in alternative analyses.

| **Censored patients (if no prior recurrence)** | **Number of events** | | **Log-rank p-value** |
|---|---|---|---|
| | **Test group** | **Control group** | |
| None | 68 | 83 | 0.0619 |
| Colon cancer patient | 67 | 83 | 0.0511 |
| Non-melanoma deaths | 63 | 80 | 0.0424 |

Also in these analyses, borderline significant efficacy is demonstrated. Off-study recurrence, however, is considered likely to be detected later than on-study. Furthermore there were 10 cases of melanoma death without previously reported recurrence in the control group vs. none in the experimental arm. Therefore the analyses presented above are conservative.

In the subgroup defined by the IRC as being of particular interest and before survival data were available, the following results were obtained.

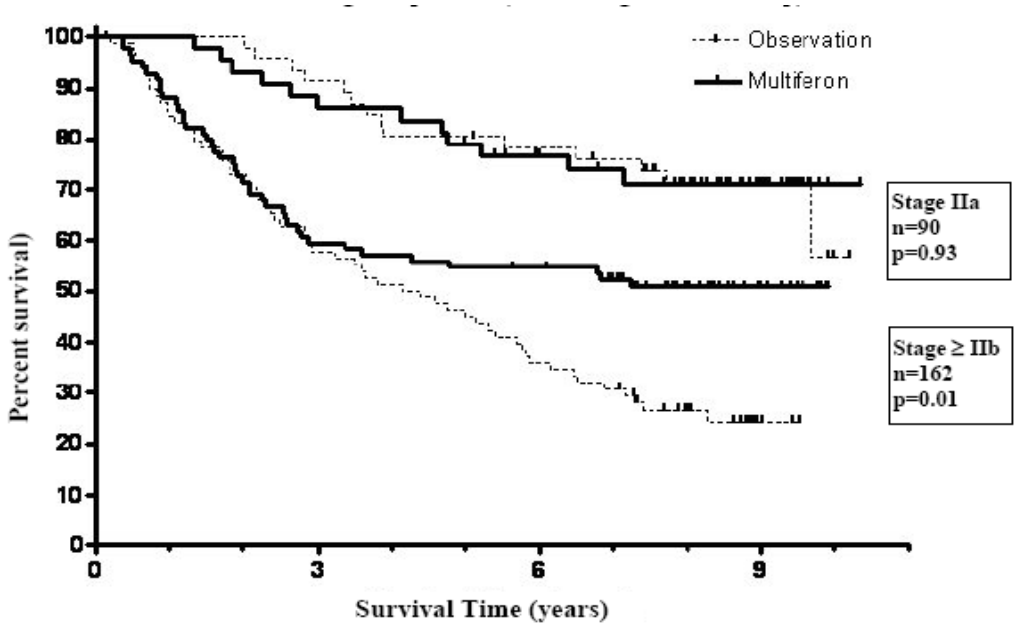
**Overall survival, stage IIa patients excluded**

| Treatment | Dead (%) | Censored | Log rank | Number (%) alive at follow-up |
|---|---|---|---|---|

| group | | (%) | p-value | (years) 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Control | 57 (75) | 19 (25) | 0.011 | 35 (46) | 27 (36) | 23 (30) |
| Test | 39 (49) | 41 (51) | | 44 (55) | 43 (54) | 41 (51) |
| p-value (Chi-square) | | | | 0.26 | 0.02 | 0.01 |

The HR in the full study population was 0.7, while in the subgroup excluding stage II a patients it was 0.6, a clinically very relevant treatment effect. However, even though this subgroup was defined in advance by the IRC, the primary efficacy population was that of all patients randomised. Thus these results should be confirmed in order to support claims. The indication should be restricted as no trends supporting meaningful activity in stage II a patients were detectable.

**Overall survival by subgroups**

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*Second-line treatment of patients who initially respond to recombinant interferon-alpha, but for whom treatment subsequently failed, most likely as the result of neutralising antibodies:*

It is known that the epitopes recognised by the neutralising antibodies are located in the N-terminal part of rIFN-α and that many of the pharmacodynamic activities of IFN-α are reduced or inhibited in the presence of these antibodies. It has been demonstrated ex vivo that antibodies inhibiting the activity of rIFN-α2 do not inhibit the activity of leukocyte or lymphoblastoid derived "polyclonal" interferons (including Multiferon). While the reverse is true, i.e. that antibodies inhibiting the activity of "polyclonal" alpha interferons inhibits the activity of rIFN-α.

Due to the rarity of the condition, approval was based on a series of individual case reports and a strong pharmacological rationale. In addition published data derived from another leukocyte derived IFN alpha and a lymphoblastoid IFN alpha (Wellferon) provided supportive evidence.

Out of 26 patients, 18 met all criteria for evaluation. These patients had an initial response to rIFN-α and then experienced a relapse during treatment. All these patients also had positive binding and neutralizing antibodies in their serum upon relapse. The patients had polycythemia vera or essential thrombocythemia (2 patients), CML or HCL (12 patients), midgut carcinoid or endocrine pancreas tumour (2 patients), or chronic hepatitis C infection (2 patients). The response observed following cross-over to Multiferon was similar to the initial response observed with rIFN-α and was seen in 17/18 patients.

The quality and the informative value of the individual reports varied and there were no predefined response criteria, rather "activity" after re-treatment was demonstrated in the cases considered positive. This is especially true in the group of patients treated after initial non-response where e.g. reappearance of typical IFN adverse reactions due to their subjective nature cannot be viewed as strong evidence. The selected dose of Multiferon was in most cases similar to the dose of rIFN previously administered. This is considered appropriate, but in some cases the dose was doubled while in other cases the dose was halved.

## IV.5 Clinical safety

### Clinical safety

Altogether 667 patients were reported in the course of treatment with Multiferon, and of these 229 patients received Multiferon monotherapy and 438 patients received Multiferon in the context of combination with another agent that may include significant toxicity of its own (including interleukin-2, chemotherapeutic agent, or ribavirin for example). In all studies subjects were of Caucasian origin. Maximum doses ranged between 3 and 63 MIU/week, with subject exposure extending from 1 to 57 months.

**Overall occurrence of moderate to very severe adverse events.**

| | Combination Therapy | | | Combination Therapy Total | Monotherapy | | | Monotherapy Total | Grand Total |
|---|---|---|---|---|---|---|---|---|---|
| Number of Patients (N) | | | | 229 | | | | 438 | 667 |
| Severity | moderate | severe | very severe | | moderate | severe | very severe | | |
| Preferred Term | | | | | | | | | |
| Pyrexia | 34.93% | 6.99% | 1.31% | 43.23% | 29.45% | 0.68% | 0.23% | 30.37% | 34.78% |
| Fatigue | 27.51% | 24.89% | 0.87% | 53.28% | 9.82% | 3.20% | 0.68% | 13.70% | 27.29% |
| Malaise | 11.79% | 13.10% | 4.37% | 29.26% | 3.20% | 1.37% | 0.23% | 4.79% | 13.19% |
| Anorexia | 11.35% | 6.11% | 0.87% | 18.34% | 3.42% | 5.25% | 1.60% | 10.27% | 13.04% |
| Headache | 10.04% | 2.18% | 0.00% | 12.23% | 8.22% | 1.37% | 0.23% | 9.82% | 10.64% |
| Nausea | 14.85% | 4.80% | 0.00% | 19.65% | 3.20% | 1.60% | 0.23% | 5.02% | 10.04% |
| Dyspnoea | 10.04% | 6.11% | 1.31% | 17.47% | 3.65% | 0.23% | 0.00% | 3.88% | 8.55% |
| Muscle spasms | 9.61% | 2.18% | 0.44% | 12.23% | 5.02% | 1.60% | 0.00% | 6.62% | 8.55% |
| Vomiting | 7.42% | 6.99% | 0.00% | 14.41% | 2.51% | 0.68% | 0.23% | 3.42% | 7.20% |
| Pruritus | 10.48% | 0.00% | 0.00% | 10.48% | 3.65% | 0.23% | 0.00% | 3.88% | 6.15% |
| Diarrhoea | 5.68% | 2.62% | 0.44% | 8.73% | 3.42% | 0.91% | 0.00% | 4.34% | 5.85% |
| Arthralgia | 9.17% | 2.62% | 0.00% | 11.79% | 1.83% | 0.68% | 0.00% | 2.51% | 5.70% |
| Alopecia | 3.93% | 0.44% | 0.00% | 4.37% | 5.25% | 0.46% | 0.00% | 5.71% | 5.25% |
| Pain | 3.49% | 1.75% | 0.00% | 5.24% | 4.34% | 0.23% | 0.00% | 4.57% | 4.80% |
| Localised infection | 3.06% | 2.18% | 0.00% | 5.24% | 3.20% | 0.23% | 0.00% | 3.42% | 4.05% |
| Hyperhidrosis | 7.86% | 0.00% | 0.00% | 7.86% | 0.68% | 0.23% | 0.00% | 0.91% | 3.30% |
| Chills | 3.93% | 1.75% | 0.00% | 5.68% | 1.60% | 0.00% | 0.00% | 1.60% | 3.00% |

The reported adverse events are considered qualitatively and quantitatively what would be expected for an alpha IFN. However, it cannot be assumed that the safety profile of Multiferon is identical to licensed rIFN products.

**Common adverse events in the adjuvant treatment group (n=128), study R13-86a**

| AE | Number (month 1-8) | DTIC (month 1-2) WHO all grades | WHO grade III/IV | IFN (month 3-8) WHO all grades | WHO grade III/IV |
|---|---|---|---|---|---|
| Fever | 82 | 10 | | 72 | 2 |
| Malaise | 79 | 31 | 2 | 48 | |
| Anorexia | 79 | 37 | 1 | 42 | 8 |
| Nausea | 71 | 37 | 1 | 29 | |
| Somnolence | 33 | 11 | | 22 | |
| Diarrhoea | 29 | 16 | 1 | 13 | 1 |
| Alopecia | 29 | 8 | 1 | 21 | |
| Other skin AE | 26 | 1 | | 25 | |
| Constipation | 24 | 14 | | 10 | |
| Fatigue | 21 | 4 | | 17 | |
| Headache | 21 | 4 | | 17 | |
| Infection | 20 | 9 | 1 | 11 | |
| Arthralgia | 18 | 3 | | 15 | |
| Dyspnoea | 18 | 5 | | 13 | 1 |
| Rigor | 17 | | | 17 | |
| Arrhythmia | 14 | 4 | | 10 | |
| Peripheral neuropathy | 13 | 4 | | 9 | |
| Stomatitis | 10 | 4 | | 9 | |
| Myalgia | 7 | | | 7 | |
| Transpiration | 10 | 3 | | 7 | |

In the adjuvant trial, reported events were those expected in relation to DTIC and Multiferon.

The estimated number of patients treated with Multiferon outside clinical studies is 2500.Of special interest is a report from Mexico where a patient with chronic hepatitis C developed severe rhabdomyolysis on treatment with Multiferon and ribavirin.

**Periodic Safety Update Report (PSUR)**
The first PSUR should cover the period 1 Aug 2008 - 31 Dec 2009.
The MAH would like to keep 31st of December as DLP because it corresponds to the EU Harmonised Birth Date (EU-HBD).
Forthcoming PSURs should have a submission scheme of 1 yearly PSURs.

## IV.6 Discussion on the clinical aspects

Multiferon contains as prevalent subtypes IFN-α1, -α2, -α8, -α10, -α14 and -α21 of which two, IFN-α2 and IFN-α14, are glycosylated. Experimental data support the notion that these subtypes vary in biological activity with respect to antiproliferative, anti-viral and immune modulating activity and that neutralising antibodies raised against rIFN alpha do not inhibit the activity of Multiferon.

*Adjuvant treatment of high-risk patients with cutaneous melanoma, stages IIb-III*

Benefit
A regimen based on two cycles of DTIC 850 mg/m$^2$ IV, followed by Multiferon 3MIU three times weekly for 6 months compared with a no-treatment control group has been shown to provide borderline statistically significant, but clinically relevant patient benefit in terms of disease-free survival and overall survival. The benefit in terms of DFS is considered

conservatively estimated and survival data provide supportive evidence of a beneficial effect. Survival data per se are considered too borderline to support a claim, however. Further studies in the adjuvant setting, preferably in comparison with a licensed rIFN, would be needed to support claims of superior activity.

Risk
DTIC is a well known cytotoxic compound with documented activity against advanced malignant melanoma and the risk associated with two cycles of treatment at a dose 850 mg/m$^2$ IV is foreseeable and toxicity is considered moderate. Multiferon 3MIU three times weekly for 6 months regimen, seems similar to rIFN at the same dose and duration from a safety perspective and is reasonably well tolerated. Altogether the regimen has an acceptable tolerability profile.

Balance
The demonstrated benefit in terms of prolonged disease-free survival outweighs the risk associated with therapy. No benefit has been shown in patients with stage IIa (low risk) disease and the indication is therefore restricted to patients with stages IIb and III disease.

*Second line treatment of patients who initially respond to recombinant interferon-alpha, but for whom treatment subsequently fails, most likely as the result of neutralising antibodies.*

Benefit
This patient group constitute a very small target population and benefit has been demonstrated in a series of individual case reports where reversal of resistance to rIFN alpha due to neutralising antibodies has been shown on treatment with nIFN-α. Given the pharmacological rationale and external supportive evidence, this is considered sufficient.

Risk
The risk associated with treatment with IFN alpha is dose and duration related. In this second-line indication the same dose of nIFN-α as previously used with rIFN should be used. Until neutralising antibodies developed, the individual patient's tolerability to treatment with rIFN can be evaluated. Currently available safety data for nIFN-α indicate that tolerability and toxicity is similar to rIFN.

Balance
As initial benefit of therapy with rIFN-α has to be demonstrated, the target population for treatment with nIFN-α had been enriched. At the same time, adverse reactions to rIFN therapy have been documented in the individual patient who later develops neutralizing antibodies. Therefore an informed individualized decision is possible with respect to treatment with nIFN-α. No restriction of the indication to specific disease conditions is therefore considered appropriate and benefit – risk is considered favourable.

## IV.7 Risk Management Plan

The content of the RMP is consistent with the template for EU-risk management plans. The list of identified and potential risks is considered to cover the important ongoing safety concerns. Currently available safety data for nIFN-α indicate that tolerability and toxicity are similar as for rIFN-α. For all safety concerns, routine pharmacovigilance (including intensified monitoring of events of special interest) and appropriate labelling are presently considered sufficient. The proposals for the current and future risk management of Multiferon are agreed to.

# V. OVERALL CONCLUSION AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Multiferon, 3 million IU, solution for injection in pre-filled syringe is recommended for approval.

# VI. APPROVAL

The Mutual recognition procedure for Multiferon, 3 million IU, solution for injection in pre-filled syringe was successfully finalised on 2009-04-07.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Scope | Procedure number | Product Information affected | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| | | | | | | Y/N (version) |

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