Summary of risk management plan for Fingolimod Mylan 0.5 mg hard capsules (Fingolimod)

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

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

This summary of the RMP for Fingolimod Mylan should be read in the context of all the 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 Fingolimod Mylan's RMP.

I. The medicine and what it is used for

Fingolimod Mylan 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. It contains fingolimod as the active substance and it is given by oral administration.

Further information about the evaluation of Fingolimod Mylan's benefits can be found in Fingolimod Mylan's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/fingolimod-mylan

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

Important risks of Fingolimod Mylan, together with measures to minimise such 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 Mylan, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

In addition to these measures, information about adverse events 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 Mylan is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fingolimod Mylan are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. 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 Mylan. 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/use in special patient populations etc.);

Table Part VI: 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 (slow heart rate or conduction abnormality of heart leading to low blood pressure after first dose) • Liver transaminase elevation (elevation of liver enzymes in blood) • Macular edema (gradual visual loss due to fluid accumulation in part of the retina) • Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection • Reproductive toxicity (effect on fertility or birth defects in babies born to parents exposed to fingolimod) • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Convulsions (fits) • Lymphoma (a cancer in the blood)
Important potential risks	• Other malignant neoplasms (other cancers)
Missing information	• Long-term use in paediatric patients, including impact on growth and development (including cognitive development)

II.B Summary of important risks

Important identified risks:	
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.

Risk factors and risk groups	Patients with particular medical history and/or co-medications in whom bradycardia may be poorly tolerated or might be at increased risk for bradycardia. This includes patients with: • Second degree Mobitz type II or higher AV block, • Sick-sinus syndrome • Sino-atrial heart block, • History of symptomatic bradycardia or recurrent syncope, • significant QT prolongation (QTc>470msec (female) or >450msec (male)). Avoid in patients with risk factors for QT prolongation such as hypokalemia, hypomagnesemia or congenital QT prolongation • known ischemic heart disease (including angina pectoris), • cerebrovascular disease, • history of myocardial infarction, • congestive heart failure, • history of cardiac arrest, • uncontrolled hypertension, • severe sleep apnea, Other potential risk factors include concomitant administration with: Class Ia (e.g. quinidine, dysopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products. • Beta blockers, • Heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances

	which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide
Liver transaminase elevation	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	None.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Macular edema	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	Patients with diabetes and history of uveitis are considered at increased risk of developing macular oedema. Such patients should undergo an ophthalmic evaluation prior to initiating fingolimod therapy and have follow-up evaluations while receiving fingolimod therapy.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8

	PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) should not receive fingolimod.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Reproductive toxicity	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	Females of childbearing potential not using an effective form of contraception. Fingolimod is excreted in milk of treated animals during lactation. Because of the potential for serious ADRs in nursing infants from fingolimod, women receiving fingolimod should not breast feed.

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.6 and 5.3 PL section 2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide • Pregnancy-specific patient reminder card
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Convulsions	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No attributable increase due to fingolimod has been established.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 (Pediatric patients) and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population

	• Patient/Parent/Caregiver's guide
Lymphoma	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	No attributable increase due to fingolimod has been established.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.8 and 5.3 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.

Important potential risks:	
Other malignant neoplasms	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	Since this is a potential risk, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3 and 4.4 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.

Missing information:
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric 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 Mylan.

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

There are no studies required for Fingolimod Mylan.