Summary of the Risk Management Plan for Rebif® (Interferon beta-1a)

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

Summary of Important updates to the RMP:

Reclassification of important identified risks, important potential risks, missing information and events under close monitoring for removal and addition as safety concerns.

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

This summary of the RMP for Rebif® 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 Rebif®'s RMP.

I. The Medicine and What it is used for

Rebif® (Initiation Pack & Rebif® 44) is authorised for the treatment of:

- Patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite MS.
- Patients with relapsing MS.

Rebif® (Rebif® 22) is authorized for the treatment of patients with relapsing MS (see SmPC for the full indication). It contains Interferon-β-1a as the active substance and it is given by injection in cartridge or in pre-filled pen/ pre-filled syringe.

Further information about the evaluation of Rebif®'s benefits can be found in Rebif®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Rebif®, together with measures to minimise such risks and the proposed studies for learning more about Rebif®'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 package leaflet 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR 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 Rebif® is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Rebif® 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 Rebif®. 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);

List of missing information	
Missing information	Use during 2nd and 3rd trimester of pregnancy

II.B Summary of Important Risks

Missing information: Use during 2nd and 3rd trimester of pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication: EU-SmPC, Section 4.6 (Fertility, pregnancy and lactation) Routine risk minimisation activities recommending specific clinical measures to address the risk: EU-SmPC section 4.6: If clinically needed, the use of Rebif may be considered during pregnancy. Other routine risk minimisation measures beyond the Product Information: **Legal status:**

Missing information: Use during 2nd and 3rd trimester of pregnancy	
	Prescription only medicine. Use restricted to physicians experienced in the treatment of MS. **Additional risk minimisation:** None

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Rebif®.

II.C.2 Other Studies in the Post-authorisation Development Plan

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 1st trimester of pregnancy, the period of most vulnerability due to organogenesis.

To further address the remaining uncertainty for exposure during 2nd and 3rd 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 years 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 years 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 years 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.