Part VI: Summary of the risk management plan

Summary of risk management plan for fingolimod 0.5 mg hard capsules

This is a summary of the risk management plan (RMP) for 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.

I. The medicine and what it is used for

Fingolimod is authorised for the treatment of as single disease modifying therapy in highly active relapsing remitting multiple sclerosis of adult and paediatric patients aged 10 years and older (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 so that immediate action can be taken as necessary. Special attention is given to a number of adverse events. 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);

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 edema • Infections, including opportunistic infections (PML, 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 • Thrombo-embolic events • QT interval prolongation
Missing information	• Long-term use in paediatric patients, including impact on growth and development (including cognitive development) • Elderly patients • 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 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

<u>Important identified risks</u>

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.3, 4.4, 4.5 and 4.8 • Prescription medicine only Additional risk minimisation measures • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

Hypertension	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.4 and 4.8 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Liver transaminase elevation	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 • Prescription medicine only Additional risk minimisation measures • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

Posterior Reversible Encephalopathy Syndrome (PRES)	
Risk minimisation measures	Routine risk minimisation measures:

	• Routine risk communication in SmPC sections 4.4 and 4.8 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Macular edema	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.4 and 4.8 • Prescription medicine only Additional risk minimisation measures • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.3, 4.4 and 4.8 • Prescription medicine only Additional risk minimisation measures • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

Reproductive toxicity	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC section 4.3, 4.4 and 4.6 • Prescription medicine only Additional risk minimisation measures • Pregnancy prevention • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

	- Pregnancy-specific patient reminder card

Bronchoconstriction	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.4, 4.8 and 5.1 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.4 and 4.8 • Prescription medicine only Additional risk minimisation measures • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

Convulsions	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.4 and 4.8 • Prescription medicine only Additional risk minimisation measures • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

<u>Important potential risks</u>

Acute disseminated encephalomyelitis-like (ADEM-like) events	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC section 4.8

	• Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Lymphoma	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.8 and 5.3 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Other malignant neoplasms	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC section 4.4 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Thrombo-embolic events	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC section 4.8 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

QT interval prolongation	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.4 and 4.9 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Missing information

Long-term use in paediatric patients, including impact on growth and development (including cognitive development)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.2 and 5.2 • Prescription medicine only Additional risk minimisation measures • Educational materials for physicians and patients: − Physician's checklist for adult and paediatric population − Patient/parent/caregiver guide

Elderly patients (≥ 65 years)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.2 and 5.2 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Lactating women	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC section 4.6 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Patients with diabetes mellitus	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.2, 4.4 and 4.8 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Patients with cardiovascular conditions	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC section 4.3 and 4.4

	• Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Long-term risk of cardiovascular morbidity / mortality	
Risk minimisation measures	Routine risk minimisation measures: • No risk minimization measures • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Long-term risk of malignant neoplasms	
Risk minimisation measures	Routine risk minimisation measures: • No risk minimization measures • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Unexplained death	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC section 4.8 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

Switch from other disease modifying therapy	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC sections 4.4, 4.5 and 5.1 • Prescription medicine only Additional risk minimisation measures • No additional risk minimization measures

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.