RISK MANAGEMENT PLAN
For
Fingolimod
Version 4.1

RMP Version to be Assessed as Part of this Application:

RMP Version Number	4.1
Data Lock Point for this RMP	14-Jan-2025
Date of Final Sign Off	22-Oct-2025
Rationale for Submitting an Updated RMP	RMP updated in line with Gilenya RMP v21.1 sign off 23-Jul-2025 Core RMP is prepared to harmonise the RMPs of all fingolimod marketing authorisations for which the MAH has an approved RMP. RMP updated in line with CHMP Type IB WS variation assessment report for Procedure No. EMA/VR/0000280709, WSA: Mylan Pharmaceuticals Limited dated 05-Aug-2025
Summary of Significant Changes in this RMP	The following significant changes were made in the current RMP: Parts I-VI: • Removal of safety concern Convulsions, removal of TFU questionnaire and aRMMs related to it. • Removal of table 2 from part II: Module SVII (in line with CHMP Type IB WS variation assessment report for Procedure No. EMA/VR/0000280709) • Removal of pregnancy specific follow-up questionnaires for safety concern 'Reproductive toxicity' (in line with Gilenya RMP v21.1 sign off 23-Jul-2025) • Correction of the term 'macular degeneration' to 'macular edema' in Annex 6 Physician's checklist (in line with Gilenya RMP v21.1 sign off 23-Jul-2025) • Addition of details of both regulatory procedures for which the MAH has an approved RMP in the EU (EMEA/H/005661 and DE/H/6367)

Other RMP Versions Under Evaluation:

RMP Version Number	4.0
Submitted On	10-Jul-2025

Procedure Number	WS EMA/VR/0000280709 for EMEA/H/005661 and DE/H/6367

Details of the Current RMP:

Version Number	EMEA/H/005661: v.3.1 DE/H/6367: V2.1
Approved with Procedure	EMEA/H/005661 DE/H/6337
Date of Approval (Opinion Date)	EMEA/H/C/005661: 11-Oct-2022 DE/H/6367: 21-Jan-2022

QPPV: Dr. Eiko Soehlke, MD MPH, EEA QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
DLP	Data Lock Point
CNS	Central Nervous System
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DCP	Decentralised Procedure
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
HCP	Healthcare Professional
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
ICSR	Individual Case Safety Report
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MRI	Magnetic Resonance Imaging
MRP	Mutual Recognition Procedure
PAC	Patient Alert Card
PML	Progressive Multifocal Leukoencephalopathy
PRES	Posterior Reversible Encephalopathy Syndrome
PL	Package Leaflet
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTC	Patient Treatment Course
PTD	Patient Treatment Days
PTM	Patient Treatment Months
PTY	Patient Treatment Years
PVA	Pharmacovigilance Agreement
QPPV	Qualified Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities
DLP	Data Lock Point
SmPC	Summary of Product Characteristics
S1P	Sphingosine 1-Phosphate
WHO	World Health Organization
VZV	Varicella-Zoster Virus

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Fingolimod (hydrochloride)
Pharmacotherapeutic Group(s) (ATC Code)	Selective immunosuppressants (ATC code: L04AE01)
Marketing Authorisation Holder	EMEA/H/C/005661: Mylan Pharmaceuticals Limited DE/H/6367/001: Mylan Germany GmbH
Medicinal Products to Which this RMP Refers	02
Invented Name(s) in the European Economic Area (EEA)	EMEA/H/C/005661: Fingolimod Mylan 0.5 mg - DE/H/6367/001: Mulfinya 0.5 mg hard capsules -
Marketing Authorisation Procedure	EMEA/H/C/005661 DE/H/6367/001
Brief Description of the Product	Chemical class: Fingolimod (ATC code: L04AE01) belongs to the pharmacotherapeutic group of selective immunosuppressants. Summary of mode of action: Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the infiltration of pathogenic lymphocytes cells into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells. Important information about its composition: None.
Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier

Indication(s) in the EEA Current	Fingolimod 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: • Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy. or • 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.
Dosage in the EEA Current	In adults, the recommended dose of fingolimod is one 0.5 mg capsule taken orally once daily. In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight: - Paediatric patients with body weight ≤40 kg: one 0.25 mg capsule taken orally once daily. - Paediatric patients with body weight >40 kg: one 0.5 mg capsule taken orally once daily. Paediatric patients who start on 0.25 mg capsules and subsequently reach a stable body weight above 40 kg should be switched to 0.5 mg capsules. When switching from a 0.25 mg to a 0.5 mg daily dose, it is recommended to repeat the same first dose monitoring as for treatment initiation.
Pharmaceutical Form(s) and Strengths	0.5 mg hard capsule.
Is the Product Subject to Additional Monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Not applicable.

Part II: Module SII - Non-clinical Part of the Safety Specification

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable

Part II: Module SIV - Populations Not Studied in Clinical Trials

Not applicable.

Part II: Module SV - Post-authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Viatris submitted an updated RMP in line with Gilenya RMP published on EMA website on 03-Aug-2021, as follows: Safety concerns Hypertension, Posterior reversible encephalopathy syndrome and bronchoconstriction, previously classified as Important identified risks, have been removed from the list of safety concerns.

Safety concerns Acute disseminated encephalomyelitis-like (ADEM-like) events, Thrombo-embolic events and QT interval prolongation, previously classified as Important potential risks, have been removed from the list of safety concerns.

Safety concerns 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 brady-arrhythmia 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 and Switch from other disease modifying therapy, previously classified as Missing information, have been removed from the list of safety concerns.

Safety concern Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) classified as Important identified risk has been reworded to Opportunistic infections including (PML, VZV, herpes viral infections other than VZV, fungal infection).

Safety concern Lymphoma, previously classified as Important potential risk, has been reclassified as Important identified risk.

As per the Brand leader Gilenya RMP v20.2 sign off 13-Nov-2024, published on EMA website on 18-Dec-2024, safety concern "Convulsions" has been removed from the list of important identified risks.

As per the Brand leader Gilenya RMP v21.1 sign off 23-Jul-2025, published on EMA website on 23-Sep-2025, the Pregnancy specific follow-up questionnaires for important identified risk 'Reproductive toxicity' have been removed from Part III, Part V and Annex 4.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable, as this RMP for fingolimod follows the same safety concerns as the safety concerns of the reference substance RMP.

SVII.3.2. Presentation of the missing information

Not applicable, as this RMP for fingolimod follows the same safety concerns as the safety concerns of the reference substance RMP.

Part II: Module SVIII - Summary of the Safety Concerns

Table 2: SVIII- Summary of safety concerns

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)

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH has in place to identify and characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection: Specific adverse reaction follow-up questionnaires for risks:

Safety concerns		**Specific adverse drug reaction follow-up form**
Important Identified Risks	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	S1P modulator and Cardiac rate and rhythm disorders checklist.
	Liver transaminase elevation	Liver injury checklist.
	Macular edema	S1P modulator and Macular edema checklist
	Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection)	Suspected PML checklist.
		VZV infection checklist.
		Cryptococcal meningitis check list for Multiple Sclerosis Products check list.
	Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Multiple sclerosis product and Skin Cancer checklist.
	Lymphoma	Malignancy and neoplasm checklist
		Cervical dysplasia/ cancer checklist
Important Potential Risks	Other malignant neoplasms	Malignancy and neoplasm checklist
		Cervical dysplasia/ cancer checklist

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES ((INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES))

The safety information in the proposed product information is aligned to the reference medicinal product (Gilenya 0.5 mg Capsule hard, Novartis Europharm Limited).

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 3: Part V.1- Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post first dose	Routine risk communication: 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: The SmPC, Section 4.3, includes contraindications in patients with specific cardiac conditions. The SmPC section 4.4 and PL section 2 include the recommendation for electrocardiogram (ECG) and blood pressure measurements to be performed prior to and 6 hours after the first dose of fingolimod. All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6-hour period is recommended. Recommendations regarding post-dose bradyarrhythmia-related symptoms and extended monitoring are also included. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription.
Liver transaminase elevation	Routine risk communication: 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: The SmPC Section 4.4 includes the recommendation for liver function monitoring (also included in the PL section 2) and provides guidance for discontinuing and resuming treatment. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription.

Safety Concern	Routine Risk Minimisation Activities
Macular oedema	Routine risk communication: SmPC sections 4.4 and 4.8. PL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: The SmPC section 4.4 and PL section 2, include the recommendation for an ophthalmological evaluation at 3-4 months after treatment initiation and if patients report visual disturbances at any time while on therapy. Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription.
Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	Routine risk communication: 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: The SmPC, Section 4.4, instructs physicians to carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. This section also includes the recommendation for a complete blood count before starting fingolimod, periodically during treatment and in case of signs of infection and to delay treatment initiation in patients with severe active infections. In addition, SmPC section 4.4 and PL section 2 provide recommendations regarding varicella immunity and opportunistic infections including instructing patients to report symptoms of infection to their physician Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription.
Reproductive toxicity	Routine risk communication: SmPC sections 4.3, 4.4 and 4.6. PL section 2. Contraindication in pregnant women and in women of childbearing potential (WCBP) not using effective contraception in Section 4.3. Warnings in Section 4.4 Risk addressed in SmPC Section 4.6: regarding the increased risk of malformation and the malformations types. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety Concern	Routine Risk Minimisation Activities
	The SmPC section 4.6 and PL section 2 state that fingolimod should not be used during breastfeeding. Women of childbearing potential must use effective contraception. A negative pregnancy test result is required before initiation. Other routine risk minimisation measures beyond the Product Information: None Medicine's legal status: Restricted medical prescription.
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Routine risk communication: 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: The SmPC, Section 4.4, instructs physicians to carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. This section also includes the recommendation for a medical evaluation of the skin at initiation of treatment with fingolimod, 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. Recommendations on regular skin examinations and eventual consultation of a specialist are also provided in PL section 2. Other routine risk minimisation measures beyond the Product Information: None Medicine's legal status: Restricted medical prescription.
Lymphoma	Routine risk communication: SmPC sections 4.4, 4.8 and 5.3. PL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: The SmPC, section 4.4, recommends treatment discontinuation if lymphoma is suspected. Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription.
Other malignant neoplasms	Routine risk communication: SmPC sections 4.3 and 4.4. PL section 2.

Safety Concern	Routine Risk Minimisation Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: The SmPC, section 4.4, includes the recommendation that physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription.
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Routine risk communication: SmPC sections 4.2 and 5.2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription.

V.2 Additional Risk Minimisation Measures

The additional risk minimisation measures consist of: Physician's checklist, Patient/Parent/Caregiver's guide, and Pregnancy-specific patient reminder card.

Objective

To provide physicians and patients with educational information on 7 safety areas of interest:

- Bradyarrhythmias upon treatment initiation
- Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection,
- Reproductive toxicity & prevention of pregnancy
- Macular edema
- Liver transaminase elevation
- Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
- Long-term use in pediatric patients

The goal is for this information to assist the physician in managing and counselling patients who are either currently being treated with Fingolimod Mylan/Mulfinya, or in whom therapy with Fingolimod Mylan/Mulfinya is proposed as well as for educating patients about the risks while using Fingolimod Mylan/Mulfinya Local Marketing Authorisation Holders will distribute the educational materials to physicians

involved in treatment with Fingolimod Mylan/Mulfinya.

Rationale for the Additional Risk Minimisation Activity:

In order to increase understanding of the safe and effective use of Fingolimod Mylan/Mulfinya, physicians will be provided with a physician information pack containing the following elements:

- Product information
- The Physician's checklist for adult and pediatric patients prior to prescribing Fingolimod Mylan/Mulfinya.
- The Patient / Parent / Caregiver guide to be provided to all patients, their parents (or legal representative and caregivers
- The Pregnancy-specific patient reminder card to be provided to all patients, their parents (or legal representatives), and caregivers, as applicable.

Target Audience and Planned Distribution Path:

Target audience: Physicians who are managing and counselling patients who are either currently being treated with Fingolimod Mylan/Mulfinya, or in whom therapy with Fingolimod Mylan/Mulfinya is proposed. The specific risk regarding Reproductive toxicity will be communicated to women of child-bearing potential using the 'pregnancy-specific patient reminder card'.

Local Marketing Authorisation Holders will distribute the educational materials to physicians involved in treatment with Fingolimod Mylan/Mulfinya.

Plans for Evaluating the Effectiveness of the Interventions and Criteria for Success:

Effectiveness of risk minimisation measures for the safety concern will be measured by routine pharmacovigilance activities during signal detection activity as per internal procedures.
Effectiveness of additional RMMs will be evaluated on annual basis after MA approval.

Pregnancy Prevention
The following set of interventions aims at minimizing pregnancy exposure and is intended to inform the prescribers and patients about the teratogenic risk associated with the use of fingolimod during pregnancy and required actions to minimize this risk:

Physician's checklist with mention of the following key messages:

- Confirmation of a negative pregnancy test result and Counselling on the need for effective contraception in women of childbearing age.
- Risk of teratogenicity information and reproductive risk with Fingolimod Mylan/Mulfinya
- Contraindication and the need for counselling women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers before treatment initiation and regularly, facilitated by the pregnancy-specific patient reminder card.
- Cross reference to 'pregnancy-specific patient reminder card'

Patient/Parent/Caregiver's guide with mention of the following key message messages:

- Information regarding the contraindication

- Cross reference to the pregnancy-specific patient reminder card

Pregnancy-specific patient reminder card contains the following key messages:
While on treatment, women must not become pregnant.

- Patients will be informed by their doctor about the teratogenic risk and required actions to minimise this risk.
- Need for effective contraception while taking Fingolimod Mylan/Mulfinya
- Ensure that a pregnancy test is carried out and negative results are verified by your doctor before treatment. It must be repeated at suitable intervals.
- Effective contraception is needed while on treatment and for 2 months after discontinuation
- Your treating physician will provide counselling before treatment initiation and regularly
- Your treating physician will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy
- If a woman becomes pregnant or wants to become pregnant while on treatment, Fingolimod Mylan/Mulfinya must be discontinued.
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with Fingolimod Mylan/Mulfinya.

As per the EU SmPC, use of fingolimod is contraindicated in pregnant women and in women of child-bearing potential not using effective contraception (SmPC and Package leaflet).

This is to ensure that women of child-bearing potential (including adolescent females), are not. pregnant when starting therapy and do not become pregnant during the course of and/or soon. after stopping the therapy.

Rationale for Proposing to Remove Additional Risk Minimisation Measures:

As safety concern Convulsions was removed from the list of safety concerns in line with the Brand leader Gilenya RMP v21.1 sign off 23-Jul-2025, published on EMA website on 23-Sep-2025, the key messages concerning “Convulsions” were also deleted from Physician’s checklist and Patient/ Parent / Caregiver guide.

V.3 Summary of Risk minimisation measures

Table 4 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician’s checklist for adult and paediatric population • Patient/Parent/Caregiver’s guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Liver transaminase elevation	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures • Physician's checklist for adult and pediatric population Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None.
Macular edema	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population. • Patient/Parent/Caregiver's guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire questionnaire for PML, CM and VZV.
Reproductive toxicity	Routine risk minimisation measures: SmPC sections 4.3, 4.4, and 4.6 PL section 2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population. • Patient/Parent/Caregiver's guide • Pregnancy-specific patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities: None
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Lymphoma	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 5.3 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Other malignant neoplasms	Routine risk minimisation measures: SmPC sections 4.3 and 4.4 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Fingolimod Mylan/Mulfinya (fingolimod)

This is a summary of the risk management plan (RMP) for Fingolimod Mylan/Mulfinya. The RMP details important risks of Fingolimod Mylan/Mulfinya, how these risks can be minimised, and how more information will be obtained about Fingolimod Mylan/Mulfinya risks and uncertainties (missing information).
Fingolimod Mylan/Mulfinya's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.
This summary of the RMP for Fingolimod Mylan should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in updates of Fingolimod Mylan's RMP.

I. The Medicine and What it is Used For

Fingolimod Mylan/Mulfinya 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:
Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see SmPC sections 4.4 and 5.1).
Or
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. It contains fingolimod as the active substance and it is given by oral administration.
Further information about the evaluation of Fingolimod Mylan's benefits can be found in Fingolimod Mylan's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Fingolimod Mylan/Mulfinya, together with measures to minimise such risks and the proposed studies for learning more about Fingolimod Mylan/Mulfinya '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 Mylan/Mulfinya, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

In addition to these measures, information about adverse events 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 Mylan/Mulfinya is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Fingolimod Mylan/Mulfinya are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. 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 Mylan/Mulfinya. 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/use in special patient populations etc.).

Table 5: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose (slow heart rate or conduction abnormality of heart leading to low blood pressure after first dose) • Liver transaminase elevation (elevation of liver enzymes in blood) • Macular edema (gradual visual loss due to fluid accumulation in part of the retina) • Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection • Reproductive toxicity (effect on fertility or birth defects in babies born to parents exposed to fingolimod) • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Lymphoma (a cancer in the blood)
Important Potential Risks	• Other malignant neoplasms (other cancers)
Missing Information	• Long-term use in paediatric patients, including impact on growth and development (including cognitive development)

II.B Summary of Important Risks

Table 6: Part VI.2- Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
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 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures:

	• Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide
Liver transaminase elevation	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	None.
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 Restricted medical prescription. Additional risk minimisation measures • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Macular edema	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	Patients with diabetes and history of uveitis are considered at increased risk of developing macular oedema. 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 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
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.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Reproductive toxicity	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important identified risk.
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 PL section 2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide • Pregnancy-specific patient reminder card
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: 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	In line with the reference RMP, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription.

	Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Lymphoma	
Evidence for linking the risk to the medicine	In line with the reference RMP, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	No attributable increase due to fingolimod has been established.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 5.3 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None

Table 7: Part VI.3- Important potential risks:

Other malignant neoplasms	
Evidence for Linking the Risk to the Medicine	In line with the reference RMP, this safety concern has been classified as an important potential risk.
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 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None

Table 8: Part VI.4- Missing Information

Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	
Risk Minimisation Measures	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's 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 Mylan/Mulfinya.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Fingolimod Mylan/Mulfinya.

PART VII: ANNEXES

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Safety concerns		**Specific adverse drug reaction follow-up form**
Important Identified Risks	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	S1P modulator and Cardiac rate and rhythm disorders checklist
	Liver transaminase elevation	Liver injury checklist
	Macular edema	S1P Modulator and Macular edema checklist
	Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	Suspected Progressive Multifocal Leukoencephalopathy checklist
		Varicella Zoster Virus (VZV) infections checklist
		Cryptococcal meningitis for Multiple Sclerosis Products
	Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Multiple sclerosis product and Skin Cancer checklist
	Lymphoma	Malignancy and neoplasm checklist
		Cervical dysplasia/cancer checklist
Important Potential Risks	Other malignant neoplasms	Malignancy and neoplasm checklist
		Cervical dysplasia/cancer checklist

Important identified risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

S1P modulator and cardiac rate and rhythm disorders checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed for first dose events and/or other events.

1. Patient Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	

Height	

2. Drug information at the time of event:

Tradename		
Strength		
Batch number		
Expiry date		
Route of admin-istration		
Dose		
Dose frequency		
Start date		
Stop date		
Onset date for event		

3. Event details:

Did the patient experience any symptoms? ☐ No ☐ Yes (*please specify*)
Did the patient receive treatment for the event? ☐ No ☐ Yes (*please specify*)
Were any of the following diagnostic tests performed? Check all that apply and please specify which test(s), dates and results

☐ ECG (*please include baseline*)
☐ Holter monitor (*please include baseline*)
☐ Blood tests (e.g. electrolytes)
☐ Stress test
☐ Echocardiogram
☐ Coronary angiography
☐ Electrophysiology study (EPS)
☐ Others (*please specify*)
☐ Cardiac biomarkers (specify e.g., creatinine kinase-MB, troponin)
☐ None of the above

4. Patient's medical history:

Did the patient have a history of any of the following prior to the start of the suspect drug?
Check all that apply. Please specify medical condition and date of onset.

☐ ECG abnormalities *(please* specify)
☐ Syncope
☐ Valvular disease *(please* specify)
☐ Symptomatic bradycardia
☐ Pacemaker (specify if temporary or permanent)
☐ Cardiovascular disease (e.g. angina, CAD, MI, CHF)
☐ Wolff-Parkinson-White syndrome *(please specify)*

☐ Other (e.g. COPD, sleep apnea, hyperthyroidism) *(please specify)*
☐ Congenital heart disease
☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**
☐ Anti psychotics/ Antidepressants
☐ Theophylline
☐ Beta blockers
☐ Drugs of abuse (*e.g. cocaine)*
☐ Cholinomimetics *(e.g. metoclopramide)*
☐ Antiarrhythmics (e.g. quinidine, digoxin, beta-blockers, calcium channel blockers)
☐ Anticonvulsants (e.g. phenytoin, gabapentin, topiramate)
☐ Calcium channel blockers (dihydropyridine or non-)
☐ None of the above
☐ Others *(please specify)*

First dose observation (FDO) period: Please provide details of events occurring during/post FDO.

- First dose of (S1P modulator) fingolimod: Date: __ / _ / _ Time: __ _
- Heart rate at baseline: Date: __ / _ / _ Time: ___ Rate: ___ bpm
- The minimum heart rate measured during the event: ___ bpm
- The time interval between the first dose of fingolimod and the minimum heart rate: ___ minutes/ hours/ days/ weeks *(please specify units)*
- ECGs performed at time of event? If yes, please provide details on any abnormalities noted other than bradycardia.
- Did the patient receive any treatment for the event?

☐ Yes - pharmacological (*e.g. atropine, please specify)*
☐ Yes - non-pharmacological *(e.g. IV fluids, please specify)*
☐ No

Vital signs during observation period *(hourly heart rate and BP):*

4. Outcome of event:

☐ Recovered/resolved	☐ Not recovered/resolved
☐ Resolved with sequelae	☐ Fatal
☐ Unknown	☐ Other

If 'Other', please specify:

_____

_____

_____

5. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.
Name: Sign
Occupation: Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Important identified risk: Liver transaminase elevation

Liver injury checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

1. Patient Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Drug information at the time of event:

Tradename		
Strength		
Batch number		
Expiry date		
Route of administration		
Dose		
Dose frequency		
Start date		
Stop date		
Onset date for event		

3. Event details:

A. Diagnosis and date of diagnosis:

_____

B. Did the patient present with any of the following signs or symptoms?
(Check all that apply)

☐ Jaundice	☐ Ascites	☐ Asterixis (flapping tremor)
☐ Dark urine	☐ Fever	☐ Altered mental status
☐ Pale stool	☐ Fatigue	☐ Abdominal pain (specify location)
☐ Pruritus	☐ Bleeding (specify location)	☐ Anorexia
☐ Nausea	☐ Spider angiomata	☐ Variceal Bleeding

☐ Caput medusa	☐ Peripheral edema	☐ Fetor hepaticus
☐ Gynecomastia	☐ Muscle wasting	☐ Other (specify)
☐ None		

C. Were any of the following diagnostic tests performed?

If yes, please specify the dates and results including reference range and pre- and post-treatment values (wherever applicable):

☐ Liver function tests
☐ Serology & PCR testings for Hepatitis A, B, C &/or E virus
☐ Autoantibody tests
☐ Abdominal or hepatobiliary ultrasound (with or without Doppler's)
☐ Abdominal CT scan
☐ Liver biopsy
☐ Liver transplant (planned or completed)
☐ Other (specify)
☐ None

D. Does the patient have a history of any of the following prior to the start of the suspect drug? Check all that apply and include date(s) of onset as well as status (i.e. active/inactive) and details:

☐ Previously elevated liver enzymes	☐ Tattoos
☐ Hepatitis	☐ Transfusion or blood product administration
☐ Other hepatobiliary disease or dysfunction	☐ Gilbert's disease
☐ Autoimmune disease (specify type)	☐ Alcohol intake (quantify if possible)
☐ Active or chronic pancreatitis	☐ Drug abuse
☐ Diabetes mellitus (Type I or II)	☐ Foreign travel
☐ Non-alcoholic steatohepatitis	☐ Active gall bladder disease
☐ Cirrhosis	☐ Portal hypertension
☐ Ascites	☐ Variceal bleeding/esophageal varices
☐ Spider angiomata	☐ Thrombocytopenia
☐ None	☐ Other (specify)

E. Has the patient recently (i.e. within the past 6 months) taken any of the following?
(Check all that apply)

☐ Sulphonamides	☐ Furosemide	☐ ACE Inhibitors

☐ Valproic acid	☐ NSAIDS (e.g. ibuprofen)	☐ Estrogens (oral contraceptives)
☐ Metronidazole	☐ Acetaminophen/Paracetamol	☐ Amiodarone
☐ COX II inhibitors (e.g. celecoxib)	☐ Tetracycline	☐ Steroids
☐ Thiazide diuretics	☐ 6-Mercaptopurine	☐ Statins
☐ Nicotinic acid	☐ Methotrexate	☐ Other (specify)
☐ None		

4. Outcome of event:

☐ Recovered/resolved ☐ Not recovered/resolved

☐ Resolved with sequelae ☐ Fatal

☐ Unknown ☐ Other

If 'Other', please specify:

_____

_____

_____

5. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Important identified risk: macular edema

S1P Modulator and Macular edema checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

1. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Drug information at the time of event:

Tradename		

Strength		
Batch number		
Expiry date		
Route of admin-istration		
Dose		
Dose frequency		
Start date		
Stop date		
Onset date for event		

Relevant Medical History (concurrent and preexisting conditions):

(Please specify medical condition and date of onset)

☐ Eye diseases (e.g., uveitis, optic neuritis) ► If yes (specify)

☐ Intraocular surgery ► If yes (provide type and date of surgery)

☐ Diabetes mellitus ► If yes, provide:

• Date of diagnosis

• Was there evidence of retinopathy prior to starting the drug? ☐ Yes, grade ☐ No

☐ Other (specify)

☐ None

Has the patient recently (i.e. within the past 6 months) taken any other medications?

☐ Yes (specify) ☐ No

If Yes, please list:

_____
_____

_____
_____

_____
_____

_____
_____

3. Event details:

1. Date of diagnosis: __ / _ / _

2. Was macular edema diagnosed in ☐ Left eye ☐ Right eye ☐ Both eyes

3. Did the patient experience any symptoms due to the macular edema? ☐ Yes (list the symptoms) ☐ No

4. Were any of the following diagnostic tests performed? ► If yes, please specify the dates and results at baseline (i.e. pre-Fingolimod) and at the time of the event

☐ Fundoscopy

☐ Optical Coherence Tomography (OCT)

☐ Fluorescein angiography (FA)

☐ Visual acuity

☐ Other: --------

A. Course of the event after diagnosis:

1. Details of any treatment prescribed for the macular edema:

Right eye ☐Photocoagulation / Laser ☐ Intravitreal steroid injection ☐ Surgery

☐Other (specify) ☐ None

Left eye ☐Photocoagulation / Laser ☐ Intravitreal steroid injection ☐ Surgery

☐Other (specify) ☐ None

2. Current status of the macular edema

☐ Resolved ☐ Improving ☐ Unchanged ☐ Deteriorated

☐ Results of tests performed (e.g., fundoscopy, Optical coherence tomography (OCT), FA, specify the dates and results)

3. Current status of vision impairment related to macular edema (if any)?

☐ Resolved ☐ Improving ☐ Unchanged ☐ Deteriorated

☐ Visual acuity (specify the dates and results)

4. Outcome of event:

☐ Recovered/resolved ☐ Not recovered/resolved

☐ Resolved with sequelae ☐ Fatal

☐ Unknown ☐ Other

If 'Other', please specify:

_____

_____

_____

5. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Suspected Progressive Multifocal Leukoencephalopathy checklist
Varicella Zoster Virus (VZV) infections checklist
Cryptococcal meningitis for Multiple Sclerosis Products

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

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

1. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Drug information at the time of event:

Tradename		
Strength		
Batch number		
Expiry date		
Route of administration		
Dose		

Dose frequency		
Start date		
Stop date		
Onset date for event		

3. Event Details

3.1 Suspected Progressive Multifocal Leukoencephalopathy checklist
Please provide the following information in addition to routine information request forms.
Did the patient present with any of the following sigs and symptoms? Check all that apply.
□ Hemiparesis
□ Cognitive impairment
□ Weakness
□ Headaches
□ Hemianopsia
□ Personality changes
□ Aphasia
□ Brainstem deficits
□ Dysarthria
□ Visual impairments
□ Clumsiness/cerebellar deficits
□ Sensory deficits
□ Fever
□ Others (please specify):
□ None of the above

Was brain MRI/MRA performed?
□ Yes (provide recent and prior reports and/or summarize below) Date/results:

□ No
□ Unknown

CSF JCV analysis □ yes (provide results below) □ no □ unknown

Type of test (PCR, JCV anti-body)	Test date	Result

Please include results of other relevant test

Type of test (PCR, JCV anti-body)	Test date	Result
JCV (serum or urine)		

Type of test (PCR, JCV antibody)	Test date	Result
Anti JCV antibody index		
Absolute lymphocyte count		
WBC – including lymphocyte subsets (e.g. CD4, CD8)		
Brain biopsy		
Other		

Absolute lymphocyte counts (please provide up to 12 months prior to PML onset)

Date	Absolute lymphocyte counts

PML-IRIS

Did this patient receive a diagnosis of IRIS (immune reconstitution inflammatory syndrome)?
□ Yes Onset date: DD/MMM/YYYY
□ No
□ Unknown
What is the outcome of the patient's PML – IRIS?
□ Recovered □ Recovered with sequelae □ Not recovered □ Fatal □ Unknown

Provide the date of the assessment outcome of PML – IRIS (DD/MMM/YYYY)

Patient history:
Does the patient have a history of any immunosuppressive disorders prior to the start of the suspect drug (e.g HIV infection, malignancy (leukemia, lymphoma, myeloproliferative diseases), sarcoidosis, other disturbances of the immune system (e.g history of low CD4/CD8 ratio; other)?
□ yes (summarize below)
□ no
□ unknown

Immune disorder	**Date of onset**	**Status (active/inactive)**	**Other details**

List prior MS therapies:

Drug	**dose**	**Start date**	**Stop date**

Has the patient taken any of the following medications in the past or currently? Check all that apply and include dates of starting and completing and medication indication in the space below:

□ Chemotherapy/cytoreductive therapy (please specify)
□ Corticosteroids (specify dose and duration)
□ Other immunosuppressant drugs (please specify)
□ Radiation therapy
□ Additional details:

3.2 Varicella Zoster Virus (VZV) infection checklist

Event description
3.2.1 Confirm the type of varicella zoster virus infection:
□ Primary infection (e.g. varicella/chickenpox)
□ Reactivation (e.g. herpes zoster/shingles)
□ Unknown/undetermined
3.2.2. Specify diagnosis (including complications, if any), the date the diagnosis was made (e.g. radiculitis, post-herpetic neuralgia, polyneuritis, facial paralysis, etc.) and current clinical status.
3.2.3. Infection location:
Skin: □ Yes □ No □ Unknown
If yes, please provide clinical description and specify the involved dermatome(s):
If yes, any complication: □ Eye □ Ear □ Post-herpetic neuralgia
Disseminated infection: □ Yes □ No □ Unknown
If yes: □ Cutaneous □ Meningitis □ Myelitis □ Encephalitis □ Vasculitis □ Other (please specify):

Other: □ yes (please specify):
□ no □ unknown
3.2.4. Treatment for this event, including response (please provide treatment drugs, dose, route and dates of treatment)
3.2.5. Were any of the following diagnostic tests performed?
If yes, please specify the dates and results.
□ VZV IgM/IgG □ VZV PCR
□ other (specify)
□ none
Patient history
3.2.6. Does the patient have a history if VZV exposure (infection and/or vaccination)?
History of varicella (please provide date and/or age of the patient) □ yes □ no □ unknown
History of shingles (please provide number of episodes (if recurrent), date and/or age of the patient) □ yes □ no □ unknown
Varicella vaccination (please provide number of doses, date and/or age of the patient at the time of vaccination) □ yes □ no □ unknown

Shingles vaccination (please provide date and/or age of the patient at the time of vaccination)
□ yes □ no □ unknown
3..2.7. Has the patient recently (i.e. within the past 6 months) taken any immunosuppressive therapies? (specify dose and duration of therapy)
□ corticosteroids □ yes □ no □ unknown
□ other immunosuppressive or immunomodulator therapies □ yes □ no □ unknown
□ cytotoxics □ yes □ no □ unknown
□ Other yes □ no □ unknown
□ None □ yes □ no □ unknown

3.3 S1P Modulator Cryptococcal Meningitis

Critical Information - Please provide the following

Approximate onset date of symptoms that led to the diagnosis: _____

Action taken with fingolimod: ☐ Discontinued ☐ Continued ☐ Unknown

Event Outcome: ☐ Complete recovery ☐ Recovered with sequelae ☐ Condition improving ☐ Condition unchanged ☐ Condition deteriorating ☐ Fatal ☐ Unknown

What were the initial presenting symptom(s)?

☐ Subacute Headache	☐ Nausea / vomiting	☐ Others *(please specify)*
☐ Confusion	☐ Seizure(s) _____	
☐ Lethargy	☐ Cranial nerve palsies _____	
☐ Coma	☐ Papilledema	
☐ Fever	☐ Neck stiffness	☐ None of the above

CBC (specifically absolute lymphocyte counts):

Test	**Date**	**Result (please provide units)**

Please indicate Cryptococcus diagnostic testing:

CSF cryptococcus antigen test ☐ Positive (titer) ☐ Negative ☐ Not done

Serum cryptococcus antigen test ☐ Positive (titer) ☐ Negative ☐ Not done

India inkmicroscopy ☐ Positive ☐ Negative ☐ Not done

Fungal culture results: _____

Additional Information that is helpful if available

Anti-Cryptococcal Treatment:

Drug	**Dose**	**Start and stop dates of therapy**

4. Patient History, Concurrent Conditions, and Relevant Therapy:

Does the patient have a history of any of the following prior to the start of fingolimod?

Check all that apply and please include date(s) of onset as well as status (i.e. active/ inactive) and details

☐ HIV Infection ☐ Malignancy (e.g. Leukemia, Lymphoma, Myeloproliferative disease) ☐ Sarcoidosis ☐ Other disturbances of the immune system (e.g. history of low CD4/CD8 ratio) ☐ Close contact with birds ☐ Contact with eucalyptus trees ☐ Other relevant history *(please* specify) ☐ None of the above

_____

How long has the patient had Multiple Sclerosis (years/months or specific date of diagnosis)

_____

List all MS treatments and duration:

Drug	**Dose**	**Start and stop dates of therapy**

List all concomitant or prior immunosuppressive therapies (e.g., monoclonal antibodies, cancer chemotherapy or cytoreductive treatments, corticosteroids, radiation therapy):

Drug/Intervention	**Dose**	**Start and stop dates of therapy**

5. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Important identified risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)

S1P Modulator and Skin Cancer checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

1. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Drug information at the time of event:

Tradename		
Strength		
Batch number		
Expiry date		
Route of administration		
Dose		
Dose frequency		
Start date		
Stop date		
Onset date for event		

3. Event details:

1. Event description:

☐ Diagnosis and date of diagnosis

☐ Signs /symptoms

☐ Anatomical location and clinical description of the skin lesion

☐ Biopsy done ☐ Biopsy not done

If done, provide pathological stage of tumor:

A. Please select one item in each column of the table below to identify the patient's skin type (Fitzpatrick 1975)

Skin Type	Sunburn Tendency	Tan tendency	Skin, hair and eye color
I	☐ Always sunburns	☐ Never tans	☐ White skin, freckles, blond or red hair, blue or green eyes.
II	☐ Usually sunburns	☐ Sometimes tans	☐ White skin, blond hair, blue or green eyes
III	☐ Seldom sunburns	☐ Usually, tans	☐ White skin, usually dark hair, brown eyes
IV-VI	☐ Never sunburns	☐ Always tans darkly	☐ Brown to dark skin/ brown or black hair brown eyes

B. Patient history prior to the start of the drug:

Does the patient have a history of skin cancer?

☐ Squamous cell carcinoma ☐ Basal cell carcinoma ☐Melanoma ☐other (specify)

☐ None

- If yes, provide:
  - Source of diagnosis (biopsy/ clinical only)
  - Date of diagnosis
  - Location of the lesion and treatment

Does the patient have a history of skin cancer?

☐ Squamous cell carcinoma ☐ Basal cell carcinoma ☐Melanoma ☐other (specify)

☐ None

Does the patient have skin moles or pre-cancerous lesions like actinic keratosis? ☐ Yes ☐ No

- If moles, provide:
  - Number of moles
  - Location of moles

Does the patient have any risk factors for decreased immune system?

☐ Yes ☐ No

Has the patient previously been treated with immunosuppresors/ immunomodulators?

☐ Yes ☐ No

- If yes, please provide the following information:
  - Reason (MS or other than MS -specify)
  - Drug generic name
  - Treatment duration
  - Dose

Has the patient previously been treated with Chemotherapy/radiation

☐ Yes ☐ No

- If yes, please specify:

Does the patient have any immune system disorders like HIV/AIDS or any other autoimmune condition?

☐ Yes ☐ No

- If yes, please specify:

Is the patient a smoker?

☐ Yes ☐ No

- If yes, provide:
  - Smoking duration in years
  - Number cigarettes a day

Does the patient have a history of prolonged sun/ultraviolet ray exposure?
☐ Yes ☐ No

Does patient use sunscreen regularly?
☐ Yes ☐ No

Does the patient have a history of exposure to carcinogens (e.g. arsenic, industrial tar, coal, paraffin)
☐ Yes ☐ No

5. Outcome of event:

☐ Recovered/resolved ☐ Not recovered/resolved

☐ Resolved with sequelae ☐ Fatal

☐ Unknown ☐ Other

If 'Other', please specify:

_____

_____

_____

6. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Please be aware that information provided to Mylan relating to you, may be used to comply with applicable laws and regulations. Mylan processes your personal or sensitive data in accordance with applicable data protection laws and the Mylan Privacy Statement, available to you either on www.mylan.com/en/privacy-statement or upon request.

Additional Information:

_____

_____

_____

IIR: Lymphoma; IPR: Other malignant neoplasms.

Malignancy & Neoplasm checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

1. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Drug information at the time of event:

Tradename		
Strength		
Batch number		
Expiry date		

Route of administration		
Dose		
Dose frequency		
Start date		
Stop date		
Onset date for event		

3. Description of the event (malignancy / neoplasm):

- Diagnosis/date of diagnosis:
- Symptoms:
- Location:
  - Is the cancer localized? If not, please provide details on further locations:
- Location of biopsy site(s) and result (**for lymphomas, please provide lymph node biopsy or an English summary as well as gene rearrangement studies if performed**):
- Histological typing of cancer including immunophenotyping and molecular profile (please provide a copy of report or an English summary):
- Staging of the neoplasm:
- ECOG Status of patient/Current treatment plan:

3.a. Were any of the following diagnostic tests performed? Check all that apply and specify which test(s), dates and results

☐ Biopsies
☐ Bone marrow aspiration
☐ Blood test, urine test, biomarkers
☐ Imaging tests (e.g. x-ray, CT scan, MRI scan, PET scan, mammogram, PSA screening)
☐ Exploratory surgery (planned or completed)
☐ EBV serology test
☐ Other viral serology tests (e.g. HIV, HCV)
☐ None of the above

3.b. Relevant medical history (concurrent and pre-existing conditions)
(Please specify medical condition and date of onset)

Check all that apply and provide details as applicable:

☐ Infection
☐ UV exposure, PUV A/UVB
☐ Smoking

- ☐ Alcohol abuse
- ☐ Personal history of malignancy
- ☐ Family history of malignancy
- ☐ Immunosuppression condition (e.g. HIV, transplantation)
- ☐ Immunosuppression therapy
- ☐ Autoimmune disease (e.g. psoriasis, Sjogren Syndrome, rheumatoid arthritis)
- ☐ Exposure to carcinogens (environmental, occupational)
- ☐ None of the above

4. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Sign

Name:

Date:

Occupation:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request

IIR: Lymphoma; IPR: Other malignant neoplasms

Cervical dysplasia/cervical cancer checklist

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

1. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Drug information at the time of event:

Tradename		
Strength		
Batch number		
Expiry date		
Route of admin-istration		
Dose		
Dose frequency		
Start date		
Stop date		
Onset date for event		

3. Event description:

Current diagnosis _____ Date: __/ __ / _

PAP results (date)

_____

☐ Not done ☐ Unknown

Biopsy results (date)_____ ☐ Not done ☐ Unknown

Current HPV results, genotype_____ Test date __/ __ / _

4. Patient history

1. How often has the subject had PAP tests? _____
   Date of last PAP test (before current one): ___/___/___

   a. Was it normal? ☐ Yes ☐ No ☐ Unknown
   b. If not normal: What were PAP results? _____ ☐ Not done ☐ Unknown
   What were biopsy results? _____ ☐ Not done ☐ Unknown

2. When was the last normal PAP test (date)? _____ ☐ Not done ☐ Unknown
3. Has the patient ever been tested for HPV(Human papilloma virus) ☐ Yes ☐ No ☐ Unknown
   a. HPV test results and genotype _____ ☐ Unknown

4. Has the patient been vaccinated for HPV? ☐ Yes: Date: ___/___/___ ☐ No ☐ Don't know

5. Smoking status: ☐ Current smoker How long_____ ☐ Never smoked
   ☐ Smoked in past: How long _____ Quit date: ___/___/___

6. Has the patient ever used contraceptive pills? ☐ Yes: How long: __ ☐ No ☐ Don't know

7. How many pregnancies has the patient had? _____ How many live births: _____
   How many miscarriages: _____
   How many elective abortions: _____
8. Age of patient at first pregnancy? _____

9. Is there a family history of cervical cancer? ☐ Yes: Relationship: _____ ☐ No ☐ Don't know

10. Has the patient had a sexually transmitted disease? (Gonorrhea, Chlamydia, Trichomoniasis, Herpes, other): ☐ Yes: Specify: _____ Date: ___/___/___ ☐ No ☐ Don't Know

11. Does the patient have (or have history of) the following?

    ☐ HIV Date: ___/___/___ ☐ Cancer Type: _____ ☐ Autoimmune disease Type: _____

12. Has the patient taken immunosuppressant medications?

    ☐ Yes: Specify: _____ Date: ___/___/___ ☐ No ☐ Don't Know

13. How many sexual partners in patient's lifetime? _____

14. Age when patient became sexually active? _____

5. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign:

Occupation: Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Prior to launch of Fingolimod Mylan/Mulfinya in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).
The MAH shall ensure that in each Member State (MS) where Fingolimod Mylan/Mulfinya is marketed, all physicians who intend to prescribe Fingolimod Mylan/Mulfinya are provided with the following educational materials:

1. Summary of Product Characteristics (SmPC)
2. Physician's checklist for adult and pediatric patients, to consider prior to prescribing Fingolimod Mylan/Mulfinya
3. The Patient / Parent / Caregiver's guide, to be provided to all patients, their parents (or legal representatives), and caregivers.
4. The pregnancy-specific patient reminder card, to be provided to all patients, their parents (or legal representatives), and caregivers, as applicable.

Physician's checklist
The physician's checklist shall contain the following key messages:

Safety topics	HCP Key safety messages
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	Do not initiate Fingolimod Mylan/Mulfinya in patients with a cardiac condition or who are taking medicinal products for which Fingolimod Mylan/Mulfinya is contraindicated. Prior to initiating Fingolimod Mylan/Mulfinya in patients with underlying medical conditions or who are concomitantly taking medicinal products which carry an increased risk of serious rhythm disturbance or bradycardia, ensure the anticipated benefits outweigh the potential risks and seek advice from a cardiologist regarding appropriate monitoring (at least overnight extended monitoring for treatment initiation) and/or adjustment of the concomitant medicinal product. Monitor all patients for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of Fingolimod Mylan/Mulfinya, including performing an electrocardiogram (ECG) and blood pressure measurement prior to and 6 hours after first dose. If post-dose signs and symptoms of bradyarrhythmia occur, extend first dose monitoring per guidelines until resolution; be familiar with criteria (i.e. need for pharmacological intervention, age-specific heart rate limits, new ECG findings) that would warrant overnight monitoring. Follow first-dose monitoring recommendations after treatment interruption or increase in daily dose.

Safety topics	HCP Key safety messages
Liver transaminase elevation	Do not initiate Fingolimod Mylan/Mulfinya in patients with severe liver impairment (Child-Pugh class C) Transaminase and bilirubin levels should be obtained prior to initiation of Fingolimod Mylan/Mulfinya, monitored every 3 months for the first year on therapy, and periodically thereafter, up to 2 months after Fingolimod Mylan/Mulfinya discontinuation. For asymptomatic elevations in liver function tests (LFTs), perform LFTs more frequently if increases in transaminase are greater than 3 times to less than 5 times upper limit of normal (ULN) without increase in serum bilirubin. Discontinue Fingolimod Mylan/Mulfinya for transaminase increase at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin. Restart Fingolimod Mylan/Mulfinya only after careful consideration of benefit-risk. For patients with clinical symptoms of liver dysfunction, evaluate promptly and discontinue Fingolimod Mylan/Mulfinya if significant liver injury is confirmed. If serum levels return to normal (including if an alternative cause of the liver dysfunction is discovered), Fingolimod Mylan/Mulfinya may be restarted based on a careful benefit-risk assessment of the patient.
Macular oedema	Obtain an ophthalmological assessment before starting Fingolimod Mylan/Mulfinya in patients with diabetes or a history of uveitis. Obtain an ophthalmological assessment in all patients 3 to 4 months after initiating Fingolimod Mylan/Mulfinya. It is recommended to discontinue Fingolimod Mylan/Mulfinya in patients who develop macular edema. Restart Fingolimod Mylan/Mulfinya only after careful consideration of benefit-risk.
Opportunistic infections including varicella zoster virus (VZV), herpes viral infections other than VZV, fungal infections	Do not initiate Fingolimod Mylan/Mulfinya in patients with immunodeficiency syndrome, increased risk for opportunistic infections including immunocompromised patients or severe active or active chronic infections (i.e. hepatitis or tuberculosis). Fingolimod Mylan/Mulfinya may be initiated in patients who have had severe active infection that has resolved. Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects. Carefully consider any decision regarding prolonged concomitant corticosteroid use.

Safety topics	HCP Key safety messages
	Monitor peripheral blood lymphocyte counts prior to and during treatment with Fingolimod Mylan/Mulfinya. Interrupt treatment for lymphocyte count <0.2x109/l until recovery. Instruct patients to report signs and symptoms of infections during, and for up to two months after, treatment with Fingolimod Mylan/Mulfinya. For potentially serious infections, evaluate the patient promptly and consider an infectious disease referral. Consider suspending Fingolimod Mylan/Mulfinya and the benefit-risk of any subsequent reinitiation. Be aware that serious, life-threatening and sometimes fatal cases of opportunistic infections of the central nervous system (CNS) have occurred on Fingolimod Mylan/Mulfinya treatment, including herpes viral infection (encephalitis, meningitis and meningo-encephalitis; observed at any time) and cryptococcal meningitis, (observed after approximately 2-3 years). Fingolimod Mylan/Mulfinya should be discontinued in patients with CNS herpes infections. Fingolimod Mylan/Mulfinya should be suspended in patients with cryptococcal meningitis with careful consideration with a specialist before reinitiating. Inform patients that during Fingolimod Mylan/Mulfinya treatment, they should not receive live attenuated vaccines and that other vaccines may be less effective. Prior to initiation of Fingolimod Mylan/Mulfinya, check varicella status and recommend a full course of vaccination for VZV in antibody negative patients. Postpone initiation of treatment for 1 month to allow the full effect of vaccination. Recommend vaccination against human papilloma virus (HPV) prior to initiation of treatment.
Progressive multifocal leukoencephalopathy (PML)	Do not treat with Fingolimod Mylan/Mulfinya in patients with suspected or confirmed PML. Be aware that PML has been predominantly observed after 2 or more years of fingolimod treatment. Ensure patients have a baseline magnetic resonance imaging (MRI) usually within 3 months before initiating Fingolimod Mylan/Mulfinya. Annual MRIs may be considered especially in patients with multiple risk factors generally associated with PML.

Safety topics	HCP Key safety messages
	If there is suspicion of PML, perform a diagnostic MRI immediately and suspend Fingolimod Mylan/Mulfinya until PML has been excluded. If PML is confirmed, treatment with Fingolimod Mylan/Mulfinya must be permanently discontinued. Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptor modulators, including fingolimod, who developed PML and subsequently discontinued treatment. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.
Reproductive toxicity	Fingolimod Mylan/Mulfinya is teratogenic and contraindicated in women of childbearing potential not using effective contraception or who are pregnant. Women of childbearing potential must use effective contraception during treatment and for two months following treatment discontinuation. Before initiating treatment and regularly thereafter, counsel women of childbearing potential, including adolescent females, their parents or legal representatives, about the risks to a foetus and to use effective contraception during treatment and for two months after discontinuation. Confirm a negative pregnancy test prior to starting treatment and repeat at suitable intervals. Discontinue Fingolimod Mylan/Mulfinya if a woman becomes pregnant and consider the possible return of disease activity. Instruct patient to stop Fingolimod Mylan/Mulfinya two months before attempting to become pregnant.
Skin cancer (basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell carcinoma, squamous cell carcinoma)	Perform skin examination prior to treatment initiation and every 6 to 12 months. Refer patients to a dermatologist if suspicious lesions are detected. Caution against exposure to sunlight without protection. Instruct patient to avoid concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Safety topics	HCP Key safety messages
Use in paediatric patients, including impact on growth and development	All warnings and precautions and monitoring in adults also apply to paediatric patients. Assess Tanner staging, height, and weight according to standard of care. Ensure that vaccination status is up to date before initiation of Fingolimod Mylan/Mulfinya. Monitor for signs and symptoms of depression and anxiety.

Patient / Parent / Caregiver guide

Safety topics	Key safety messages
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	• Inform your doctor if you have underlying cardiac conditions or are taking medicines known to decrease your heart rate. • Your doctor will perform an ECG and blood pressure measurement before the first dose of Fingolimod Mylan/Mulfinya. • Your doctor will monitor your heart rate after the first dose. Prolonged and overnight monitoring may be required. Follow-up monitoring may be required at treatment re-initiation. • Immediately inform your doctor of symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations), that develop after the first dose of Fingolimod Mylan/Mulfinya. • Call your doctor in case of missed doses as the first dose monitoring may need to be repeated
Liver transaminase elevation	• Inform your doctor if you have liver problems. • Your doctor will perform liver function tests before starting treatment, at specified intervals during treatment and for up to 2 months after discontinuation. • Inform your doctor if you notice any of the signs of liver injury (such as yellowing of your skin or the whites of your eyes, abnormally dark urine, pain on the right side of the stomach area, unexplained nausea and vomiting).
Macular oedema	• Your doctor may arrange an eye assessment before starting Fingolimod Mylan/Mulfinya and as required during treatment. A follow-up eye assessment may be done 3-4 months after starting Fingolimod Mylan/Mulfinya. • Immediately inform your doctor of any symptoms of visual changes during treatment and for up to two months after the end of treatment with Fingolimod Mylan/Mulfinya.

Safety topics	Key safety messages
Opportunistic infections including varicella zoster virus (VZV), herpes viral infections other than VZV, fungal infections	• Your doctor will monitor blood lymphocyte counts prior to and during treatment with Fingolimod Mylan/Mulfinya. Treatment with Fingolimod Mylan/Mulfinya may be interrupted if blood lymphocyte count is too low. • Immediately inform your doctor of signs and symptoms of infection, during and up to two months after Fingolimod Mylan/Mulfinya treatment (such as fever, flu-like symptoms, headache accompanied by stiff neck, sensitivity to light, nausea, shingles and/or confusion or seizures [may be symptoms of meningitis and/or encephalitis]).
Progressive multifocal leukoencephalopathy (PML)	• PML is a rare brain disorder caused by an infection that may lead to severe disability or death. • Your doctor will arrange magnetic resonance imaging (MRI) scans before you start treatment and during treatment to monitor the risk of PML. • Immediately inform your physician if you believe your MS is getting worse or if you notice any new symptoms during and after treatment with Fingolimod Mylan/Mulfinya, for example changes in mood or behaviour, new or worsening weakness on one side of the body, changes in vision, confusion, memory lapses or speech and communication difficulties. These may be symptoms of PML or of an inflammatory reaction (known as immune reconstitution inflammatory syndrome or IRIS) that can occur in patients with PML as Fingolimod Mylan/Mulfinya is removed from their body after they stop taking it. • Speak with your partner or caregivers and inform them about your treatment. Symptoms might arise that you might not become aware of by yourself.
Skin cancer (basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell carcinoma, squamous cell carcinoma)	• Immediately inform your doctor if any skin nodules (e.g. shiny, pearly nodules), patches or open sores that do not heal within weeks are noted. Skin cancers have been reported in multiple sclerosis patients treated with Fingolimod Mylan/Mulfinya. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g. unusual moles) with a change in colour, shape or size over time.
Reproductive toxicity	• Fingolimod Mylan/Mulfinya must not be used in women who could become pregnant and are not using effective contraception or who are pregnant. • If you are a woman of childbearing potential, you must use effective contraception during treatment and for two months following treatment discontinuation. • Immediately report to your doctor any (intended or unintended) pregnancy during treatment and up to two months following discontinuation of Fingolimod Mylan/Mulfinya treatment.

Safety topics	Key safety messages
Specifically for paediatric patients	All warnings and precautions and monitoring in adults also apply to paediatric patients. In addition: • Your doctor will assess height, weight, and puberty status according to standard of care. • Your doctor will ensure that your vaccination status is up to date before you start treatment with Fingolimod Mylan/Mulfinya. • Monitor for signs and symptoms of depression and anxiety.

Pregnancy-specific patient reminder card

- IF USED DURING PREGNANCY, Fingolimod Mylan/Mulfinya CAN HARM YOUR UNBORN BABY. Fingolimod Mylan/Mulfinya is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. It is important that you use effective contraception while taking Fingolimod Mylan/Mulfinya and for 2 months after you stop taking it to avoid becoming pregnant. Your doctor will provide counselling regarding effective contraception.
- Your doctor will provide counselling before treatment initiation and regularly thereafter regarding the risk of Fingolimod Mylan/Mulfinya harming an unborn baby and required actions to minimise this risk.
- A pregnancy test must be carried out and negative results verified by your doctor before starting treatment. A pregnancy test must be repeated at suitable intervals.
- Women must NOT become pregnant while on treatment. If you become pregnant or want to become pregnant, Fingolimod Mylan/Mulfinya must be discontinued.
- Inform your doctor immediately if you think you are pregnant. Your doctor will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy.
- Immediately inform your doctor if there is worsening of multiple sclerosis after stopping treatment with Fingolimod Mylan/Mulfinya.