EU Risk Management Plan
for
Fingolimod Accord 0.5 mg hard capsules
(Fingolimod)

RMP version to be assessed as part of this application:

RMP Version number	4.0
Data lock point for this RMP	09-Oct-2025
Date of final sign off	25-Dec-2025

Rationale for submitting an updated RMP: This RMP has been updated in line with EPAR - Risk-management-plan of Gilenya® (Fingolimod) Version 21.1; dated 23-Jul-2025, published by EMA on 23-Sep-2025.

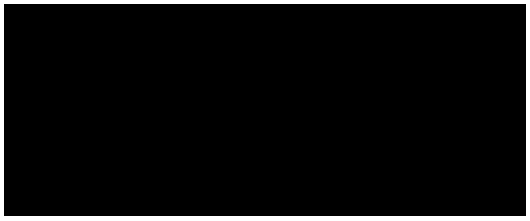
Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part III, Part V (V1and V3) and Part VII (Annex 4, Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number	Approved with procedure:	Date of approval (opinion date):
3.0	EMEA/H/C/005191	21-May-2025

QPPV name: Arletta Werynska

QPPV signature: 

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Fingolimod hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group:** Antineoplastic and Immunomodulating Agents, Immunosuppressants, Sphingosine-1-phosphate (S1P) receptor modulators **ATC code:** L04AE01
Marketing Authorisation Holder	Accord Healthcare S.L.U., Spain
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Fingolimod Accord 0.5 mg hard capsules
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/005191)
Brief description of the product	**Chemical class:** Fingolimod is a sphingosine-derivative, and Sphingosine 1-phosphate receptor modulator.
	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. Animal studies have shown that this redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 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: Each capsule contains fingolimod hydrochloride equivalent to 0.5 mg fingolimod.
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC and PL
Indication(s) in the EEA	***Current*** Fingolimod Accord 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*** **Posology** In adults, the recommended dose of Fingolimod Accord 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. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for: - 1 day or more during the first 2 weeks of treatment. - more than 7 days during weeks 3 and 4 of treatment - more than 2 weeks after one month of treatment If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned. **Method of administration:** This medicinal product is for oral use. Fingolimod Accord can be taken with or without food. The capsules should always be swallowed intact, without opening them.
Pharmaceutical form(s) and strengths	***Current*** **Pharmaceutical form(s):** Hard capsule **Strength**: 0.5 mg

Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Module SI – Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII – Non-clinical part of the safety specification

Not applicable

Module SIII – Clinical trial exposure

Not applicable

Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII – Identified and potential risks

The safety concerns of this RMP have been updated based on EPAR - Risk-management-plan of Gilenya® (Fingolimod) (EMEA/H/C/002202) Version 21.1; dated 23-Jul-2025, published by EMA on 23-Sep-2025. There is no change proposed by the MAH in these safety concerns mentioned in Module SVIII.

Hence, this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

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

Not applicable

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

SVII.3.2 Presentation of the missing information

Not applicable

Module SVIII – Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Liver transaminase elevation • Macular oedema • 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)

PML – Progressive Multifocal Leukoencephalopathy

VZV – Varicella zoster virus

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for risks:

The MAH has proposed specific adverse drug reaction follow-up checklists for the following risks and they are appended in Annex 4 of this RMP.

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 oedema
    - S1P modulator 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 checklist
- Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
    - Multiple sclerosis product and skin cancer checklist

Important identified risk and important potential risk:

- Lymphoma and Other malignant neoplasms
    - Malignancy and Neoplasm checklist
    - Cervical dysplasia/cervical cancer checklist

Purpose: For collection and reporting of safety information while use of fingolimod.

[redacted]

Other forms of routine pharmacovigilance activities:

None

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Table 3: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
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:* • Contraindications for patients with specific cardiac conditions are included in section 4.3. • Recommendation for 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. The same precautions as for the first dose are recommended when patients are switched from the 0.25 mg to the 0.5 mg daily dose, is included in SmPC section 4.4. • Recommendations regarding post-dose bradyarrhythmia-related symptoms and extended monitoring are included in SmPC Section 4.4 and PL section 2 *Other routine risk minimisation measures beyond the Product Information:*

Safety concern	Routine risk minimisation activities
	• 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:* • As per SmPC Section 4.3, fingolimod is contraindicated in severe liver impairment (Child-Pugh class C). • Instructions to monitor liver functional test including serum bilirubin and alkaline phosphatase (ALP) measurement, if liver transaminases are greater than 3 but less than 5 times the ULN without increase in serum bilirubin, are included in SmPC section 4.4. • Recommendation to discontinue Fingolimod treatment, if liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, are included in SmPC section 4.4. • Recommendations to not take fingolimod if patient have severe liver problems and to monitor liver function before, during and after the treatment , is included in PL section 2. *Other routine risk minimisation measures beyond the Product Information:* • Legal status: Restricted medical prescription
Macular edema	*Routine risk communication:* • SmPC sections 4.4 and 4.8 • PL sections 2 and 4

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Risk factor for macular oedema in patient with history of uveitis and diabetes mellitus, are included in SmPC section 4.4. • Recommendation to discontinue Fingolimod treatment, if a patient develops macular oedema is included in SmPC section 4.4. • Recommendation for an ophthalmological evaluation at 3-4 months after treatment initiation and if patients report visual disturbances at any time while on therapy, are included in SmPC Section 4.4 and PL section 2. *Other routine risk minimisation measures beyond the Product Information:* • 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:* • Recommendation regarding contraindication for patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), is included in SmPC Section 4.3. • Instructions for physicians to carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is

Safety concern	Routine risk minimisation activities
	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, are included in SmPC section 4.4. • Recommendation to check immunity against the varicella zoster virus (VZV), need of vaccination, initiation of treatment is given in SmPC Section 4.4 PL Section 2. • Recommendation on prompt diagnostic evaluation for patients with symptoms and signs consistent with cryptococcal meningitis and discontinuation of treatment if cryptococcal meningitis is diagnosed, is given in SmPC Section 4.4. • Recommendation on availability of a baseline MRI before starting treatment, physician to be vigilant for clinical symptoms or MRI findings suggestive of PML during the treatment and treatment discontinuation If PML is suspected, is given in SmPC Section 4.4. • Recommendation on vaccination against human papilloma virus (HPV) before starting treatment and cancer screening, including Pap test is given in SmPC Section 4.4 and PL Section 2. • In addition, recommendations are provided regarding opportunistic infections including instructing patients to report symptoms of infection to their physician in PL section 2 *Other routine risk minimisation measures beyond the Product Information:* • Legal status: restricted medical prescription

Safety concern	Routine risk minimisation activities
Reproductive toxicity	*Routine risk communication:* • SmPC sections: 4.3, 4.4 and 4.6 • PL section: 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • As per recommendation in SmPC Section 4.3, fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. • The SmPC section 4.4, states that before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation. • Fingolimod should not be used during breastfeeding, Is included in PL section 2. *Other routine risk minimisation measures beyond the Product Information:* • 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: 4.4 and 4.8 • PL sections: 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • In SmPC section 4.4, instructions provided for 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

Safety concern	Routine risk minimisation activities
	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. • Cautions for exposure to sunlight without protection and advise for patients to not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy considering potential risk of malignant skin growths, are included in SmPC section 4.4. • Recommendation to refer a patient to a dermatologist in case suspicious lesions are detected, is included in PL section 2. *Other routine risk minimisation measures beyond the Product Information:* • Legal status: Restricted medical prescription
Lymphoma	*Routine risk communication:* • SmPC section 4.4, 4.8 and 5.3 • PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • As per SmPC section 4.4, fingolimod should be discontinued if lymphoma is suspected. *Other routine risk minimisation measures beyond the Product Information:* • Legal status: restricted medical prescription
Important Potential Risks	
Other malignant neoplasms	*Routine risk communication:* • SmPC sections 4.4 and 4.8

Safety concern	Routine risk minimisation activities
	• PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • 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. • PL section 2 includes, 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:* • Legal status: restricted medical prescription
Missing Information	
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	*Routine risk communication:* • SmPC sections 4.4 and 5.2 • PL section 3 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • None *Other routine risk minimisation measures beyond the Product Information:* • Legal status: restricted medical prescription

V.2 Additional Risk Minimisation Measures

In-line with the reference medicinal product, the following additional risk minimisation measures (aRMMs) are proposed:

- Physician's checklist
- Patient/ Parent / Caregiver guide
- Pregnancy-specific patient reminder card

Proposed additional risk minimisation measures / key elements are listed below and are summarised in Annex 6

Objective

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

- Bradyarrhythmia upon treatment initiation
- Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection
- Reproductive toxicity & prevention of pregnancy
- Macular oedema
- 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 Accord, or in whom therapy with Fingolimod Accord is proposed as well as for educating patients about the risks while using Fingolimod Accord. Local Marketing Authorisation Holders (MAHs) will distribute the educational materials to physicians involved in treatment with Fingolimod Accord.

Rationale for the additional risk minimisation activity

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

- Product information

[redacted]

- The Physician's checklist for adult and pediatric patients prior to prescribing Fingolimod Accord.
- The Patient / Parent / Caregiver guide to be provided to all patients, their parents (or legal representatives), 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 Accord, or in whom therapy with Fingolimod Accord is proposed. The specific risk regarding Reproductive toxicity will be communicated to women of child-bearing potential using the 'pregnancy-specific patient reminder card'.
- Distribution path: Local MAHs will distribute the educational materials to physicians involved in treatment with Fingolimod.

Evaluation of the effectiveness of proposed educational program:

Distribution of the Physician's checklist, Patient / Parent / Caregiver guide and the pregnancy-specific patient reminder card will be monitored as a process indicator for effectiveness. Periodic review of pregnancy specific data will continue to be presented in PSURs.

Pregnancy Prevention:

The following set of interventions aims at minimising 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 minimise 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 Accord

- 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 Accord.
- 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 Accord must be discontinued
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with Fingolimod Accord.

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.

<u>Removal of additional risk minimisation activities</u>

[redacted]

The key messages concerning “Convulsions” were deleted from Physician’s checklist and Patient/ Parent / Caregiver guide, in line with the reference product Gilenya.

V.3 Summary of risk minimisation measures

Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
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 • Contraindications for patients with specific cardiac conditions are included in section 4.3 • Recommendation for 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. The same precautions as for the first dose are recommended when	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up checklist has been proposed for this safety concern. Additional pharmacovigilance activity: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	patients are switched from the 0.25 mg to the 0.5 mg daily dose, is included in SmPC section 4.4. • Recommendations regarding post-dose bradyarrhythmia-related symptoms and extended monitoring are included in SmPC Section 4.4 and PL section 2 • Restricted medical prescription <u>Additional risk minimisation measures</u>: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	
Liver transaminase elevation	<u>Routine risk minimisation measures:</u> • SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 • PL sections 2 and 4 • As per SmPC Section 4.3, fingolimod is contraindicated in severe	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection</u>: • Specific adverse reaction follow-up checklist has been proposed for this safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	liver impairment (Child-Pugh class C). • Instructions to monitor liver functional test including serum bilirubin and alkaline phosphatase (ALP) measurement, if liver transaminases are greater than 3 but less than 5 times the ULN without increase in serum bilirubin, are included in SmPC section 4.4. • Recommendation to discontinue Fingolimod treatment, if liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, are included in SmPC section 4.4 • Recommendations to not take fingolimod if patient have severe liver problems and to monitor liver function before, during and after the treatment, is included in PL section 2 • Restricted medical prescription	Additional pharmacovigilance activity: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	
Macular oedema	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 • Risk factor for macular oedema in patient with history of uveitis and diabetes mellitus, are included in SmPC section 4.4 • Recommendation to discontinue Fingolimod treatment, if a patient develops macular oedema is included in SmPC section 4.4 • Recommendation for an ophthalmological evaluation at 3-4 months after treatment initiation and if patients report visual disturbances at	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up checklist has been proposed for this safety concern. Additional pharmacovigilance activity: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	any time while on therapy, are included in SmPC Section 4.4 and PL section 2 • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	
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 • Recommendation regarding contraindication for patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up checklist has been proposed for PML, CM and VZV Additional pharmacovigilance activity: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	prior therapies), is included in SmPC Section 4.3. • Instructions for 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, are included in SmPC section 4.4 • Recommendation to check immunity against the varicella zoster virus (VZV), need of vaccination, initiation of treatment is	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	given in SmPC Section 4.4 PL Section 2. • Recommendation on prompt diagnostic evaluation for patients with symptoms and signs consistent with cryptococcal meningitis and discontinuation of treatment if cryptococcal meningitis is diagnosed, is given in SmPC Section 4.4. • Recommendation on availability of a baseline MRI before starting treatment, physician to be vigilant for clinical symptoms or MRI findings suggestive of PML during the treatment and treatment discontinuation If PML is suspected, is given in SmPC Section 4.4. • Recommendation on vaccination against human papilloma virus (HPV) before starting treatment and cancer screening, including Pap test is given in SmPC Section 4.4 and PL Section 2.	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• In addition, recommendations are provided regarding opportunistic infections including instructing patients to report symptoms of infection to their physician in PL section 2 • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	
Reproductive toxicity	Routine risk minimisation measures: • SmPC sections 4.3, 4.4 and 4.6 • PL section 2 • As per recommendation in SmPC Section 4.3, fingolimod is contraindicated during pregnancy and in women of childbearing potential not	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activity: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	using effective contraception. • SmPC section 4.4, states that, before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation. • Fingolimod should not be used during breastfeeding is included in PL section 2 • Restricted medical prescription <u>Additional risk minimisation measures</u>: Pregnancy Prevention and Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Pregnancy-specific patient reminder card	
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 • In SmPC section 4.4, instructions provide for 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. • Cautions for exposure to sunlight without protection and advise for patients to not	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up checklist has been proposed for this safety concern. Additional pharmacovigilance activity: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy considering potential risk of malignant skin growths, are included in SmPC section 4.4. • Recommendation to refer a patient to a dermatologist in case suspicious lesions are detected, is included in PL section 2. • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	
Lymphoma	Routine risk minimisation measures: • SmPC sections 4.4, 4.8 and 5.3 • PL sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• As per SmPC section 4.4, fingolimod should be discontinued, if lymphoma is suspected. • Restricted medical prescription <u>Additional risk minimisation measures</u>: • None	checklist has been proposed for this safety concern. <u>Additional pharmacovigilance activity</u>: • None
Important Potential Risks		
Other malignant neoplasms	<u>Routine risk minimisation measures:</u> • SmPC sections 4.4 and 4.8 • PL sections 2 • 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. • PL section 2 includes, if this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection</u>: • Specific adverse reaction follow-up checklist has been proposed for this safety concern. <u>Additional pharmacovigilance activity</u>: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Restricted medical prescription Additional risk minimisation measures: • None	
Missing information		
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Routine risk minimisation measures: • SmPC sections 4.4 and 5.2 • PL section 3 • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activity: • None

Part VI: Summary of the risk management plan

Summary of risk management plan for Fingolimod Accord 0.5 mg hard capsules (Fingolimod hydrochloride)

This is a summary of the risk management plan (RMP) for Fingolimod Accord 0.5 mg hard capsules. The RMP details important risks of Fingolimod Accord 0.5 mg hard capsules, how these risks can be minimised, and how more information will be obtained about Fingolimod Accord 0.5 mg hard capsules' risks and uncertainties (missing information).

Fingolimod Accord 0.5 mg hard capsule's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Fingolimod Accord 0.5 mg hard capsules should be used.

This summary of the RMP for Fingolimod Accord 0.5 mg hard capsules should be read in the context of all this 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 Accord 0.5 mg hard capsules' RMP.

I. The medicine and what it is used for:

Fingolimod Accord 0.5 mg hard capsules 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.

It contains fingolimod hydrochloride as the active substance and it is given by oral route.

Further information about the evaluation of Fingolimod Accord 0.5 mg hard capsule's benefits can be found in Fingolimod Accord 0.5 mg hard capsule's EPAR, including in its plain-language

summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/fingolimod-accord

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

Important risks of Fingolimod Accord 0.5 mg hard capsules, together with measures to minimise such risks and the proposed studies for learning more about Fingolimod Accord 0.5 mg hard capsules' 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 Accord 0.5 mg hard capsules, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Fingolimod Accord 0.5 mg hard capsules is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fingolimod Accord 0.5 mg hard capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely 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 Accord 0.5 mg hard capsules. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Important identified risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Liver transaminase elevation • Macular oedema • 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)

PML – Progressive Multifocal Leukoencephalopathy

VZV – Varicella zoster virus

II.B Summary of important risks

Important Identified Risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3, 4.4, 4.5 and 4.8 • PL sections 2 and 4 • Contraindications for patients with specific cardiac conditions are included in section 4.3. • Recommendation for 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. The same precautions as for the first dose are recommended when patients are switched from the 0.25 mg to the 0.5 mg daily dose, is included in SmPC section 4.4. • Recommendations regarding post-dose bradyarrhythmia-related symptoms and extended monitoring are included in SmPC Section 4.4 and PL section 2. • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide

Important Identified Risk: 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 • As per SmPC Section 4.3, fingolimod is contraindicated in severe liver impairment (Child-Pugh class C). • Instructions to monitor liver functional test including serum bilirubin and alkaline phosphatase (ALP) measurement, if liver transaminases are greater than 3 but less than 5 times the ULN without increase in serum bilirubin, are included in SmPC section 4.4. • Recommendation to discontinue Fingolimod treatment, if liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, are included in SmPC section 4.4. • Recommendations to not take fingolimod if patient have severe liver problems and to monitor liver function before, during and after the treatment in patient with severe liver problems, is included in PL section 2. • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide

Important Identified Risk: Macular oedema	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4

	• Risk factor for macular oedema in patient with history of uveitis and diabetes mellitus, are included in SmPC section 4.4 • Recommendation to discontinue Fingolimod treatment, if a patient develops macular oedema is included in SmPC section 4.4 • Recommendation for an ophthalmological evaluation at 3-4 months after treatment initiation and if patients report visual disturbances at any time while on therapy, are included in SmPC Section 4.4 and PL section 2 • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide

Important Identified Risk: Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection)	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Recommendation regarding contraindication for patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), is included in SmPC Section 4.3. • Instructions for 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, are included in SmPC section 4.4 • Recommendation to check immunity against the varicella zoster virus (VZV), need of vaccination, initiation of treatment is given in SmPC Section 4.4 PL Section 2. • Recommendation on prompt diagnostic evaluation for patients with symptoms and signs consistent with cryptococcal meningitis and discontinuation of treatment if cryptococcal meningitis is diagnosed, is given in SmPC Section 4.4. • Recommendation on availability of a baseline MRI before starting treatment, physician to be vigilant for clinical symptoms or MRI findings suggestive of PML during the treatment and treatment discontinuation If PML is suspected, is given in SmPC Section 4.4. • Recommendation on vaccination against human papilloma virus (HPV) before starting treatment and cancer screening, including Pap test is given in SmPC Section 4.4 and PL Section 2. • In addition, recommendations are provided regarding opportunistic infections including instructing patients to report symptoms of infection to their physician in PL section 2 • Restricted medical prescription <u>Additional risk minimisation measures</u>: Educational materials for physicians and patients:

	• Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide

Important Identified Risk: Reproductive toxicity	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3, 4.4 and 4.6 • PL section 2 • As per recommendation in SmPC Section 4.3, fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. • SmPC section 4.4, states that, before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation. • Fingolimod should not be used during breastfeeding is included in PL section 2 • Restricted medical prescription Additional risk minimisation measures: Pregnancy Prevention and Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide • Pregnancy-specific patient reminder card

Important Identified Risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 • In SmPC section 4.4, instructions provide for 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. • Cautions for exposure to sunlight without protection and advise for patients to not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy considering potential risk of malignant skin growths, are included in SmPC section 4.4. • Recommendation to refer a patient to a dermatologist in case suspicious lesions are detected, is included in PL section 2. • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide

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 4.4 and 5.2 • PL section 3 • Restricted medical prescription Additional risk minimisation measures: Educational materials for physicians and patients: • 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 Accord 0.5 mg hard capsules.

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

There are no studies required for Fingolimod Accord 0.5 mg hard capsules.

Annex 4 – Specific adverse drug reaction follow-up forms

The MAH has proposed targeted follow up questionnaires for following safety concerns concerning the use of fingolimod and they are appended below.

- 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 oedema
    - S1P modulator 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 checklist
- Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
    - Multiple sclerosis and skin cancer checklist
- Lymphoma and Other malignant neoplasms
    - Malignancy and Neoplasm checklist
    - Cervical dysplasia/cervical cancer checklist

Targeted follow-up checklist: 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.

Event description:

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

Relevant medical history (concurrent and pre-existing conditions)

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

- ☐ ECG abnormalities *(please specify)*
- ☐ Symptomatic bradycardia
- ☐ Pacemaker (specify if temporary or permanent)
- ☐ Cardiovascular disease (e.g. angina, CAD, MI, CHF)
- ☐ Valvular disease *(please specify)*
- ☐ Congenital heart disease
- ☐ Syncope
- ☐ Other (e.g. COPD, sleep apnea, hyperthyroidism) *(please specify)*

☐ Wolff-Parkinson-White syndrome *(please specify)*

☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

☐ Antipsychotics/ Antidepressants

☐ Antiarrhythmics (e.g. quinidine, digoxin, beta-blockers, calcium channel blockers)

☐ Anticonvulsants (e.g. phenytoin, gabapentin, topiramate)

☐ Beta blockers

☐ Drugs of abuse *(e.g. cocaine)*

☐ Theophylline

☐ Cholinomimetics *(e.g. metoclopramide)*

☐ Calcium channel blockers (dihydropyridine or non)

☐ Others *(please specify)*

☐ None of the above

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

- First dose of Fingolimod Accord: 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 Accord 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):*

Targeted follow-up checklist: Liver transaminase elevation

Liver injury checklist

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

Event Description:

1. Diagnosis and date of diagnosis_____
2. 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		

3. 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:

- ☐ 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

4. 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)

5. Has the patient recently (i.e. within the past 6 months) taken any of the following**?**

Check all that apply:

☐ Sulfonamides	☐ 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
☐ Valproic acid	☐ Methotrexate	☐ Other (specify)
☐ None		

Targeted follow-up checklist: Macular oedema

Macular edema checklist

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

Relevant medical history (concurrent and pre-existing 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

Event description:

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 Accord) and at the time of the event
   - ☐ Fundoscopy
   - ☐ Optical Coherence Tomography (OCT)
   - ☐ Fluorescein angiography (FA)
   - ☐ Visual acuity

☐ Other: _____

Course of the event after diagnosis:

5. 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

6. 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)

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

☐ Resolved ☐ Improving ☐ Unchanged ☐ Deteriorated

☐ Visual acuity (specify the dates and results)

Targeted follow-up checklist: 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 signs or symptoms? Check all that apply

☐ Hemiparesis	☐ Cognitive impairment	☐ Weakness
☐ Hemianopia	☐ Personality changes	☐ Fever_____
☐ Brainstem deficits	☐ Dysarthria	☐ Headaches
☐ Clumsiness/ Cerebellar deficits	☐ Aphasia	☐ Others (please specify)
☐ Sensory deficits	☐ Visual impairment	☐ None of the above

Was brain MRI/MRA performed?

☐ Yes *(provide recent and prior reports and/or summarise below)*

☐ No ☐ Unknown

Date/Results:

_____

_____

CSF JCV analysis ☐ **Yes** *(provide results below)* ☐ **No** ☐ **Unknown**

Type of test (PCR, JCV antibody)	Test date	Result

Please include results of other relevant tests

Type of test	Test date	Result
JCV (serum or urine)		
Anti JCV antibody index		
Absolute lymphocyte count		

Type of test	Test date	Result
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	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 assessed 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 (eg, HIV infection; malignancy, e.g., leukemia, lymphoma, myeloproliferative

[redacted]

diseases; sarcoidosis; other disturbances of the immune system, e.g., history of low CD4/CD8 ratio; other)? ☐ Yes *(summarise 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 only of the following medications in the past or currently?
Check all that apply and include dates of starting and completing and indication the medication in the space below

☐ Chemotherapy/ Cytoreductive therapy *(please specify)*_____

☐ Corticosteroids (*specify* dose *and duration)*_____

☐ Other immunosuppressant drugs (*please specify)*_____

☐ Radiation therapy

☐ None of the above

Additional details:

_____

_____

_____

[redacted]

Targeted follow-up checklist: Varicella Zoster Virus (VZV) infections

Event Description

1. Confirm the type of varicella zoster virus infection:

☐ Primary infection (e.g. varicella/chickenpox)

☐ Reactivation (e.g. herpes zoster/shingles) ☐ Unknown/undetermined

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. Infection location:

Skin: ☐ Yes ☐ No ☐ Unknown

If yes, 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 dissemination ☐ CNS dissemination ☐ Visceral dissemination.

If applicable: CNS: ☐ Meningitis ☐ Myelitis ☐ Encephalitis

☐ Vasculitis ☐ Other *(please specify)*

Other: ☐ Yes *(please specify)* ☐ No ☐ Unknown

4. Treatment for this event, including response (please provide treatment drugs, dose, route and dates of treatment)

5. Were any of the following diagnostic tests performed? ►**If yes, please specify the dates and results.**

Serum/blood	**CSF**	**Vesicles/skin lesion**
☐ VZV IgM/IgG	☐ VZV PCR	☐ VZV PCR
☐ VZV PCR	☐ Other (specify)	☐ Other (specify)
☐ Other (specify)	☐ None	☐ None
☐ None		

Patient history

6. Does the patient have a history of 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

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

Targeted follow-up checklist: Cryptococcal Meningitis for Multiple Sclerosis

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

Part I: 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 WBC and absolute lymphocyte and neutrophil 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 ink microscopy ☐ Positive (titer) ☐ Negative ☐ Not done

Fungal culture results: _____

Part II: Additional Information that is helpful if available

Anti-Cryptococcal Treatment:

Drug	Dose	Start and stop dates of therapy

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 (MS) (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

Targeted follow-up checklist: Multiple sclerosis and Skin Cancer

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

1. Event description:

- ☐ Diagnosis and date of diagnosis
- ☐ Signs /symptoms
- ☐ Anatomical Location and clinical description of the skin lesion
- ☐ Biopsy done: If done, provide pathological stage of tumor

_____

- ☐ Biopsy not done

2. 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 family 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

►If pre-cancerous skin lesion, please specify:_____

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

3. 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

Targeted follow-up checklist: Lymphoma and Other malignant neoplasms

Malignancy & Neoplasm checklist

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

Description of the event (malignancy / neoplasm):

- Diagnosis/date of diagnosis
- Symptoms
- Location

  Is the cancer localised? 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 (TNM):
- ECOG status /Current treatment plan:

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

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:

[redacted]

Infection UV exposure, PUVA/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

Cervical dysplasia/cervical cancer checklist

A. Event description:

Current diagnosis_____Date__/___/__

PAP results (date)_____ Not done Unknown

Biopsy results (date) _____ Not done Unknown

Current HPV results, genotype _____ Test Date__/___/__

B. 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

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

[redacted]

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? _____

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 inpatient's lifetime _____

14. Age when patient became sexually active? _____

Annex 6 – Details of proposed additional risk minimisation activities

This annex contains key safety messages of the proposed educational program for Fingolimod Accord, which includes a Physician's checklist for adult and pediatric patients, a Patient / Parent / Caregiver guide, and a Pregnancy-specific patient reminder card.

Approved Key Messages of the Additional Risk Minimisation Measures

Physician's checklist

Safety Topics	HCP Key Safety Messages
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	• Do not initiate Fingolimod Accord in patients with a cardiac condition or who are taking medicinal products for which Fingolimod Accord is contraindicated. • Prior to initiating Fingolimod Accord 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 Accord, 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.
Liver transaminase elevation	• Do not initiate Fingolimod Accord in patients with severe liver impairment (Child-Pugh class C). • Transaminase and bilirubin levels should be obtained prior to initiation of Fingolimod Accord, monitored every 3 months for the first year on therapy, and periodically thereafter, up to 2 months after Fingolimod Accord 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 Accord 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 Accord only after careful consideration of benefit-risk. • For patients with clinical symptoms of liver dysfunction, evaluate promptly and discontinue Fingolimod Accord if significant liver injury is confirmed. If serum levels return to normal (including if an alternative cause of the liver dysfunction is discovered), Fingolimod Accord may be restarted based on a careful benefit-risk assessment of the patient.
Macular oedema	• Obtain an ophthalmological assessment before starting Fingolimod Accord in patients with diabetes or a history of uveitis.

	• Obtain an ophthalmological assessment in all patients 3 to 4 months after initiating Fingolimod Accord. • It is recommended to discontinue Fingolimod Accord in patients who develop macular edema. Restart Fingolimod Accord 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 Accord 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 Accord 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 corticosteroids use. • Monitor peripheral blood lymphocyte counts prior to and during treatment with Fingolimod Accord. Interrupt treatment for lymphocyte count $<0.2x10^9$/L until recovery. • Instruct patients to report signs and symptoms of infections during, and for up to two months after, treatment with Fingolimod Accord. • For potentially serious infection, evaluate the patient promptly and consider an infectious disease referral. Consider suspending Fingolimod Accord 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 Accord treatment, including herpes viral infection (encephalitis, meningitis and

	meningo-encephalitis; observed at any time), and cryptococcal meningitis, (observed after approximately 2-3 years). • Fingolimod Accord should be discontinued in patients with CNS herpes infections. Fingolimod Accord should be suspended in patients with cryptococcal meningitis with careful consideration with a specialist before reinitiating. • Inform patients that during Fingolimod Accord treatment, they should not receive live attenuated vaccines and that other vaccines may be less effective. • Prior to initiation of Fingolimod Accord, check varicella status and recommend a full course of vaccination for VZV in anti-body 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 Accord 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 Accord. Annual MRIs may be considered especially in patients with multiple risk factors generally associated with PML. If there is suspicion of PML, perform a diagnostic MRI immediately and suspend Fingolimod Accord until PML has been excluded. If PML is confirmed, treatment with Fingolimod Accord must be permanently discontinued. • Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors

	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 Accord 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 Accord if a woman becomes pregnant and consider the possible return of disease activity. • Instruct patient to stop Fingolimod Accord 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.
Use in pediatric patients, including impact on growth and development	• All warnings and precautions and monitoring in adults also apply to pediatric patients. • Assess Tanner staging, height, and weight according to standard of care. • Ensure that vaccination status is up to date before initiation of Fingolimod Accord. • Monitor for signs and symptoms of depression and anxiety.

Patient/Parent/Caregivers 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 Accord. • Your doctor will monitor for 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 Accord. • 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 Accord and as required during treatment. A follow-up eye assessment may be done 3-4 months after starting Fingolimod Accord. • 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 Accord.
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 Accord. Treatment with Fingolimod Accord 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 Accord 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 Accord, 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 Accord 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 Accord. 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 Accord 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 Accord treatment.
Specifically for pediatric patients	All warnings and precautions and monitoring in adults also apply to pediatric 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 Accord. • Monitor for signs and symptoms of depression and anxiety.

Pregnancy specific patient reminder card

- IF USED DURING PREGNANCY, FINGOLIMOD ACCORD CAN HARM YOUR UNBORN BABY. Fingolimod Accord 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 Accord 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 Accord 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 Accord 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 Accord.