EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/CHMP/386085/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fingolimod Mylan

International non-proprietary name: fingolimod

Procedure No. EMEA/H/C/005661/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADEM-like	Acute disseminated encephalomyelitis-like events
ADR	Adverse drug reaction
AE	Adverse event
Alu	Aluminium
ANOVA	Analysis of variance
AUC	Area under the curve
AV	Atrio-Ventricular
BLQ	Below limit of quantitation
BMI	Body-mass index
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CQA	Critical Quality Attribute
CRFs	Case Report Forms
CRO	Clinical Research Organisation
CV	Coefficient of Variation
DHPC	Direct healthcare professional communication
DILI	Drug induced liver injury
DMF	*N,N*-Dimethylforamide
EDQM	European Directorate for the Quality of Medicines
EMA	European Medical Agency
EURD	European Union Reference Date
FING	Fingolimod
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GCP	Good clinical practice
GPL	Good laboratory practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HSGC	Headspace Gas Chromatography

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
JCV	John Cunningham virus
K_2EDTA	Potassium (K_2) Ethylene Diamine Tetraacetic Acid
KF	Karl Fischer titration
LC-ESI-MSMS	Liquid chromatography/electrospray ionisation tandem mass spectroscopy
LDPE	Low density polyethylene
LLOQ	Lower limit of quantitation
IEC	Independent Ethics Committee
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MS	Mass Spectrometry
PCTFE	Polychlorotrifluoroethylene
PDA	Photo diode array
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Polypropylene
PRES	Posterior reversible encephalopathy syndrome
PSMF	Pharmacovigilance system master file
PSUR	Periodic Safety Update Report
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
PXRD	see XRPD
QA	Quality assurance
QC	Quality Control
QTPP	Quality target product profile
QPPV	Qualified person responsible for pharmacovigilance in the EU
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
S1P	sphingosine 1-phosphate receptor

SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
$t_{1/2}$	Half-life
T_{max}	Time to maximum plasma concentration
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
VZV	Varicella zoster virus
WCBP	Women of childbearing potential
WIRB	Western Institutional Review Board
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 5 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Fingolimod Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2020.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Fingolimod Mylan 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 (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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Gilenya instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Gilenya 0.5 mg hard capsules
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 17-03-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/677/001-006

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Gilenya 0.5 mg hard capsules

- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 17-03-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/677/001-006

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Gilenya 0.5 mg hard capsules
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 17-03-2011
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/11/677/001-006
- Bioavailability study number(s): study FING-CAZ-1001

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Nevenka Trsinar Brodt

The application was received by the EMA on	5 November 2020
The procedure started on	26 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 February 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	01 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 March 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 April 2021

The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	31 May 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fingolimod Mylan on	24 June 2021

2. Scientific discussion

2.1. Introduction

The product Fingolimod Mylan 0.5 mg hard capsules was developed as a generic equivalent to the innovator's product Gilenya 0.5 mg hard capsules. Gilenya was authorised in the EU on 17.03.2011.

The indication proposed for Fingolimod Mylan is the same as authorised for the reference medicinal product Gilenya:

Fingolimod Mylan 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 (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.

Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells, into the CNS, where they would be involved in nerve inflammation and nervous tissue damage.

In accordance with the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)and Fingolimod product-specific bioequivalence guidance (EMA/CHMP/154812/2016), the applicant submitted one fasting bioequivalence study to support the application (study FING-CAZ-1001 on 0.5 mg strength).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 0.56 mg of fingolimod hydrochloride as the active substance, corresponding to 0.5 mg of fingolimod.

Other ingredients are:

- Capsule content: calcium hydrogen phosphate dihydrate, glycine, colloidal anhydrous silica and magnesium stearate,
- Capsule shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172),
- Printing ink: shellac (E904), propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide.

The product is available in PVC/PCTFE-Alu blisters, PVC/PE/PVdC-Alu blisters and HDPE bottles with child-resistant PP closure with wad containing aluminium induction sealing liner as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is 2-amino-2-(4-octylphenethyl)propane-1,3-diol hydrochloride corresponding to the molecular formula $C_{19}H_{33}NO_2$.HCl. It has a relative molecular mass of 343.93 g/mol and the following structure:

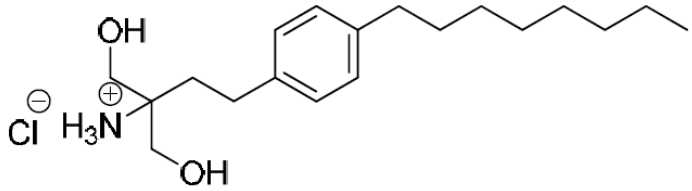

Figure 1: Active substance structure

The active substance is a white or almost white powder, freely soluble in water and in ethanol (96 %) and practically insoluble in heptane.

The active substance has a non-chiral molecular structure.

Fingolimod hydrochloride exhibits polymorphism and 4 distinct polymorphic forms are known (form I, form II, form III and hydrate form). The manufacturing process used by the CEP holder consistently produces one polymorphic form. An identification test is included in the active substance specification to confirm the desired polymorphic form. Conversion to other polymorphic forms occurs at elevated temperature and at elevated humidity. The material rapidly transitions back to the desired polymorphic form once returned to room temperature.

As there is a monograph of fingolimod hydrochloride in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for fingolimod hydrochloride which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Details of container closure system are specified in the CEP issued by EDQM for Fingolimod Hydrochloride Ph. Eur.

Specification

The active substance specification includes tests for: appearance (visual), solubility (Ph. Eur.), identification (IR, test for chloride), water content (KF), sulphated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (HSGC), particle size (Malvern) and identification (XRPD).

The active substance specification applied by the finished product manufacturer includes the tests and requirements stated in Ph. Eur. monograph for fingolimod hydrochloride and those on the CEP, including the additional tests for residual solvents which are included in the CEP. Two additional specification parameters are tested by the active substance manufacturer: identification (by PXRD) to confirm formation of desired polymorph form and testing for one additional impurity. The relevant information regarding these tests has been assessed by EDQM before issuing the Certificate of Suitability. The finished product manufacturer uses the same analytical methods as the active substance manufacturer.

Particle size is only tested by the finished product manufacturer. The analytical method has been adequately described and validated in accordance with the ICH guidelines. The specification limit has been set based on the particle size distribution of the active substance batches used to manufacture finished product, including those that were used in the bioequivalence study.

Stability

The relevant CEP for fingolimod hydrochloride does not include a re-test period.

Stability data from three production-scale batches of active substance from the proposed manufacturer stored in a container closure system representative of the commercial packaging for up to 60 months under long term conditions (5°C ± 3°C) and for up to 6 months under accelerated conditions (25ºC / 60% RH) according to the ICH guidelines were provided.

The stability studies were performed before the Ph. Eur monograph for fingolimod hydrochloride became effective. For the stability studies, loss on drying (NMT 0.5%) was tested instead of the water content according to Ph. Eur. The limits for impurities were higher than the Ph. Eur. specification limits (not more than 0.10%) for the specified impurities. All results were within the Ph. Eur. specification for fingolimod hydrochloride.

The analytical method used for assay and related substances has been demonstrated to be stability indicating.

The applicant did not test photolytic degradation of the active substance according to ICH Q1B and this can be accepted as the active substance is stored protected from light.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period and storage conditions.

Description of the product and Pharmaceutical development

The finished product is a hard capsule with brown-orange opaque cap and white opaque body, printed with 'MYLAN' over 'FD 0.5' in black ink on both the cap and body. Each capsule is approximately 16 mm in length.

The capsules are purchased as pre-printed empty capsule shells; therefore, the finished product manufacturer does not test and release the individual components of the capsule shells.

The description and composition of the finished product is adequate. All excipients, capsule shell components and printing ink components are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except iron oxide yellow, red and black which are not described in Ph. Eur. but comply with Commission Regulation (EU) No. 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of pharmaceutical development was to develop a generic version of the reference medicinal product Gilenya, 0.5 mg hard capsules.

The qualitative composition of the excipients is different in Fingolimod Mylan compared to the reference medicinal product and optimisation studies were conducted to select fill weight, filers and disintegrants. The compatibility of the excipients with the active substance has been confirmed.

The reference medicinal product is an immediate release product with low dose of active substance. Therefore, content uniformity and maintenance of assay were considered critical criteria for selecting an appropriate manufacturing process. During development, the manufacturing process was optimised.

The quality target product profile (QTPP) was defined and critical quality attributes (CQAs) were identified. These CQAs include assay, content uniformity, dissolution and related compounds. A risk assessment of the active substance attributes, formulation variables and manufacturing process variables was performed to evaluate their impact on the finished product CQAs. No design space was applied.

The choice of routine dissolution method has been adequately justified. The applicant adequately demonstrated the optimal concentration for the surfactant. The discriminatory power of the proposed dissolution method has been demonstrated at the dissolution specification limit.

A bioequivalence study was performed with relevant batches of the test and the reference medicinal products. Please refer to the clinical section for further details of this study. The test product used in the bioequivalence study is identical to the proposed commercial formulation.

Comparative dissolution profiles of the bioequivalence batches of the test product and the reference product have been presented in 3 media with addition of surfactant (release media, pH 4.5 acetate buffer and pH 6.8 phosphate buffer). The similarity factor (f2) values were calculated. In release media the dissolution profiles are similar for test and reference medicinal product. In pH 4.5 and 6.8 dissolution profiles are different. This difference was justified by the difference in qualitative and quantitative composition and in the manufacturing process between test and reference medicinal product.

Comparative *in vitro* dissolution tests between test and reference medicinal product in 3 media (pH 1.2, 4.5 and 6.8) without the use of surfactant have also been conducted in accordance with the Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). At pH 1.2, the dissolution profiles are comparable. At pH 4.5 and pH 6.8, the dissolution results show that the inclusion of SLS is required

to enhance the dissolution kinetics and solubility of the product. Fingolimod hydrochloride is insoluble in pH 6.8, therefore the dissolution is minimal for the reference and the test medicinal product. The information provided is sufficient to justify the selected dissolution conditions.

The finished product is proposed for use in adult patients and paediatric patients from 10 years and older. Relevant aspects of the specific needs of the paediatric population have been sufficiently discussed.

The product is presented in the following packaging types:

- PVC/PE/PVdC - Alu blister pack
- PVC/PCTFE - Alu blister pack
- High density polyethylene (HDPE) bottle pack with polypropylene (PP) child resistant closure with wad containing aluminium induction sealing liner

Adequate data has been provided for the container closure systems and the materials comply with Ph. Eur. and EC requirements.

In addition to the commercial packaging, bulk packs are described in the dossier (low-density polyethylene (LDPE) bags in an outer triple laminated bag placed in suitable tertiary packaging.)

Manufacture of the product and process controls

The finished product manufacturing process is a non-standard manufacturing process due to the low content of active substance in the medicinal product. The manufacturing process consists of a combination of several blending steps, dry granulation and final encapsulation.

The manufacturing process is described in sufficient detail and the in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

A holding-time study of process intermediates has not been performed. The entire manufacturing process is completed within 30 days. The start of shelf life of the finished product is determined in compliance with the Note for Guidance on start of shelf life of the finished dosage form (CPMP/QWP/072/96).

The filled capsules may be stored and transported as bulk product packaged in LDPE bags. The bulk packaging is described in the dossier and stability data is provided. The proposed shelf life of 12 months for bulk product is acceptable based on the provided stability data.

The control strategy for the critical steps is based on the process development studies performed.

The manufacturing process is considered as a non-standard as the amount of active substance in the medicinal product is low. Therefore, the manufacturing process has been validated as required by three consecutive production-scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC-PDA, HPLC), dissolution (HPLC), uniformity of dosage units (by content uniformity), related compounds (HPLC), assay (HPLC), microbial test (Ph. Eur.), colour identification (visual) and water content (KF.).

The proposed specifications are compliant with ICH Q6A and cover appropriate parameters for this dosage form.

The proposed limits for the impurities have been appropriately justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines or reference is made to the relevant Ph. Eur. chapters.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

Considering the synthetic route of active substance, a risk of nitrosamine formation was identified. Confirmatory testing was conducted, and several batches of active substance were analysed for nitrosamine impurities. The results were below the detection limit of the analytical method. This is acceptable considering the maximum daily dose of finished product. In response to a major objection raised during the procedure, confirmatory testing was also conducted on the finished product. Several finished product batches were also tested using a validated analytical method (GC-MS/MS). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the finished product. Therefore, no additional control measures are deemed necessary.

Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for three production-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production-scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH), for up to 12 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing (blister packs PVC/PE/PvdC, blister packs PVC/PCTFE and HDPE bottles).

Samples were tested for description, assay, dissolution, water, microbiological purity and related substances. The analytical procedures used are stability indicating. Under intermediate and long-term storage condition, all tested parameters remained within specification. Under accelerated storage conditions, the level of two impurities increased above the specification limit and a significant decrease in assay was observed.

In addition, a photostability study was conducted as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The capsules were found not to be sensitive to light.

An in-use stability study has been conducted for the bottle pack which confirmed stability for 180 days.

Data was presented for an open-pot stability study and the product was found to be stable for 90 days at 25°C / 60 % RH.

A holding-time study of process intermediates has not been performed. A bulk pack is proposed for holding the finished product before packaging or for transportation to any other approved re-packaging site in European Economic Area. A simulated bulk pack has been studied for 6 months at accelerated conditions (40ºC / 75% RH), for 12 months at intermediate conditions (30ºC / 65% RH) and for 12 months at long-term conditions (25ºC / 60% RH). The stability data justify the proposed shelf life of 12 months for the bulk pack.

The start of shelf life of the finished product is determined in compliance with the Note for Guidance on start of shelf life of the finished dosage form (CPMP/QWP/072/96).

Based on available stability data, the proposed shelf-life of 24 months as stated in the SmPC (section 6.3) is acceptable with the special precautions for storage outlined in section 6.4 of the SmPC (Do not store above 25°C; Store in the original package in order to protect from moisture).

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.3. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A major objection raised during the procedure in relation to the risk of presence of nitrosamine impurities has been resolved and acceptable results from confirmatory testing of the finished product have been presented. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.5. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to

generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The impurity profile has been discussed.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Fingolimod Mylan manufactured by Mylan Ireland Limited is considered unlikely to result in any significant increase in the combined sales volumes for all fingolimod containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to remain unchanged.

2.3.3. Discussion on non-clinical aspects

No non-clinical studies for fingolimod have not been performed by the applicant. The non-clinical data are based on literature review of published studies in animals and *in vitro* models. Fingolimod is well-known active substance clinically used in humans for more than 10 years and the CHMP agreed that no further non-clinical studies are required.

The impurity profiles and excipients are discussed adequately.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product Gilenya.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for omission of an environmental risk assessment is considered acceptable.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a hard capsule containing 0.5mg of fingolimod hydrochloride. To support the marketing authorisation application, the applicant conducted one bioequivalence study (FING-CAZ-1001) with parallel design under fasting conditions. This study was the pivotal study for the assessment.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) and the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09), as well as the fingolimod product specific bioequivalence guidance (EMA/CHMP/154812/2016) are of particular relevance.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study (FING-CAZ-1001):

Table 1: Tabular overview of clinical study

CTD SECTION	STUDY NUMBER AND TITLE	STUDY TYPE	STUDY SUB TYPE	DOSAGE
CTD section-5.3.1.2	Single-Dose Fasting Bioequivalence Study of Fingolimod Capsules (0.5 mg; Mylan) and GILENYA® Capsules (0.5 mg; Novartis) in Healthy Adult Male Volunteers FING-CAZ-1001	Pharmacokinetics	Fasting	1 x 0.5 mg

2.4.2. Pharmacokinetics

Methods

Study design

The study FING-CAZ-1001 was a single-dose, randomised, one-period, two-treatment, parallel-designed study with the objective to investigate the bioequivalence of Mylan Fingolimod capsules, 0.5 mg to Novartis Gilenya capsules, 0.5 mg following a single, oral 0.5 mg dose administration in healthy male volunteers under fasting conditions.

The study was conducted in six groups on 56 subjects total. In each group (28 subjects per treatment arm), the subjects received one capsule of 0.5 mg of either test or reference products randomly on the day of dosing as per the randomisation schedule under fasting conditions. Drug product was administered after at least 10 hours overnight fasting. A fast was maintained for at least 4 hours after dosing.

Blood samples were collected in K_2EDTA tubes at pre-dose (0 hours) and at intervals over 72 hours after administration of dose, which is sufficient for a substance with a long half-life to characterise the plasma concentration-time profile.

Each blood sample was divided equally into two (2) aliquots and stored upright in a freezer at −70°C until shipment to the bio-analytical department for analysis.

Test and reference products

Test product (A): **Fingolimod capsules, 0.5 mg**

Batch No.: #2018990

Manufactured date: 04/2020

Expiry date (Retest Date):03/2022

Reference product (B): **GILENYA capsules, 0.5 mg**

Batch No.: #SUC32

MAH: Novartis Pharma GmbH, Germany

Batch site (biobatch): Not applicable

Exp. Date: 07/2021

Population(s) studied

A total of 72 subjects were planned for enrolment as per protocol. Due to difficulties in recruitment resulting from the COVID-19 pandemic, only 56 (28 per treatment arm) non-smoker, healthy, adult, male volunteers of Asian ethnicity, black and white between 19 to 55 years of age weighing from 62.8 to 102.3 kg, with a Body Mass Index (BMI) range of 19.8 to 29.6 kg/m^2, met eligibility requirements per protocol, were enrolled for the study.

The subjects were dosed as per randomisation, one at a time, consecutively, at their scheduled intervals during period 1 in six groups. On study day 1, each subject received either a single oral dose of 0.5 mg (1 x 0.5 mg capsule) of the test product or the reference product.

All 56 subjects completed the clinical portion of the study successfully. However, 2 subjects (subject 19 and subject 20) had pre-dose fingolimod concentrations greater than 5% of C_{max} and were excluded from the pharmacokinetic analysis as per EMA guideline (CPMP/EWP/QWP/1401/98 Rev,1/Corr**) and the protocol exclusion criteria. Therefore, only 54 subjects are included in the pharmacokinetic and statistical analysis.

Analytical methods

Pre-study validation of the test method

A high-performance liquid chromatographic tandem mass spectrometric method for the determination of fingolimod in K_2EDTA human whole blood using automated sample preparation with liquid-liquid extraction has been developed in 2014 and later modified three times (Project #13-026-00 - Project #13-026-03). The method has been validated in 2014 and revalidated six times (from 03.06.2014 to 26.9.2020) in accordance with the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

Adequate certificates of analysis of the reference (fingolimod hydrochloride) and the internal standard (fingolimod-d4) were provided, as well as the method SOPs and statements on GLP compliance.

The method met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance.

Sensitivity of the lower limit of quantification (LLOQ) of 12 pg/ml with an acceptable accuracy and precision has been demonstrated.

Long-term stability data of fingolimod co-spiked with fingolimod phosphate metabolite in human whole blood at -70°C for 145 days showed stability of the subject samples stored under these conditions for 94 days.

Neither carry–over nor matrix effect was observed.

Selectivity of the fingolimod in the presence of co-administered drug (acetaminophen) and the fingolimod phosphate metabolite has been demonstrated. The method has acceptable selectivity and specificity and can accurately quantify concentration of fingolimod in human plasma.

The possibility of back-conversion of metabolite fingolimod phosphate was evaluated at the stage of bioanalytical method validation. The stability in the presence of fingolimod phosphate showed that there is no back-conversion of fingolimod phosphate to the fingolimod during the sample analysis and storage and thus considered acceptable.

Bioanalytical report

The analysis of the blood samples for fingolimod were carried out by the Bioanalytical Department of Mylan Pharmaceuticals Inc.

A validated high-performance liquid chromatography electrospray ionisation tandem mass spectrometric method (LC-ESI-MS/MS) for the determination of fingolimod in K_2EDTA human whole blood was used to assay all biostudy samples. Sample processing involved liquid-liquid extraction followed by LC-MS/MS analysis. The method used a standard curve range of 12-600 pg/mL, based on analysis of 150 µL of K_2EDTA male whole blood with the limit of quantification was 12 pg/mL. A weighted (1/X2) linear regression was used to determine slopes, intercepts, and correlation coefficients.

The bioanalytical laboratory study report including the complete analytical method package associated with the biostudy and statement on GLP, protocol and SOP compliance and quality insurance audit have been provided.

Adequate certificate of analysis for reference standard (USP Fingolimod hydrochloride) and internal standard (Fingolimod-d4) were included in the dossier.

A total number of 1792 collected samples were received frozen and intact at the bioanalytical site. However, only the primary set of samples (896 subject samples) was analysed for the biostudy.

Samples were stored at -70°C from the date of initial sample collection until the final day of sample resulting in the maximum sample storage period of 94 days at -70°C. Stability of fingolimod co-spiked with fingolimod phosphate in human whole blood has been demonstrated for 145 days of storage at -70°C.

All samples of one subject were analysed together in one analytical run. Each run consisted of zero sample, blank samples, ten calibration standards (12 pg/mL to 600 pg/mL), quality control samples in duplicate (30 pg/mL, 125 pg/mL, 325 pg/mL and 450 pg/mL) and study samples. Correlation coefficients (r) were >0.9982.

For the Quality control samples of fingolimod, at a low level, two middle levels, and a high-level concentration, accuracy values were 96.82% - 98.43% and precision values 3.72% - 6.40%, respectively.

The number of QC samples per one analytical run (4 QC levels in duplicate) corresponding to 12.5% of 64 study samples (4 subjects X 16 samples) analysed in one analytical run, which is considered adequate.

The re-assay of individual study samples and re-analysis of complete analytical batches was performed according to the SOP MPI-SOP-BIO-GEN-0020. A total number of re-analysed individual study samples was 2 of 896 samples. The reason for re-analysis was in both cases measurable concentration in subject zero sample (pre-dose) and it is considered justified.

A total of 108 incurred samples were re-analysed according to SOP MPI-SOP-BIO-GEN-0023. Re-analysed samples corresponding to 12,1% of 896 study samples and 98.1% of them met the acceptance criteria specified in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). The incurred sample reanalysis confirmed the reproducibility of the method.

Pharmacokinetic variables

Single-dose pharmacokinetic parameters for fingolimod were calculated using non-compartment techniques.

The following pharmacokinetic parameters were determined:

Primary pharmacokinetic parameters: C_{max}, AUC_{0-72}

Secondary pharmacokinetic parameters: T_{max}

Statistical methods

Statistical analysis: Statistical analysis was performed on log-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} of fingolimod using the SAS® Software (SAS Institute, Cary, NC).

Analysis of variance: Analysis of variance (ANOVA) was performed on log-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} of fingolimod using PROC GLM of SAS® Software (SAS Institute, Cary, NC).

The presented data shows that groups and treatments were comparable in all known variables (e.g., age, sex, race, weight, BMI, height) that may affect the pharmacokinetics of the active substance.

Bioequivalence between the Test (Treatment A) and Reference (Treatment C) was tested by the 90% confidence intervals for the ratio of the population geometric means (T/R) for the parameters.

Confidence intervals (CI) were determined for the ln- transformed AUC_{72}, and C_{max} for fingolimod using the treatments least squares means (LS-Means) obtained from ANOVA.

Bioequivalence was concluded when the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptance range of 80% -125% for ln-transformed C_{max} and AUC_{0-72}.

Pharmacokinetic and statistical analyses were performed on the 54 subjects who completed study period with test and reference product.

Results

The pharmacokinetic variables and statistical evaluation of fingolimod pharmacokinetic variables are shown in the following Table 2 and Table 3.

Table 2: Pharmacokinetic parameters of Fingolimod of Test and Reference; N=54

Pharmacokinetic Parameter	Arithmetic Means (± SD)	
	Test Product	Reference Product
$AUC_{(0-72\ h)}$ (pg•hr/mL)	20924 (± 3791)	21548 (± 3591)
Cmax (pg/mL)	347.4 (± 64.32)	355.6 (± 59.53)
tmax (hr)†	36.00 (14.00 - 36.00)	36.00 (16.00 - 36.00)

†median (minimum-maximum)

Table 3: Statistical evaluation of Fingolimod pharmacokinetic parameters; N=54

Fingolimod n = 54						
Parameter	**Arithmetic Mean (%CV) A = Mylan n=27**	**Arithmetic Mean (%CV) B = GILENYA® n=27**	**LSMEANS Ratio (A/B)***	**90% Confidence Interval****	**Inter-Subject CV (%)**	**Power (%)**
pAUC72 (pg•hr/mL)	20924 (18.12)	21548 (16.66)	0.97	89.43% – 104.87%	17.61	98.97
CPEAK (pg/mL)	347.4 (18.51)	355.6 (16.74)	0.97	89.86% – 105.59%	17.83	> 99
TPEAK (hr)	29.19 (33.75)	34.22 (15.32)				

* Ratio (A/B) = $e^{[LSMEAN\ of\ (LNA - LNB)]}$; **Used Natural Log Transformed Parameter

The test to reference ratio of geometric LS means and corresponding 90% confidence interval of the C_{max} and AUC_{0-72} were all within the acceptance range of 80-125%.

Concentrations for both reference and test drug in pre-dose time point were below the limit of quantification except for 2 subjects (subjects 19 and 20). Those 2 subjects were excluded from PK and statistical analysis.

No subject reached C_{max} at the first sample time.

Considering the sampling period of 72h, and quantifiable concentrations at 72h, $AUC_{(0-\infty)}$ and residual area do not need to be reported and it is sufficient to report AUC truncated at 72h, $AUC_{(0-72h)}$.

Safety data

All 54 subjects were included in the safety and tolerability evaluation.

Six post-dose adverse events were experienced by 5 subjects over the course of this study. The AEs were mild in severity. No serious adverse events (SAEs) were reported.

There was 1 pre-dose adverse event (thermal burn) reported after signing of the ICF but prior to dosing and, therefore, considered unrelated to either treatment.

There were 4 AEs (back pain, bradycardia, nasal congestion, rhinorrhoea) that were considered probably related and 2 AEs (headache) that were considered possibly related to study drug (reference).

There were no AEs reported after the oral administration of test product.

Overall, Fingolimod Mylan was well tolerated as a single, oral 0.5 mg dose administered under fasting conditions.

Conclusions

Based on the results of the bioequivalence study, Fingolimod Mylan 0.5 mg hard capsules is considered bioequivalent with the reference product Gilenya 0.5 mg hard capsules.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support this application, the applicant has submitted a review of clinical data as well as one bioequivalence study performed in 2020.

The bioequivalence study was designed as a one-period, two-treatment, parallel study bioequivalence study to compare the bioavailability of 2 formulations of fingolimod (0.5 mg) under fasting conditions.

A total of 72 healthy, adult, human subjects were planned for enrolment as per protocol. However, due to difficulties in recruitment resulting from the COVID-19 pandemic, only 56 (28 per treatment arm) met eligibility requirements per protocol. The subjects were dosed in 6 groups as per randomisation, one at a time, consecutively, at their scheduled intervals during period 1. All 56 subjects completed the clinical portion of the study. Two subjects had pre-dose fingolimod concentrations greater than 5% of C_{max} and were excluded from the pharmacokinetic analysis as per EMA guideline. Therefore, only 54 subjects are included in the pharmacokinetic and statistical analysis.

Overall, the study design is acceptable for substances with very long half-life and in line with the Bioequivalence Guideline. According to the Fingolimod capsules 0.5 mg product-specific bioequivalence guidance (EMA/CHMP/154812/2016), one single dose, parallel, fasting study with blood sampling for 72 hours is appropriate. The bioequivalence study was conducted under standardised conditions.

The study was conducted under fasting conditions, which is acceptable as the drug product can be taken with or without food and the fasting condition is the most sensitive to identify differences between the formulations.

Sampling time schedule seems adequate taking into account long t_{max} of fingolimod of around 12 - 16 hours.

As fingolimod is highly distributed in red blood cells, blood was used as matrix for the evaluation of fingolimod (parent) concentrations, which is acceptable. The measurement of the parent compound (fingolimod) in blood is in line with the requirements of the Fingolimod product-specific bioequivalence guidance (EMA/CHMP/154812/2016).

Adequate information is provided on the test and reference products. The reference product marketed in Germany is a suitable comparator of the generic product. The assayed content of the batch used as test product did not differ more than 5% from that of the batch used as reference product.

The analytical method was validated, either pre-study or within study according to Guideline on bioanalytical method validation (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Bioanalytical method had satisfactory performance and was adequately validated.

The pharmacokinetic parameters measured/calculated are standard for a single-dose study. They are acceptable and according to the Guideline on the Investigation of Bioequivalence and Fingolimod capsules 0.5 mg product-specific bioequivalence guidance (EMA/CHMP/154812/2016).

The statistical method used for the pharmacokinetic analyses is considered acceptable. The ANOVA model used is adequate for a bioequivalence study. Given that the study was conducted in 6 groups and those groups were dosed at different time, exclusion of the interaction terms (Group, Group*Formulation) from the ANOVA model was justified.

Furthermore, in view of the parallel design and in accordance with the guideline, a detailed analysis comparing treatment groups was provided and showed that groups and treatments were comparable in all known variables (e.g., age, sex, race, weight, BMI, height) that may affect the pharmacokinetics of the active substance.

The 90% confidence intervals for ln-transformed pharmacokinetic variables AUC_{0-72h} and C_{max} were within the conventional bioequivalence range of 80% to 125%.

Both the formulations (Test and Reference) were well tolerated during the conduct of the study.

The clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.4.6. Conclusions on clinical aspects

Based on the results of the bioequivalence study, Fingolimod Mylan 0.5 mg hard capsules is considered bioequivalent with the reference product Gilenya 0.5 mg hard capsules.

The CHMP agrees that Fingolimod Mylan is acceptable from a clinical point of view.

2.5. Risk management plan

Safety concerns

Table 4: Summary of safety concerns

Summary of safety concerns	
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) • Reproductive toxicity • Bronchoconstriction • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Convulsions

Summary of safety concerns	
Important potential risks	• Acute disseminated encephalomyelitis-like (ADEM-like) events • Lymphoma • Other malignant neoplasms • Thrombo-embolic events • QT interval prolongation
Missing information	• Long-term use in pediatric patients, including impact on growth and development (including cognitive development) • Elderly patients (≥65 years) • Lactating women • Patients with diabetes mellitus • Patients with cardiovascular conditions including myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for 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 apnoea • Long-term risk of cardiovascular morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy

Pharmacovigilance plan

Only routine pharmacovigilance activities have been proposed.

Risk minimisation measures

Table 5: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures:	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide	
Hypertension	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities
Liver transaminase elevation	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Posterior Reversible Encephalopathy Syndrome (PRES)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Macular edema	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Reproductive toxicity	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.6 and 5.3 PL section 2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and paediatric population • Patient/Parent/Caregiver's guide • Pregnancy-specific patient reminder card	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Bronchoconstriction	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 5.1 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Convulsions	Routine risk minimisation measures: SmPC sections 4.4 (Pediatric patients) and 4.8 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Acute disseminated encephalomyelitis-like (ADEM-like) events	Routine risk minimisation measures: SmPC section 4.8 PL section 4 Restricted medical prescription.	Routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	
Lymphoma	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.8 and 5.3 PL sections 2 and 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Other malignant neoplasms	Routine risk minimisation measures: SmPC sections 4.3 and 4.4 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Thrombo-embolic events	Routine risk minimisation measures: SmPC section 4.8. Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
QT interval prolongation	Routine risk minimisation measures:	Routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC sections 4.3, 4.4 and 4.9 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Restricted medical prescription. Additional risk minimisation measures: • Physician's checklist for adult and pediatric population • Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities
Elderly patients (≥65 years)	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities
Lactating women	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures for this safety concern.	
Patients with diabetes mellitus	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities
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 apnoea	Routine risk minimisation measures: SmPC sections 4.3 and 4.4 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities
Long-term risk of cardiovascular morbidity/mortality	Routine risk minimisation measures: None Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term risk of malignant neoplasms	Routine risk minimisation measures: SmPC section 4.3 PL section 2 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities
Unexplained death	Routine risk minimisation measures: SmPC section 4.8 PL section 4 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities and Specific adverse reaction follow-up questionnaire
Switch from other disease modifying therapy	Routine risk minimisation measures: SmPC sections 4.4, 4.5 and 5.1 Restricted medical prescription. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.	Routine pharmacovigilance activities

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Gilenya (for content) and to Duloxetine Mylan (for design and layout). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of fingolimod hydrochloride hard capsules. The reference product Gilenya is indicated for as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

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

No non-clinical studies have been provided for this application. An adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics or on the efficacy and safety of the active substance. The clinical overview, based on information from published literature, was considered sufficient.

The bioequivalence study forms the pivotal basis with a single-dose, randomised, one-period, two-treatment, parallel-designed study in healthy adult male subjects under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Fingolimod Mylan met the protocol-defined criteria for bioequivalence when compared with the reference product Gilenya. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72h} and C_{max} were all contained within the protocol-defined acceptance range (80 to 125%). Bioequivalence of the two formulations was therefore demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fingolimod Mylan is favourable in the following indication:

Fingolimod Mylan 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 (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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Fingolimod Mylan in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each Member State (MS) where Fingolimod Mylan is marketed, all physicians who intend to prescribe it are provided with the following educational materials:

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

Physician's checklist

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

- Monitoring requirements at treatment initiation:

  <u>Before first dose</u>
  - Perform baseline ECG prior to the first dose of Fingolimod Mylan;
  - Perform blood pressure measurement prior to the first dose of Fingolimod Mylan;
  - Perform a liver function test including transaminases and bilirubin, prior to (within 6 months) treatment initiation;
  - Arrange ophthalmological assessment before starting Fingolimod Mylan treatment in patients with diabetes mellitus or with a history of uveitis.
  - A negative pregnancy test result must be confirmed prior to starting treatment.

  <u>Until 6 hours after first dose</u>
  - Monitor the patient for 6 hours after the first dose of Fingolimod Mylan has been administered for signs and symptoms of bradycardia, including hourly pulse and blood pressure checks. Continuous (real time) ECG monitoring is recommended;
  - Perform an ECG at the end of the 6-hour monitoring period.

  <u>> 6 to 8 hours after first dose</u>
  - If, at the 6-hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.

- Recommendation for re-initiating Fingolimod Mylan therapy after treatment interruption:
  The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:
  - One 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 at least one month of treatment.

- Recommendation for overnight monitoring after the first dose (or if the first dose monitoring applies during treatment re-initiation):
  - Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients requiring pharmacological intervention during monitoring at treatment initiation/re-initiation. Repeat the first dose monitoring after the second dose of Fingolimod Mylan;
  - Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients:
    - With third degree AV block occurring at any time;
    - Where at the 6-hour time point:
      a. Heart rate < 45 bpm, < 55 bpm in paediatric patients aged 12 years old and above, or < 60 bpm in paediatric patients 10 to below 12 years of age;
      b. New onset second degree or higher AV block;
      c. QTc interval ≥ 500 msec.

- Fingolimod Mylan is contraindicated in patients with:
  - Known immunodeficiency syndrome;
  - Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies);
  - Severe active infections, active chronic infections (hepatitis, tuberculosis);
  - Known active malignancies;
  - Severe liver impairment (Child-Pugh class C);
  - In the previous 6 months, myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure;
  - Severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products;
  - Second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker;
  - Patients with a baseline QTc interval ≥ 500 msec;
  - Pregnant women and women of childbearing potential not using effective contraception;
  - Hypersensitivity to the active substance or to any of the excipients.

- Fingolimod Mylan is not recommended in patients with:
  - Sino-atrial heart block;
  - QTc prolongation > 470 msec (adult females), QTc > 460 msec (paediatric females) or > 450 msec (adult and paediatric males);
  - History of cardiac arrest;
  - Severe sleep apnoea;
  - History of symptomatic bradycardia;
  - History of recurrent syncope;
  - Uncontrolled hypertension.

  If Fingolimod Mylan treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to determine appropriate monitoring, at least overnight extended monitoring is recommended.

- Fingolimod Mylan is not recommended in patients concomitantly taking medicines known to decrease the heart rate. If treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to switch to non heart-ratelowering therapy or, if not possible, to determine appropriate monitoring. At least overnight extended monitoring is recommended.

- Fingolimod Mylan reduces peripheral blood lymphocyte counts. Peripheral lymphocyte count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of

prior therapy) and monitored during treatment. Treatment should be interrupted if lymphocyte count is confirmed as < $0.2x10^9$/L. The approved dosing of 0.5 mg once daily (or 0.25 mg once daily in paediatric patients 10 years of age and above with a body weight of ≤ 40 kg) when restarting Fingolimod Mylan should be administered. Other dosing regimens have not been approved.

- Fingolimod Mylan has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas (including mycosis fungoides) and other malignancies, particularly those of the skin. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.

    - Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Suspension of treatment during serious infections should be considered. Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.

    - Vigilance for basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma is recommended, with skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Specific recommendations regarding vaccination for patients initiating fingolimod treatment.

    - Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is recommended and treatment initiation should be delayed for one month to allow full effect of vaccination to occur.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with Fingolimod Mylan.

    - Prompt diagnostic evaluation should be performed in patient with symptoms and signs consistent with encephalitis, cryptococcal meningitis or meningoencephalitis; appropriate treatment, if diagnosed, should be initiated.
    - Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus (HSV) and VZV were reported while on Fingolimod Mylan treatment.
    - Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2-3 years of treatment, although an exact relationship with the duration of treatment is unknown.
    - Cases of progressive multifocal leukoencephalopathy (PML) have occurred after approximately 23 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown. Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with fingolimod Mylan should be suspended until PML has been excluded.
    - Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV related cancer, has been reported in the post-marketing setting. Cancer screening, including Pap test, and vaccination for HPV-related cancer is recommended for patients, as per standard of care.

- A full ophthalmological assessment should be considered:
    - 3-4 months after starting Fingolimod Mylan therapy for the early detection of visual impairment due to drug-induced macular oedema;
    - During treatment with Fingolimod Mylan in patients with diabetes mellitus or with a history of uveitis.

- Fingolimod Mylan is teratogenic. It is contraindicated in women of childbearing potential (including female adolescents) not using effective contraception and in pregnant women.

    - A negative pregnancy test result must be confirmed prior to starting treatment, and it must be repeated at suitable intervals.
    - Women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers, should be counselled before treatment initiation and regularly thereafter about the serious risks of Fingolimod Mylan to the foetus, facilitated by the pregnancy-specific patient reminder card.
    - Women of childbearing potential must use effective contraception during treatment and for two months following treatment discontinuation.
    - While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, Fingolimod Mylan must be discontinued. When stopping Fingolimod Mylan therapy due to pregnancy or for planning a pregnancy, the possible return of disease activity should be considered. Medical advice should be given regarding the risk of harmful effects to the foetus associated with Fingolimod Mylan treatment and ultrasonography examinations should be performed.
    - Fingolimod Mylan must be stopped 2 months before planning a pregnancy.

- Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported. Therefore, liver function should be monitored carefully.

    - Before initiation of treatment, recent (i.e. within last 6 months) transaminase and bilirubin levels should be available;
    - During treatment, in the absence of clinical symptoms, liver transaminases and serum bilirubin should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after Fingolimod Mylan discontinuation;
    - During treatment, in the absence of clinical symptoms, if liver transaminases are greater than 3 but less than 5 times the upper limit of normal (ULN) without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present. If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, Fingolimod Mylan should be discontinued. Hepatic monitoring should be continued. If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), Fingolimod Mylan may be restarted based on a careful benefit-risk assessment of the patient.

- The approved dosing of 0.5 mg daily (or 0.25 mg once daily in paediatric patients 10 years of age and above with a body weight of ≤ 40 kg) should be administered. Other dosing regimens have not been approved.

- In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping Fingolimod Mylan. The possibility of recurrence of exceptionally high disease activity should be considered.

- Cases of seizure, including status epilepticus, have been reported. Physicians should be vigilant for seizures and especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy.

- Physicians should reassess on an annual basis the benefit of Fingolimod Mylan treatment versus risk in each patient, especially paediatric patients.

- Physicians should provide patients/parents/caregivers with the patient/parents/caregiver guide and with the pregnancy-specific patient reminder card.

The safety profile in paediatric patients is similar to adults and therefore the warnings and precautions in adults also apply for paediatric patients.

Specifically, with paediatric patients, physicians should also:

- Assess Tanner staging and measure height and weight as per standard of care;
- Perform cardiovascular monitoring;

- Take precautions when the first dose is administered / patients are switched from 0.25 to 0.5 mg daily, due to the potential for bradyarrhythmia;
- Monitor the patient for sign and symptoms of depression and anxiety;
- Emphasise treatment compliance and misuse to patients, especially about treatment interruption and the importance of repeating cardiovascular monitoring;
- Emphasise Fingolimod Mylan immunosuppressive effects;
- Consider a complete vaccination schedule before starting Fingolimod Mylan;
- Provide guidance on seizure monitoring.

Patient / Parent / Caregiver guide

The patient/parents/caregiver guide shall contain the following key messages:
- What Fingolimod Mylan is and how it works;
- What multiple sclerosis is;
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it again during treatment;
- Importance of reporting adverse reactions;
- Patients should have a baseline ECG and blood pressure measurement prior to receiving the first dose of Fingolimod Mylan;
- Heart rate should be monitored for 6 or more hours after the first dose of Fingolimod Mylan, including hourly pulse and blood pressure checks. Patients may be monitored with continuous ECG during the first 6 hours. An ECG at 6 hours should also be performed and, in some circumstances, monitoring may involve an overnight stay;
- Patients should call their doctor in case of treatment interruption as the first dose monitoring may need to be repeated, depending on duration of interruption and time since starting of Fingolimod Mylan treatment;
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of Fingolimod Mylan;
- Fingolimod Mylan is not recommended in patients with cardiac disease or those taking medicines concomitantly known to decrease heart rate, and they should tell any doctor they see that they are being treated with Fingolimod Mylan;
- Signs and symptoms of infection, which should be immediately reported to the prescriber physician during and up to two months after Fingolimod Mylan treatment; including the following:
    - Headache accompanied by stiff neck, sensitivity to light, fever, flu-like symptoms, nausea, rash, shingles and/or confusion or seizures (fits) (may be symptoms of meningitis and/or encephalitis, either caused by a fungal or viral infection);
    - Symptoms such as weakness, visual changes, or new/worsening MS symptoms (may be symptoms of progressive multifocal leukoencephalopathy [PML]).
- The need to undergo cancer screening, including Pap test, and vaccination for HPV-related cancer, as per standard of care, will be assessed by the prescriber physician;
- Any symptoms of visual impairment should be reported immediately to the prescriber during and for up to two months after the end of treatment with Fingolimod Mylan;
- Fingolimod Mylan is teratogenic. Women of child-bearing potential, including adolescent females, should:
    - Be informed before treatment initiation and regularly thereafter by their physician about Fingolimod Mylan's serious risks to the foetus, and about the contraindication in pregnant women and in women of childbearing potential not using effective contraception, facilitated by the pregnancy-specific patient reminder card;
    - Have a negative pregnancy test before starting Fingolimod Mylan;
    - Be using effective contraception during and for at least two months following discontinuation of Fingolimod Mylan treatment;
    - Report immediately to the prescribing physician any (intended or unintended) pregnancy during and up to two months following discontinuation of Fingolimod Mylan treatment;
- A liver function test should be performed prior to treatment initiation; liver function monitoring should be performed at months 1, 3, 6, 9 and 12 during Fingolimod Mylan therapy, and periodically thereafter until 2 months after Fingolimod Mylan discontinuation. Patients should inform their doctor if they notice yellowing of their skin or the whites of their eyes, abnormally dark urine, pain on the right side of the stomach area, tiredness, feeling less hungry than usual or unexplained nausea and vomiting as these can be signs of liver injury;
- Skin cancers have been reported in multiple sclerosis patients treated with Fingolimod Mylan. Patients should inform their doctor immediately if any skin nodules (e.g., shiny, pearly nodules), patches or open sores that do not heal within weeks are noted. 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;

- Seizure may occur. The doctor should be informed about a pre-existing history or family history of epilepsy;
- Stopping Fingolimod Mylan therapy may result in return of disease activity. The prescribing physician should decide whether and how the patient should be monitored after stopping Fingolimod Mylan.

Specifically for paediatric patients:

The following should be considered:
- Physicians should assess Tanner staging and measure height and weight as per standard of care;
- Precautions should be taken during the first dose of Fingolimod Mylan and when patients are switched from 0.25 to 0.5 mg daily;
- Depression and anxiety are known to occur with increased frequency in the multiple sclerosis population and have been reported also in paediatric patients treated with Fingolimod Mylan;
- Cardiac monitoring guidance;
- Patients should ensure medication compliance and avoid misuse, especially treatment interruption, and repeat cardiac monitoring;
- Signs and symptoms of infection;
- Seizure monitoring guidance.

Pregnancy-specific patient reminder card

The pregnancy-specific patient reminder card shall contain the following key messages:
- Fingolimod Mylan is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
- Doctors will provide counselling before treatment initiation and regularly thereafter regarding the teratogenic risk of Fingolimod Mylan and required actions to minimise this risk.
- Patients must use effective contraception while taking Fingolimod Mylan.
- A pregnancy test must be carried out and negative results verified by the doctor before starting treatment. It must be repeated at suitable intervals.
- Patients will be informed by their doctor of the need for effective contraception while on treatment and for 2 months after discontinuation.
- Doctors will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy.
- While on treatment, women must not become pregnant. If a woman becomes pregnant or wants to become pregnant, Fingolimod Mylan must be discontinued.
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with Fingolimod Mylan.