Summary of Risk Management Plan for Betaferon® / Extavia® (Interferon beta-1b)

This is a summary of the risk management plan (RMP) for Betaferon® / Extavia®. The RMP details important risks of Betaferon® / Extavia®, how these risks can be minimised, and how more information will be obtained about Betaferon®'s / Extavia®'s risks and uncertainties (missing information).

Betaferon®'s / Extavia®'s summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Betaferon® / Extavia® should be used.

This summary of the RMP for Betaferon® / Extavia® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Betaferon®'s / Extavia®'s RMP.

1. The Medicine and what it is used for

Betaferon® / Extavia® is authorised for the treatment of:

- Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.
- Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years.
- Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

It contains interferon beta-1b as the active substance and it is administered by subcutaneous injection.

Further information about the evaluation of Betaferon®'s / Extavia®'s benefits can be found in Betaferon®'s / Extavia®'s EPAR, including in its plain-language summary, available on the website of the European Medicine Agency (EMA), under the medicine's webpage found under the following links:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000081/human_med_000673.jsp&mid=WC0b01ac058001d124.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000933/human_med_000781.jsp&mid=WC0b01ac058001d124.

2. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

Important risks of Betaferon® / Extavia®, together with measures to minimise such risks and the proposed studies for learning more about Betaferon®'s / Extavia®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Betaferon® / Extavia®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Betaferon® / Extavia® is not yet available, it is listed under 'missing information' below.

2.1 List of Important Risks and Missing Information

Important risks of Betaferon® / Extavia® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Betaferon® / Extavia®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Summary of safety concerns	
Important identified risks	▪ None
Important potential risks	▪ None
Missing information	▪ Use during second and third trimester of pregnancy

2.2 Summary of Important Risks

Missing information: Use during second and third trimester of pregnancy	
Risk factors and risk groups	Pregnancy outcome data of use of interferon beta-1b during second and third trimester of pregnancy is limited, what is expected due to the previous contraindication of initiation of treatment with interferon-beta during pregnancy. Limited data available from post-marketing experience, including pregnancy registries, do not indicate increased risk of abnormal pregnancy outcomes.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.6 Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None

2.3 Post-authorisation Development Plan

2.3.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Betaferon® / Extavia®.

2.3.2 Other Studies in Post-authorisation Development Plan

3.3.2.1 Interferon beta utilization in pregnancy

Study short name and title:

Drug utilization study in pregnancy (exposure in 2nd and 3rd trimester)

Rationale and study objectives:

Analysis of 948 pregnancy outcomes from the European Interferon-beta Pregnancy Registry and of cohorts from the Nordic Registers Pregnancy Study [EUPAS13054] indicated that the prevalence of both major congenital anomalies in live births and spontaneous abortions were within the background rate of both the untreated MS population and the general population. However, most of these available data correspond to exposure during first trimester of pregnancy, the period of most vulnerability due to organogenesis.

To further address the remaining uncertainty for exposure during second and third trimesters, a first stage of study is planned to evaluate IFN-beta utilization among pregnant women in Sweden and Finland using a staggered approach at 3 and, if needed, 5 years following label implementation using aggregate-level data.

- Evaluation of interferon-beta utilization among pregnant women with MS in Sweden and Finland at 3 and, if needed, 5 years following label implementation using aggregate level data

- Evaluation of trends in drug utilization (DU) patterns in the target population before and after label implementation.

Aggregate data analysis at 3 and, if needed, 5 years will inform an overall assessment of whether it is appropriate and feasible to proceed with the second stage, full study on the effect on pregnancy outcomes of IFN exposure during 2nd and 3rd trimester of pregnancy using individual level data, based on the observed pattern of IFN beta use among pregnant women.