NOVARTIS

Drug Regulatory Affairs

Gilenya®

Summary of the Risk Management Plan (RMP) v13.1 for Gilenya® (Fingolimod)

Document version:	1
Document status:	Final
Document Date:	14-Feb-2019

Summary of the Risk Management Plan (RMP) for Gilenya® (Fingolimod)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Gilenya® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le médicament“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document, which is valid and relevant for the effective and safe use of Gilenya® in Switzerland, is the „Arzneimittelinformation / Information sur le médicament“(see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Gilenya®

Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Gilenya®, together with measures to minimize such risks and the proposed studies for learning more about Gilenya's® risks, are outlined below.

Measures to minimize 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Gilenya®, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (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 Gilenya® is not yet available, it is listed under 'missing information' below.

List of important risks and missing information

Important risks of Gilenya® are risks that need special risk management activities to further investigate or minimize 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 Gilenya®. 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);

Summary of safety concerns

Table 1 List of important risks and missing information

Important identified risks	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose Hypertension Liver transaminase elevation Posterior Reversible Encephalopathy Syndrome (PRES) Macular edema Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) Leukopenia and lymphopenia Reproductive toxicity Bronchoconstriction Hypersensitivity Basal Cell Carcinoma Convulsions
Important potential risks	Skin cancer other than BCC Acute disseminated encephalomyelitis-like (ADEM-like) events Lymphoma Other malignant neoplasms Thrombo-embolic events

	QT interval prolongation
	Off-label use
	Atypical MS relapse
	Hemophagocytic syndrome
	Interaction with Ketoconazole
	Interaction with Carbamazepine
	Interaction with Beta blockers
	Interaction with Class la or Class Ill antiarrhythmic medicinal products
Missing information	Long-term use in pediatric patients
	Elderly patients
	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 bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher AV block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea
	Long-term risk of cardiovascular morbidity/mortality
	Long-term risk of malignant neoplasms Unexplained death
	Switch from other disease modifying therapy

NOVARTIS

Summary of important risks

Table 2 Important Identified Risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post- first dose

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product
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 (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 la (e.g. quinidine, dysopyramide) or Class Ill (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 minimization measures	Routine risk minimization measures: SmPC section 4.4, 4.5 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver reminder card
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction

Table 3 Important Identified Risk: Hypertension

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Routine risk minimization measures SmPC section 4.4 and 4.8 Additional risk minimization measures: No additional risk minimization measures

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose

Table 4 Important Identified Risk: Liver transaminase elevation

Table	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Routine risk minimization measures: SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: --Physician's checklist for adult and pediatric population - PatienUParenUCaregiver reminder card

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy

Table 5 Important Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES)

Evidence for linking the risk to the medicine	**Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.**
Risk factors and risk groups	None identified for fingolimod
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: No additional risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS

	newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy

Table 6 Important Identified Risk: Macular edema

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product
Risk factors and risk groups	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver reminder card
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily

	or treated with another approved disease-modifying therapy.

Table 7 Important Identified Risk: Important Identified Risk: Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product
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 Gilenya. **Varicella-zoster virus infections** Patients receiving concomitant immunosuppressive therapy may be at increased risk for VZV infections. The patient who died because of disseminated varicella zoster infection reported no history of varicella infection, no previous vaccination against varicella zoster (VZ) virus and was VZ virus-lgG negative. Therefore, patients with negative VZ virus-lgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in case of an MS relapse. **Herpes viral infections other than VZV** Patients receiving concomitant immunosuppressive therapy may be at

increased risk for Herpes viral infections other than VZV.

Progressive Multifocal Leukoencephalopathy (PML)

PML primarily affects individuals with suppressed immune systems. In recent years, the most common underlying immunosuppressive illness has been AIDS. However, a variety of non-AIDS immunosuppressive illnesses has been associated with the occurrence of PML. These include lymphoreticular malignancy, most commonly chronic lymphocytic leukemia or non-Hodgkin lymphoma. JC virus is a double- stranded DNA human polyomavirus acquired in childhood. After infection, it remains latent in the body. 50-70% of the adult population is seropositive. It is believed that all seropositive individuals harbor latent virus in kidney, lymphoreticular tissue, or brain. PML is considered a reactivation infection. Whether the reactivation occurs systemically, with immunosuppression causing dissemination to the brain at that time, or the reactivation occurs from latent virus in the brain remains unclear.

In people who are immunosuppressed, JC virus can reactivate and cause PML which is usually fatal.

Cases of PML have been reported with another MS drug, natalizumab, a monoclonal antibody that blocks lymphocyte migration into the CNS (i.e. an effect on all lymphocyte subsets, including effector memory cells). Additionally, natalizumab has effects, such as mobilization of JC virus-carrying bone marrow precursor cells and splenic marginal zone B cells, which are not seen

	with fingolimod. The natalizumab label describes 3 risk factors that are known to increase the risk of PML in patients under therapy with natalizumab: treatment duration longer than 2 years, prior treatment with an immunosuppressant and presence of anti-JCV antibodies. Patients with all 3 known risk factors have an estimated risk of PML of 11/1,000. When evaluating the potential/theoretical risk with fingolimod, the specific risk factors should be considered: The presence of anti-JCV antibodies Switching to fingolimod after treatment with natalizumab for >2 years and duration of washout of natalizumab Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide).
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3, 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver reminder card
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or

	treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 8 Important Identified Risk: Leukopenia and lymphopenia

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product
Risk factors and risk groups	Reduction in peripheral blood lymphocyte count is an expected pharmacodynamic effect of fingolimod.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: No additional risk minimization measures

Table 9 Important Identified Risk: Reproductive toxicity

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 Gilenya should not breast feed.

Risk minimization measures	Routine risk minimization measures: SmPC section 4.6 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver reminder card
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Enhanced Pharmacovigilance Program: PRIM (Gilenya Pregnancy outcomes Intensive Monitoring) Study FTY720D2404: The Multinational Pregnancy Gilenya Exposure Registry in Multiple Sclerosis to prospectively collect outcome data on the babies born to women treated with fingolimod.

Table 10 Important Identified Risk: Bronchoconstriction

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	No specific risk factors have been identified to predict the occurrence of bronchoconstriction in individual patients. Patients with pre-existing pulmonary conditions such as severe respiratory disease, pulmonary fibrosis, tuberculosis, and asthma requiring daily therapies were excluded from the pivotal MS studies.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4, 4.8 and 5.1 Additional risk

	minimization measures: No additional risk minimization measures.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 11 Important Identified Risk: Hypersensitivity

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Risk factors for developing drug hypersensitivity reactions include a prior history of a drug allergy, female sex, repeated exposure to the same or related drugs, some comorbidities (i.e., HIV/AIDS, EBV), the duration of treatment, and an immunogenetic predisposition in patients with human leukocyte antigen B (HLA-B) alleles.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: No additional risk minimization measures.

Table 12 Important Identified Risk: Basal Cell Carcinoma

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	None identified for fingolimod.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13 Important Identified Risk: Convulsions

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 14 Important Identified Risk: Skin cancer other than BCC

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures	SmPC section 4.4 and 4.8
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or

	treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 15 Important Identified Risk: Acute disseminated encephalomyelitis-like (ADEM-like) events

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: No additional risk minimization measures.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with

	fingolimod once daily or treated with another approved disease-modifying therapy.

Table 16 Important Identified Risk: Lymphoma

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures	Routine risk minimization measures: SmPC section 4.8 and 5.3 Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2399: A single arm, open-label, multicenter study.

	evaluating the long-term safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with MS.

Table 17 Important Identified Risk: Other malignant neoplasms

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2399: A single arm, open-label, multicenter study evaluating the long-term safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with MS.

Table 18 Important Identified Risk: Thrombo-embolic events

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: No additional risk minimization measures.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 19 Important Identified Risk: QT interval prolongation

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.9 Additional risk minimization measures: No additional risk minimization measures.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 20 Important Identified Risk: Off-label use

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

.

Table 21 Important Identified Risk: Atypical MS relapse

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Table 22 Important Identified Risk: Hemophagocytic Syndrome

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
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 minimization measures	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Table 23 Important Identified Risk: Interaction with Ketoconazole

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.5 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 24 Important Identified Risk: Interaction with Carbamazepine

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 25 Important Identified Risk: Beta blockers

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.5 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 26 Important Identified Risk: Interaction with Class la or Class Ill antiarrhythmic medicinal products

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.5 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 27 Important Missing information: Long-term use in pediatric patients

Risk minimization measures	Routine risk minimization measures: SmPC section 4.2 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver reminder card

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2311: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon 13-1a (IFN 13-1a) im once weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.

Table 28 Important Missing information: Elderly patients

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2 and 5.2 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 29 Important Missing information: Lactating women

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.6 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Table 30 Important Missing information: Patients with diabetes mellitus

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2, 4.4, and 4.8 Additional risk minimization measures: No additional risk minimization measure**.**
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

	Study FTY720D2403: Long-term, prospective, parallel-cohort study monitoring safety in patients with MS, either recently initiated on fingolimod or receiving another DMT according to local label and exclude patients previously treated with Natalizumab. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 31 Important Missing information: Patients with cardiovascular conditions*

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or

	treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

*Cardiovascular conditions includes myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher AV block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea.Multiply table for each important risk/ missing information.

Table 32 Important Missing information: Long-term risk of cardiovascular morbidity/mortality

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

	Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose

Table 33 Important Missing information: Long-term risk of malignant neoplasms

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

	Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2399: A single arm, open-label, multicenter study evaluating the long-term safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with MS.

Table 34 Important Missing information: Unexplained death

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities:

	Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 35 Important Missing information: Switch from other disease modifying therapy

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4, 4.5 and 5.1 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

	Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel- cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Post-authorization development plan

Studies which are conditions of the marketing authorization

Table 36 Studies which are conditions of the marketing authorization

Study short name: Study CFTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose	Purpose of the study: This study is a post-authorization follow-up measure to assess the longterm cardiovascular risk of fingolimod in patients who experience a serious cardiovascular event during the first 24-hours of fingolimod treatment initiation in study FTY72002406. The primary objective of this study is to estimate the long-term cardiovascular risk of fingolimod, as defined by the incidence of selected cardiovascular events over the course of the study, in patients who experienced a cardiovascular event during treatment initiation in Study 2406.

Other studies in post-authorization development plan

Table 37 Other studies in the post-authorization development plan

Study short name: CFTY720D2399: A single arm, open-label, multicenter study evaluating the long-term safety and tolerability of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of MS.	**Rationale and study objectives:** The purpose of this study is to collect long-term safety, tolerability, efficacy, and health outcomes data in patients who participated in the fingolimod multiple sclerosis clinical development program. This study is designed to evaluate the long-term safety and tolerability of fingolimod 0.5 mg/day in patients with MS for the duration of the study.
Study short name: CFTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease- modifying therapy	**Rationale and study objectives:** The purpose of this multi- national prospective parallel-cohort study in patients with relapsing forms of MS, either newly treated with fingolimod or receiving another disease-modifying therapy, is to further monitor the overall safety profile of fingolimod under conditions of routine medical practice and to explore the incidence of selected safety- related outcomes . Patients enrolled in this study will have the option to complete PRO questionnaires, as part of an optional PRO sub-study under conditions of routine medical practice. The purpose of collecting these PRO data is to evaluate outcomes that are important to patients which include disability, health-related quality of life, productivity, and treatment satisfaction and preference. The PRO sub-study

	will help describe the effect of treatment on long-term outcomes under conditions of routine medical practice which is important to understand the real-world value of fingolimod treatment. The primary objective of this study is to further explore the overall safety profile of fingolimod over the long term in patients with relapsing MS under conditions of routine medical practice.
Study short name: CFTY720D2404: Prospective, observational study in pregnant MS patients with confirmed or suspected maternal exposure to fingolimod any time during pregnancy or shortly before pregnancy (up to 8 weeks before last menstrual period).	**Rationale and study objectives:** The purpose of the Multi- National Gilenya Pregnancy Exposure Registry in Multiple Sclerosis (MS) is to continuously monitor, evaluate, and assess for major and minor teratogenic effects in the offspring of women exposed to fingolimod before (up to 8 weeks before last menstrual period (LMP)) and during pregnancy in routine clinical practice. The overall aim is to collect and evaluate data on maternal, fetal, and infant outcomes and compare it with reference populations. The primary objective of the registry is to describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy.
Program short name: PRIM: Gilenya Pregnancy outcomes Intensive Monitoring (enhanced pharmacovigilance data collection).	**Rationale and study objectives:** To collect data regarding fingolimod exposure during pregnancy and maternal, fetal and infant outcomes

Study short name: Study CFTY720D2406: Long- term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease- modifying therapy.	**Rationale and study objectives:** Purpose is to monitor the overall safety profile of fingolimod under conditions of routine medical practice and to explore the incidence of selected safety- related outcomes. This is a post approval commitment study to health authorities. The primary objective of the registry is to explore the overall safety profile of fingolimod over the long term in patients with relapsing MS under conditions of routine medical practice.
Study short name: CFTY720D2311: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon 13- 1a (IFN 13-1a) im once weekly in pediatric patients with multiple sclerosis, with a five- year fingolimod Extension Phase.	**Rationale and study objectives:** **Core Phase** The primary objective of the Core Phase of the study was to evaluate the efficacy of fingolimod relative to intramuscular IFN 13-1 a in reducing the frequency of relapses as assessed by the annualized relapse rate (ARR) in children/adolescent MS patients aged 10 to <18 years when treated for up to 24 months. The key secondary objective was to evaluate the efficacy of fingolimod relative to IFN 13-1a in reducing the number of new/newly enlarging T2 (n/neT2) lesions in children/adolescent MS patients aged 10 to <18 years treated for up to 24 months. Extension Phase: To examine long-term safety, tolerability and efficacy parameters in patients treated with Fingolimod.