Part VI: Summary of the risk management plan

Summary of risk management plan for Efigalo, Fingolimod Krka, Fingod, Fingolimod HCS (fingolimod)

This is a summary of the risk management plan (RMP) for Efigalo, Fingolimod Krka, Fingod, Fingolimod HCS (hereafter referred to as fingolimod). The RMP details important risks of fingolimod, how these risks can be minimised, and how more information will be obtained about fingolimod's risks and uncertainties (missing information).
Fingolimod's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how fingolimod should be used.
Important new concerns or changes to the current ones will be included in updates of fingolimod's RMP.

I. The medicine and what it is used for

Fingolimod is authorised for treatment of highly active relapsing remitting multiple sclerosis (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 fingolimod, together with measures to minimise such risks and the proposed studies for learning more about fingolimod'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, 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, 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 is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of fingolimod 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. 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
	Opportunistic infections, including 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)
	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

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for ECG and blood pressure measurement before and after fingolimod administration, the need for monitoring for signs and symptoms of bradycardia and appropriate actions are included in SmPC section 4.4. Furthermore, recommendation for obtaining cardiologist's advice regarding the use of fingolimod concomitantly with heart-lowering drugs is included in SmPC section 4.4 and 4.5. Symptoms and signs of bradycardia are presented in SmPC section 4.8. How to recognize bradycardia, what to do and monitoring for bradycardia are described in PL section 2. Legal status: restricted medical prescription (applies only for Slovakia) 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 sections 4.2, 4.3, 4.4, 4.8 and 5.2 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for monitoring transaminase and bilirubin and appropriate actions are included in SmPC section 4.4. Furthermore, signs and symptoms of hepatic dysfunction are included in SmPC section 4.4. How to recognize liver dysfunction and regular monitoring of liver liver function are described in PL section 2. Legal status: restricted medical prescription (applies only for

Liver transaminase elevation	
	Slovakia) Additional risk minimisation measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide

Macular oedema	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for ophthalmological evaluation and appropriate actions are included in SmPC section 4.4. Symptoms of macular oedema are presented in SmPC section 4.8. The need for eye examination in certain cases is described in PL section 2. Legal status: restricted medical prescription (applies only for Slovakia) Additional risk minimisation measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infections	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for careful monitoring patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy and appropriate actions are included in SmPC section 4.4. Recommendation for assessment of patient's immunity to varicella prior to fingolimod treatment and periodical assessment

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infections	
	of the complete blood count (CBC) and appropriate actions are included in SmPC section 4.4. Furthermore, recommendation for effective diagnostic and therapeutic strategies in patients with symptoms of infection while on therapy and appropriate actions are included in SmPC section 4.4. Vaccination against HPV is recommended prior to treatment in SmPC section 4.8. The need for vaccination against chickenpox, HPV is described in PL section 2. Furthermore, how to detect early signs and symptoms of infection and what to do are described in PL section 2. Legal status: restricted medical prescription (applies only for Slovakia) Additional risk minimisation measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide

Reproductive toxicity	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.6 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Pregnancy test must be performed and effective contraception must be instituted before fingolimod introduction in SmPC sections 4.4, 4.6. Furthermore, what to do if a woman becomes pregnant during treatment is described in SmPC section 4.6. Pregnancy test must be performed and effective contraception must be instituted before fingolimod introduction as described in PL section 2. Furthermore, what to do if a woman becomes pregnant during treatment is described in PL section 2. Legal status: restricted medical prescription (applies only for Slovakia) Additional risk minimisation measures: Educational materials for physicians and patients: - Physician's Checklist for adult and pediatric population - Patient/Parent/Caregiver guide

Reproductive toxicity	
	- Pregnancy-specific patient reminder card

Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkell cell carcinoma, Squamous cell carcinoma)	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for careful monitoring patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy and appropriate actions are included in SmPC section 4.4. How to detect early signs and symptoms of skin cancer and the need for skin examination before fingolimod introduction is described in PL section 2. Legal status: restricted medical prescription (applies only for Slovakia) Additional risk minimisation measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide

Lymphoma	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.8 and 5.3 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for careful monitoring patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy and appropriate actions are included in SmPC section 4.4. Legal status: restricted medical prescription (applies only for Slovakia) Additional risk minimisation measures: None

Other malignant neoplasms	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Recommendation for careful monitoring patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy and appropriate actions are included in SmPC section 4.4. Legal status: restricted medical prescription (applies only for Slovakia) Additional risk minimisation measures: None

Long term use in paediatric patients including impact on growth and development (including cognitive development)	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 PL section 3 Legal status: restricted medical prescription (applies only for Slovakia) Additional risk minimisation measures: 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.

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

There are no studies required for fingolimod.