NOVARTIS

Regulatory Affairs

Gilenya®

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Fingolimod*
Product(s) concerned (brand name(s)):	*Gilenya*
Document status:	*Final*
Version number of the RMP Public Summary:	*19.1*
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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 minimise 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.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Gilenya”.

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Summary of the risk management plan- Gilenya- Fingolimod

This is a summary of the risk management plan (RMP) for Gilenya®. The RMP details important risks of Gilenya®, how these risks can be minimized, and how more information will be obtained about Gilenya®'s risks and uncertainties (missing information).

Gilenya's® summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Gilenya® should be used.

This summary of the RMP for Gilenya® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Gilenya is authorized for a 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 in the EEA (see SmPC for the full indication):

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1).

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.It contains fingolimod (a sphingosine-1-phosphate (S1P) receptor modulator) as the active substance and it is given by 0.25 mg/day or 0.5 mg/day oral hard capsule.

Further information about the evaluation of Gilenya® benefits can be found in Gilenya's® EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. Risks associated with the medicine and activities to 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 analysed, 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.

II.A: 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);

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 Liver transaminase elevation Macular edema Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection Reproductive toxicity Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) Convulsions Lymphoma
Important potential risks	Other malignant neoplasms
Missing information	Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

II B: Summary of important risks

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 disease (including angina pectoris), • cerebrovascular disease, • history of myocardial infarction, • congestive heart failure, • history of cardiac arrest, • uncontrolled hypertension • severe sleep apnea, Other potential risk factors include concomitant administration with: Class Ia (e.g. quinidine, dysopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products. • beta blockers, • heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3, 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 guide
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 3 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	None identified for fingolimod.
Risk minimization measures	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 - Patient/Parent/Caregiver guide
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 4 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	Patients with diabetes and history of uveitis are considered at increased risk of developing macular edema. Such patients should undergo an ophthalmic evaluation prior to initiating Gilenya therapy and have follow-up evaluations while receiving Gilenya therapy.
Risk minimization measures	Routine risk minimization measures: SmPC sections 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 guide
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 5 Important Identified Risk: Opportunistic infections including 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.
Risk minimization measures	Routine risk minimization measures: SmPC sections 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 guide
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Independent review of cases of suspected PML by External Adjudication Committee None.

Table 6 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 Sections 4.3, 4.4 and 4.6. Additional risk minimization measures: Pregnancy prevention Educational materials for physicians and patients: - Physician's Checklist for adult and pediatric population - Patient/Parent/Caregiver guide - Pregnancy-specific patient reminder card Sending a DHPC in the EU to inform health professionals regarding label update and pregnancy prevention
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: 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 7 Important Identified Risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous 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.
Risk minimization measures	Routine risk minimization measures: SmPC sections 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 guide
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 8 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 sections 4.4 (pediatric patients) and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide
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 9 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 sections 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: None

Table 10 Important potential 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	Routine risk minimization measures: SmPC Section 4.4 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 11 Missing information: Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

Risk minimization measures	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. Routine risk minimization measures: SmPC sections 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 guide
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 β-1a (IFN β-1a) im once weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

None

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

Table 13 Other studies in the post-authorization development plan

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.
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 β-1a (IFN β-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 β-1a 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 β-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.