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 0.5 mg hard capsules. The RMP details important risks of Fingolimod 0.5 mg hard capsules, how these risks can be minimised, and how more information will be obtained about Fingolimod 0.5 mg hard capsule's risks and uncertainties (missing information).

Fingolimod 0.5 mg hard capsule's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Fingolimod 0.5 mg hard capsules should be used.

Important new concerns or changes to the current ones will be included in updates of Fingolimod 0.5 mg hard capsule's RMP.

I. The medicine and what it is used for

Fingolimod 0.5 mg hard capsules are 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:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy.
- 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 magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

It contains Fingolimod hydrochloride as the active substance and it is given by oral route.

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

Important risks of Fingolimod 0.5 mg hard capsules, together with measures to minimise such risks and the proposed studies for learning more about Fingolimod 0.5 mg hard capsule'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 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 0.5 mg 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 is collected continuously and regularly analysed, including Periodic safety update report (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 0.5 mg hard capsule is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fingolimod 0.5 mg 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 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 0.5 mg 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 • Hypertension • Liver transaminase elevation • Posterior Reversible Encephalopathy Syndrome (PRES) • Macular edema • Infections, including opportunistic infections [Progressive multifocal leukoencephalopathy (PML), varicella zoster virus (VZV) infections, 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 (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 (≥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 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

Important identified risks

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 minimisation measures:** • SmPC sections 4.3, 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Recommendations for regular ECG monitoring and precautions during first-dose monitoring are provided in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver guide

Hypertension	
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 minimisation measures:**

	• SmPC sections 4.4, and 4.8 • PIL sections 2 and 4 • Recommendation for regular blood pressure monitoring provided in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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 minimisation measures:** • SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 • PIL sections 2 and 4 • Recommendation for liver function monitoring including appropriate frequencies is included in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver guide

Posterior Reversible Encephalopathy Syndrome (PRES)	
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 minimisation measures:** • SmPC sections 4.4, and 4.8 • PIL sections 2 and 4 • Recommendation for regular blood pressure monitoring provided in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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 minimisation measures:** • SmPC sections 4.4 and 4.8 • PIL sections 2 and 4 • Recommendation for ophthalmologic evaluation in patients using fingolimod and multiple sclerosis patients with diabetes mellitus or a history of uveitis is provided in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver guide

Infections, including opportunistic infections (PML, VZV infections, 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. <u>Varicella-zoster virus infections</u> 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 virusIgG 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. <u>Herpes viral infections other than VZV</u> Patients receiving concomitant immunosuppressive therapy may be at increased risk for Herpes viral infections other than VZV. <u>Progressive Multifocal Leukoencephalopathy (PML)</u> 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 minimisation measures:** • SmPC sections 4.3, 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Recommendations for baseline and periodic complete blood counts (CBC) as well as MRI, assessment for their immunity to varicella (chickenpox), and vaccination against Human papilloma virus (HPV) before treatment initiation are provided in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver guide

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 should not breast feed.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.4, 4.6 and 5.3 • PIL sections 2 • Recommendations for informed decision, negative pregnancy test and use of effective contraception during treatment are provided in SmPC sections 4.4 and 4.6 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population o Patient/Parent/Caregiver guide – Pregnancy-specific patient reminder card

Bronchoconstriction	
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	No specific risk factors have been identified to predict the occurrence of bronchoconstriction in individual patients. Patients with pre-existing pulmonary conditions such as severe respiratory disease, pulmonary fibrosis, tuberculosis, and asthma requiring daily therapies were excluded from the pivotal MS studies.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.8 and 5.1 • PIL sections 2 and 4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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 minimisation measures:** • SmPC sections 4.3, 4.4 and 4.8 • PIL sections 2 and 4 • Recommendations for baseline and periodic skin evaluation is provided in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver guide

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	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 4.4 and 4.8 • PIL sections 2 and 4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis)

	Additional risk minimisation measures: • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver guide

Important potential risks

Acute disseminated encephalomyelitis (ADEM)-like events	
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 minimisation measures:** • SmPC section 4.8 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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 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, 4.4, 4.8 and 5.2 • PIL sections 2 and 4 • Legal status:

	– Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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 minimisation measures:** • SmPC sections 4.3, 4.4, and 4.8 • PIL sections 2 and 4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

Thrombo-embolic events	
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 minimisation measures:** • SmPC section 4.8 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis)

	Additional risk minimisation measures: o None

QT interval prolongation	
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 minimisation measures:** • SmPC sections 4.3 and 4.4 • PIL section 2 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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 section 4.4 • PIL section 2 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** • Educational material in the form of: – Physician information pack: which contains o SmPC o Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver guide

Elderly patients (≥65 years)	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.2 • PIL section 2 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

Lactating women	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.6 and 5.3 • PIL section 2 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

Patients with diabetes mellitus	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4 and 4.8 • PIL section 2 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3 and 4.4 • PIL section 2 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

Long-term risk of cardiovascular morbidity/mortality	
Risk minimisation measures	**Routine risk minimisation measures:** • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

Long-term risk of malignant neoplasms	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 5.3 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

Unexplained death	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.8 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

Switch from other disease modifying therapy	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4 and 4.5 • PIL section 2 • Recommendation for baseline CBC is provided in SmPC section 4.4 • Legal status: – Medicinal product subject to restricted medical prescription (treatment should be initiated and supervised by a physician experienced in multiple sclerosis) **Additional risk minimisation measures:** o None

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 0.5 mg hard capsules.

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

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