PART VI- Summary of the risk management plan

Summary of risk management plan for Golpimec 0,5 mg hard capsules.

This is a summary of the risk management plan (RMP) for Golpimec 0,5 mg hard capsules.

The RMP details important risks of Golpimec 0,5 mg hard capsules, how these risks can be minimized, and how more information will be obtained about Golpimec´s risks and uncertainties (missing information).

Golpimec´s summary of product characteristics (SmPC) and their package leaflet give essential information to healthcare professionals and patients on how these products should be used.

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

I. The medicine and what it is used for

Golpimec 0,5 mg hard capsules is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for adult patients. Full indication for fingolimod can be found in the SmPC of Fingolimod-neuraxpharm 0,5 mg hard capsules.

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

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

Important risks of Golpimec 0,5 mg hard capsules, together with measures to minimise such risks and the proposed studies for learning more about Golpimec'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 Golpimec 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 Golpimec 0,5 mg 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 Golpimec 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 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 Golpimec 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).

Summary of safety concerns	
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 (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)

Summary of safety concerns	
	• 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 pediatric 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

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk: Bradyarrhythmia

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 minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4, 4.5 and 4.8. 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. Additional pharmacovigilance activities: None.
Important Identified Risk: 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 minimization measures	Routine risk minimization measures; SmPC Sections 4.4 and 4.8 Additional risk minimization measures: No additional risk minimization measures.
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 minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2. 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. Additional pharmacovigilance activities: None.
Important Identified Risk: 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 minimization measures	Routine risk minimization measures: SmPC Sections 4.4 and 4.8. Additional risk minimization measures: No additional risk minimization measures
Important Identified Risk: Macular oedema.	
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 minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8. 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. Additional pharmacovigilance activities: None.
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 llnesses 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 doublestranded 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 minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4 and 4.8. 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. Additional pharmacovigilance activities: None.
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 should not breastfeed.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.6. Additional risk minimization measures: Pregnancy prevention Educational materials for physicians and patients: • Physician's Check-list 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: Specific adverse reaction follow-up questionnaire. All pregnancy specific data will be routinely presented in PSURs. Additional pharmacovigilance activities: None.
Important Identified Risk: 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 minimization measures	Routine risk minimization measures: SmPC Sections 4.4, 4.8 and 5.1 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. Additional pharmacovigilance activities: None
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 minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8. 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. Additional pharmacovigilance activities: None.
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	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 minimization measures	Routine risk minimization measures: SmPC sections 4.4 (pediatric patients) and 4.8. 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 Additional pharmacovigilance activities: None

Important Identified Risk: Acute disseminated encephalomyelitis-like (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 minimization measures	Routine risk minimization measures: SmPC Section 4.8. 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 due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.8 and 5.3. 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. Additional pharmacovigilance activities: None
Important Identified 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 minimization measures	Routine risk minimization measures: SmPC Section 4.4. 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.

	Additional pharmacovigilance activities: None
Important Identified Risk: 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 minimization measures	Routine risk minimization measures: SmPC Section 4.8. 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. Additional pharmacovigilance activities: None
Important Identified Risk: 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 minimization measures	Routine risk minimization measures: SmPC Section 4.4 and 4.9. Additional risk minimization measures: No additional risk minimization measures.
Important Missing information: Long-term use in pediatric patients, including impact on growth and development (including cognitive development.	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver guide
Important Missing information: Elderly patients (≥65 years).	

Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2 and 5.2. Additional risk minimization measures: No additional risk minimization measure
Important Missing information: Lactating women	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6. Additional risk minimization measures: No additional risk minimization measure.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities: None
Important Missing information: Patients with diabetes mellitus	
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: No additional risk minimization measure
Important Missing information: Patients with cardiovascular conditions	
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4. Additional risk minimization measures: No additional risk minimization measure
Important Missing information: Long-term risk of cardiovascular morbidity/mortality	
Risk minimization measures	No risk minimization measures
Important Missing information: Long-term risk of malignant neoplasms	
Risk minimization measures	No risk minimization measures
Important Missing information: Unexplained death	
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.8. Additional risk minimization measures: No additional risk minimization measure

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities: None
Important Missing information: Switch from other disease modifying therapy	
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4, 4.5 and 5.1. Additional risk minimization measures: No additional risk minimization measure

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 Golpimec 0,5 mg hard capsules.

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

There are no studies required for Golpimec 0,5 mg hard capsules.