Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for FINGOLIMOD 0.25 mg and 0.5 mg hard capsules

This is a summary of the risk management plan (RMP) for FINGOLIMOD 0.25 mg and 0.5 mg hard capsules (hereinafter referred to as Fingolimod). The RMP details important risks of Fingolimod, how these risks can be minimised, and how more information will be obtained about Fingolimod's risks and uncertainties (missing information).

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

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

I. The Medicine and What It is used for

Fingolimod is authorised as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (see SmPC for the full indication). It contains Fingolimod as the active substance and it is given orally.

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

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

II.A List of Important Risks and Missing Information

Important risks of Fingolimod 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. 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).

Table 10: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Hypertension • Liver transaminase elevation • Posterior Reversible Encephalopathy Syndrome (PRES) • Macular oedema • Infections, including opportunistic infections (progressive multifocal leukoencephalopathy, varicella zoster virus (VZV), herpes viral infections other than VZV, fungal infection) • Reproductive toxicity • Bronchoconstriction • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Convulsions
Important potential risks	• Acute disseminated encephalomyelitis-like (ADEM-like) events • Lymphoma • Other malignant neoplasms • Thromboembolic events • QT interval prolongation
Missing information	• Long-term use in paediatric patients, including impact on growth and development (including cognitive

	development) • Elderly patients (≥65 years) • Lactating women • Patients with diabetes mellitus • Patients with cardiovascular conditions including myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher atrioventricular (AV) block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea • Long-term risk of cardiovascular morbidity/ mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy

II.B Summary of Important Risks

Table 11: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important identified risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, 4.5, 4.8 and 4.9 PL sections 2 and 4. Recommendations on performing electrocardiogram and blood pressure measurement prior to the first dose and 6 hours after the first dose included in the SmPC section 4.4. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod and Patient / Parent / Caregiver guide).
Important identified risk: Liver transaminase elevation	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL sections 2 and 4. Recommendation for monitoring of levels of liver transaminases at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter included in the SmPC

	section 4.4. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod and Patient / Parent / Caregiver guide).
Important identified risk: Macular oedema	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL sections 2 and 4. Recommendation for ophthalmic evaluation prior to initiating therapy, at 3-4 months after initiating treatment, as well as regular follow-up evaluations included in SmPC section 4.4. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod and Patient / Parent / Caregiver guide).
Important identified risk: Infections, including opportunistic infections (progressive multifocal leukoencephalopathy, varicella zoster virus (VZV), herpes viral infections other than VZV, fungal infection)	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Recommendation on obtaining complete blood count before initiating treatment; and assessment of complete blood count periodically during treatment, at month 3 and at least yearly thereafter included in SmPC section 4.4. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod and Patient / Parent / Caregiver guide).
Important identified risk: Reproductive toxicity	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.6. PL section 2. Instruction that before initiation of treatment, women of childbearing potential must be informed of risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation is included in SmPC sections 4.4 and 4.6. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod, Patient / Parent / Caregiver guide and pregnancy-specific patient reminder

	card).
Important identified risk: 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. Recommendation for medical evaluation of the skin at initiation, and every 6 to 12 months included in SmPC section 4.4. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod and Patient / Parent / Caregiver guide).
Important identified risk: Convulsions	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 (paediatric patients) and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod and Patient / Parent / Caregiver guide).
Missing information: Long-term use in paediatric patients, including impact on growth and development (including cognitive development)	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2 and 4.4. PL section 2. Prescription only medicine. **Additional risk minimisation measures:** Educational Materials for Physicians and Patients (Physician's checklist for adult and paediatric patients to consider prior to prescribing fingolimod and Patient / Parent / Caregiver 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.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Fingolimod.