Part VI: Summary of the risk management plan

Summary of risk management plan for <invented name> (Fingolimod)

This is a summary of the risk management plan (RMP) for <invented name>. The RMP details important risks of <invented name>, how these risks can be minimised, and how more information will be obtained about <invented name>'s risks and uncertainties (missing information).

<invented name>'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <invented name> should be used.

Important new concerns or changes to the current ones will be included in updates of <invented name>'s RMP.

I. The medicine and what it is used for

<invented name> 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 and with a body weight > 40 kg:

- 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 MRI or a significant increase in T2 lesion load as compared to a previous recent MRI (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 <invented name>, together with measures to minimise such risks and the proposed studies for learning more about <invented name>'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 <invented name>, 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 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 <invented name> is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of <invented name> 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 <invented name>. 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 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) • 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

List of important risks and missing information	
	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 risk **Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose**	
Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.7 Effects on ability to drive and use machines • 4.8 Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: Recommendation of ECG and blood pressure monitoring to all patients prior to and 6 hours after the first dose of fingolimod. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: - Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

Important identified risk **Liver transaminase elevation**	
Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.4 Special warnings and precautions for use

	• 4.8 Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: Recommendation for liver enzyme monitoring. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: - Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

Important identified risk **Macular oedema**	
Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.2 Posology and method of administration • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: Recommendation that fingolimod to be discontinued if a patient develops macular oedema. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: - Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

Important identified risk **Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)**

Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.3 Contraindications • 4.4 Special warnings and precautions for use • 4.5 Interaction with other medicinal products and other forms of interaction • 4.8 Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: Guidance on action to be taken if infections are suspected. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: - Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

Important identified risk **Reproductive toxicity**	
Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.6 Fertility, pregnancy and lactation Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: Guidance on action to be taken in women of childbearing potential before treatment initiation, during the treatment and when stopping the therapy. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures:

	- Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

Important identified risk **Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)**	
Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: - Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

Important identified risk **Convulsions**	
Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: Requirement on caution is required regarding convulsions.

	Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: - Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

Missing information **Long-term use in paediatric patients, including impact on growth and development (including cognitive development)**	
Risk minimisation measures	Routine risk minimisation measures: Included in SPC section(s) • 4.2 Posology and method of administration • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Prescription Only Medicine Additional risk minimisation measures: - Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe fingolimod.

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 <invented name>.

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

There are no studies required for <invented name>.