Part VI: Summary of the risk management plan

Summary of risk management plan for [Fingolimod] 0.5mg hard capsules

This is a summary of the risk management plan (RMP) for [Fingolimod] 0.5mg hard capsules. The RMP details important risks of [Fingolimod] 0.5mg hard capsules, how these risks can be minimised, and how more information will be obtained about [Fingolimod] 0.5mg hard capsules risks and uncertainties (missing information).
[Fingolimod] 0.5mg hard capsules summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how [Fingolimod] 0.5mg hard capsules should be used.

I. The medicine and what it is used for

[Fingolimod] 0.5mg hard capsules is indicated 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 in the EEA (see SmPC for the full indication):

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1).

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 (a sphingosine-1-phosphate (S1P) receptor modulator) as the active substance and it is given by 0.25 mg/day or 0.5 mg/day oral hard capsule.

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

Important risks of [Fingolimod] 0.5mg hard capsules, together with measures to minimise such risks and the proposed studies for learning more about [Fingolimod] 0.5mg hard capsules 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] 0.5mg hard capsules, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions and specifically of all the received pregnancy cases shall be analysed, in the 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] 0.5mg hard capsules is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of [Fingolimod] 0.5mg hard capsules 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 [Fingolimod] 0.5mg hard capsules. 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 • Infections, including opportunistic infections (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)

List of important risks and missing information	
	• Convulsions • Lymphoma
Important potential risks	• Other malignant neoplasms
Missing information	• Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

II.B Summary of important risks

Important identified risk **Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose**	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures:* SmPC sections 4.3, 4.4, 4.5 and 4.8 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide

Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction
Important identified risk **Liver transaminase elevation**	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	None identified for fingolimod.
Risk minimisation measures	*Routine Risk minimization measures:* SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction
Important identified risk **Macular Edema**	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Patients with diabetes and history of uveitis are considered at increased risk of developing macular edema. 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 minimization measures:* SmPC sections 4.4 and 4.8 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction
Important identified risk **Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)**	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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.

	Varicella-zoster virus infections Patients receiving concomitant immunosuppressive therapy may be at increased risk for VZV infections. The patient who died because of disseminated varicella zoster infection reported no history of varicella infection, no previous vaccination against varicella zoster (VZ) virus and was VZ virus-IgG negative. Therefore, patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in case of an MS relapse. Herpes viral infections other than VZV Patients receiving concomitant immunosuppressive therapy may be at increased risk for Herpes viral infections other than VZV. Progressive Multifocal Leukoencephalopathy (PML) PML primarily affects individuals with suppressed immune systems. In recent years, the most common underlying immunosuppressive illness has been AIDS. However, a variety of non-AIDS immunosuppressive illnesses has been associated with the occurrence of PML. These include lymphoreticular malignancy, most commonly chronic lymphocytic leukemia or non-Hodgkin lymphoma. JC virus is a double-stranded DNA human polyomavirus acquired in childhood. After infection, it remains latent in the body. 50-70% of the adult population is seropositive. It is believed that all seropositive individuals harbor latent virus in kidney, lymphoreticular tissue, or brain. PML is considered a reactivation infection. Whether the reactivation occurs systemically, with immunosuppression causing dissemination to the brain at that time, or the reactivation occurs from latent virus in the brain remains unclear. In people who are immunosuppressed, JC virus can reactivate and cause PML which is usually fatal. Cases of PML have been reported with another MS drug, natalizumab, a monoclonal antibody that blocks lymphocyte migration into the CNS (i.e. an effect on all lymphocyte subsets, including effector memory cells). Additionally, natalizumab has effects, such as mobilization of JC virus- carrying bone marrow precursor cells and splenic marginal zone B cells, which are not seen with fingolimod. The natalizumab label describes 3 risk factors that are known to increase the risk of PML in patients under therapy with natalizumab: treatment duration longer than 2 years, prior treatment with an immunosuppressant and presence of anti-JCV antibodies. Patients with all 3 known risk factors have an estimated risk of PML of 11/1,000. When evaluating the potential/theoretical risk with fingolimod, the specific risk factors should be considered: The presence of anti-JCV antibodies Switching to fingolimod after treatment with natalizumab for >2 years and duration of washout of natalizumab. Prior treatment with an immunosuppressant medication (e.g

	mitoxantrone, azathioprine, methotrexate, cyclophosphamide).
Risk minimisation measures	*Routine Risk minimization measures:* SmPC sections 4.3, 4.4 and 4.8 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction
Important identified risk **Reproductive toxicity**	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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] 0.5mg hard capsules should not breast feed.
Risk minimisation measures	*Routine Risk minimization measures:* SmPC section 4.6 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide - Pregnancy-specific patient reminder card
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction

Important identified risk **Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)**	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	None identified for fingolimod.
Risk minimisation measures	*Routine Risk minimization measures:* SmPC sections 4.4 and 4.8 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population

	- Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction
Important identified risk **Convulsions**	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	None identified for fingolimod.
Risk minimisation measures	*Routine Risk minimization measures:* SmPC sections 4.4 (paediatric patients) and 4.8 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimisation measures	*Routine Risk minimization measures:* SmPC section 4.8 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* No additional risk minimization measures
Important Identified risk ***Lymphoma***	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimisation measures	*Routine risk minimization measures:* SmPC sections 4.8 and 5.3 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* No additional risk minimization measures
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*

	AE follow-up form for adverse reaction

Important potential risk: ***Other malignant neoplasms***	
Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures:* SmPC section 4.4 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* No additional risk minimization measures
Additional pharmacovigilance activities	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form for adverse reaction
Missing information **Long-term use in pediatric patients, including impact on growth and development (including cognitive development)**	
Evidence for linking the risk to the medicine	Since this is a missing information, no attributable increase due to fingolimod has been established. Thus, the risk groups and/or risk factors cannot be identified.
Risk factors and risk groups	Cannot be identified
Risk minimisation measures	*Routine risk minimization measures:* SmPC sections 4.2 and 5.2 *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide

* *Cardiovascular conditions include 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. Multiply table for each important risk/ missing information.

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] 0.5mg hard capsules.

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

There are no studies required for [Fingolimod] 0.5mg hard capsules.