Summary of the Risk Management Plan

As the safety concerns and their management are identical for all products covered by this RMP, the information in Part VI is presented only once together for all products.

Summary of risk management plan for Fingolimod Zentiva (Fingolimod)

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

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

I. The medicine and what it is used for

Fingolimod Zentiva 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 with body weight > 40 kg

- patients with highly active disease despite a full and adequate course of treatment with at least 1 disease modifying therapy or
- patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in 1 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 by oral route of administration.

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

Important risks of Fingolimod Zentiva, together with measures to minimise such risks and the proposed studies for learning more about Fingolimod Zentiva'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 Fingolimod Zentiva, 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 Fingolimod Zentiva is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fingolimod Zentiva 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 Zentiva. 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 (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 phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for

List of important risks and missing information	
	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

Summary of important risk that have corresponding additional risk minimisation activities or additional pharmacovigilance activities are:

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3, 4.4, 4.5 and 4.8 PL section 2,4 Prescription only medicine Additional risk minimisation measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Liver transaminase elevation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4, 4.8 and 5.2 PL section 2 Prescription only medicine Additional risk minimisation measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Macular edema	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2,4 Prescription only medicine Additional risk minimisation measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.3, 4.4, and 4.8 PL section 2,4 Prescription only medicine <u>Additional risk minimisation measures:</u> Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Reproductive toxicity	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.3, 4.4 and 4.6 PL section 2 Prescription only medicine <u>Additional risk minimisation measures:</u> Educational materials for physicians and patients: - Physician'scisian's Check-list for adult and pediatric population - Patient/Parent/Caregiver guide - Pregnancy-specific patient reminder card
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4 and 4.8 PL section 2,4 Prescription only medicine <u>Additional risk minimisation measures:</u> Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Convulsions	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.8 PL section 4 Prescription only medicine <u>Additional risk minimisation measures:</u> Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.2 and 5.2 Prescription only medicine <u>Additional risk minimisation measures:</u> Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver 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 Zentiva.

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

There are no studies required for Fingolimod Zentiva.