PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Fingolimod "Heumann" (Fingolimod):

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

Fingolimod "Heumann" summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Fingolimod "Heumann" should be used.

Important new concerns or changes to the current ones will be included in updates of Fingolimod "Heumann" RMP.

I. The medicine and what it is used for

Fingolimod "Heumann" is authorised as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI (see SmPC for the full indication).

It contains fingolimod (as hydrochloride) as the active substance and it is given by oral route of administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Fingolimod "Heumann", together with measures to minimise such risks and the proposed studies for learning more about Fingolimod "Heumann" 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 Fingolimod "Heumann", 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, 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 Fingolimod "Heumann" is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fingolimod "Heumann" are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Fingolimod "Heumann". 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 important risks and missing information	
Important identified risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Liver transaminase elevation • Macular edema • Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection • Reproductive toxicity • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Convulsions • Lymphoma
Important potential risks	• Other malignant neoplasms
Liver transaminase elevation	• Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

II.B Summary of important risks

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

Risk minimisation measures	**Routine risk minimisation measures:** - SmPC sections 4.3, 4.4, 4.7 and 4.8. - PL sections 2 and 4. Recommendations for ECG and blood pressure monitoring prior to and 6 hours after first dose of Fingolimod "Heumann" and recommendations for extended monitoring, in adult and pediatric patients are mentioned in SmPC section 4.4. Legal status: Prescription-only medicines **Additional risk minimisation measures:** Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Liver transaminase elevation	
Risk minimisation measures	**Routine Risk minimization measures**: - SmPC sections 4.4 and 4.8. - PL sections 2 and 4. Recommendation for monitoring of liver enzymes before, during and after treatment is included in SmPC section 4.4 and PL section 2. Legal status: Prescription-only medicines **Additional risk minimisation measures:** Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Macular Edema	
Risk minimisation measures	**Routine Risk minimization measures:** - SmPC sections 4.4 and 4.8. - PL sections 2 and 4. Recommendation for ophthalmological evaluation prior to initiation of therapy and follow-up evaluations is included in SmPC section 4.4. Legal status: Prescription-only medicines **Additional risk minimization measures:** Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	
Risk minimisation measures	**Routine Risk minimization measures**: - SmPC sections 4.3, 4.4 and 4.8. - PL sections 2 and 4. Recommendations for periodic complete blood count (CBC) assessments, antibody testing to varicella zoster virus (VZV) before initiating fingolimod therapy and effective diagnostic and therapeutic strategies to be employed in patients with symptoms of infection while on therapy are mentioned in SmPC section 4.4. Legal status: Prescription-only medicines **Additional risk minimization measures:** Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Reproductive toxicity	
Risk minimisation measures	**Routine Risk minimization measures**: - SmPC section 4.6. Fingolimod "Heumann" is contraindicated during pregnancy. It should be stopped 2 months before planning a pregnancy and if women pregnant during treatment, fingolimod must be discontinued as per the recommendation mentioned in SmPC section 4.6. Legal status: Prescription-only medicines **Additional risk minimization measures:** Pregnancy prevention Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide - Pregnancy-specific patient reminder card -

Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	
Risk minimisation measures	**Routine risk minimisation measures:** - SmPC sections 4.4 and 4.8. - PL sections 2 and 4.

	A medical evaluation of the skin is recommended at initiation of therapy and then every 6 to 12 months taking into consideration clinical judgement and patient should be referred to a dermatologist in case suspicious lesions detected, is mentioned in SmPC section 4.4. Legal status: Prescription-only medicines **Additional risk minimization measures:** Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Convulsions	
Risk minimisation measures	**Routine Risk minimization measures:** - PL sections 2 and 4. Legal status: Prescription-only medicines **Additional risk minimization measures:** Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Lymphoma	
Risk minimisation measures	**Routine Risk minimization measures:** - SmPC sections 4.4, 4.8 and 5.3. - PL sections 2 and 4. As per the SmPC section 4.4, physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case by case basis. Legal status: Prescription-only medicines **Additional risk minimization measures:** None proposed
Other malignant neoplasms	
Risk minimisation measures	**Routine Risk minimization measures:** - SmPC sections 4.4 and 4.8. Legal status: Prescription-only medicines **Additional risk minimization measures:** None proposed
Long-term use in pediatric patients, including impact on growth and development (including	

cognitive development)	
Risk minimisation measures	**Routine Risk minimization measures:** - SmPC section 4.2. Legal status: Prescription-only medicines **Additional risk minimization measures:** Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver's guide

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 Fingolimod "Heumann".

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Fingolimod "Heumann".