30 April 2020
EMA/CHMP/267804/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fingolimod Accord

International non-proprietary name: fingolimod

Procedure No. EMEA/H/C/005191/0000

Note

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

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List of abbreviations

ADI	Acceptable Daily Intake
ADR	Adverse Reaction
AE	adverse event
ANSM	National Agency for the Safety of Medicine and Health Products
AP	Applicant's Part of ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area Under the plasma Concentration
AUC_{0-inf}	Area Under the plasma Concentration-time curve from time zero to infinity
AUC_{0-t}	Area Under the plasma Concentration-time curve from time zero to t hours
BE	Bioequivalence
BLQ	Below limit of quantification
BSE/TSE	Bovine Spongiform Encephalopathy / Transmissible Spongiform Encephalopathy
CIOMS	Suspect Adverse Reaction Report Form
C_{max}	maximum plasma concentration
CL/F	Oral clearance
CoA	Certificate of Analysis
CP	Centralised procedure
CRO	Certified Research Organisation
CRS	Chemical Reference Substance
DHCP	Direct Healthcare Professional Communication
DMF	Drug Master File = Active Substance Master File, ASMF
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EEA	European Economic Area
EEG	electroencephalogram
EMA	European Medicines Agency
EU	European Union
FPM	Finish Product Manufacturer
GABA	Gamma-aminobutyric acid
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	Health Care Professional
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
CHMP	Committee for Human Medicine Products
ICD	Informed Consent Document
ICMR	Indian council of medical research
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
ICH	International Conference of Harmonization
IMS	International Marketing Sales
INN	International Non-proprietary Name
IPC	In-process control test
IR	Incidence Rate
IR	Infrared
IS	Internal standard
ISR	Incurred Sample Reanalysis
LLOQ	Lower Limit of Quantification

LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MHRA	British National Competent Authority
MR	Medical Representative
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
NCA	National Competent Authority
ND	Not detected
NMR	Nuclear Magnetic Resonance
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSR	Normal Sinus Rhythm
OECD	Organisation for Economic Co-operation and Development
OOS	Out of Specifications
OTC	Over-the-counter
PCD	Photo-Contact Dermatitis
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PhV	Pharmacovigilance
PI	Product Information
PIL	Patient Information Leaflet
PK	pharmacokinetic
PMS	Post Marketing Surveillance
PP	Polypropylene
PPCP	Polypropylene Copolymer
PS	Photo-Sensitivity
PSD	Particle Size Distribution
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QA	Quality Assurance
QC	Quality Control (samples)
QOS	Quality Overall Summary
QP	Qualified Person
Rf	Retention factor
RH	Relative Humidity
RMM	Risk Minimization Measure
RMS	Reference Member State
RR	Reporting Rate
RRT	Relative retention time
RSD	Relative standard deviation
Rt	Retention time
SAE	severe adverse event
SLS	Sodium Lauryl Sulphate
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
STD	Standard Deviation
T/R	Test/Reference
T_{max}	time for maximum concentration (* median, range)
TSE	Transmissible spongiform encephalopathy
UV	Ultraviolet
XRPD	X-ray powder diffraction

This is a general list of abbreviations. Not all abbreviations are used in this report.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 4 May 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Fingolimod Accord, 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 18 October 2018.

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 Accord as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

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/1/11/677/005
- Bioavailability study number(s): Project No. 498-14

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.

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: Selma Arapovic Dzakula

The application was received by the EMA on	4 May 2019
The procedure started on	23 May 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	27 August 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2019

The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	3 February 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2020
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	31 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2020
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 Accord on	30 April 2020

2. Scientific discussion

2.1. Introduction

The product Fingolimod Accord 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 Accord is the same as authorized for the reference medicinal product Gilenya. The proposed pack sizes are consistent with the dosage regimen and duration of use.

Both the test and the reference product contain the same active ingredient i.e. fingolimod hydrochloride.

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.

One bioequivalence (BE) study has been performed with the originator. The test product (Fingolimod Accord, 0.5 mg hard capsules) and the reference product (Gilenya, 0.5 mg hard capsules) were compared under fasting conditions (Study No. 498-14).

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:

- pregelatinised starch and magnesium stearate in the capsule fill,
- gelatin, titanium dioxide (E171) and yellow iron oxide (E172) in the capsule shell,
- shellac (E904), propylene glycol (E1520), potassium hydroxide, black iron oxide (E172) and yellow iron oxide (E172) in the printing ink.

The product is available in polyvinylchloride (PVC)/polyvinylidene chloride (PVDC)/aluminium blisters as follows:

- blister packs containing 7, 28 or 98 hard capsules.
- perforated unit dose blister packs containing 7 x 1, 28 x 1 or 98 x 1 hard capsule

2.2.2. Active Substance

There is one manufacturer of the active substance and documentation of the active substance is provided using the ASMF procedure.

General Information

The chemical name of fingolimod hydrochloride 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:

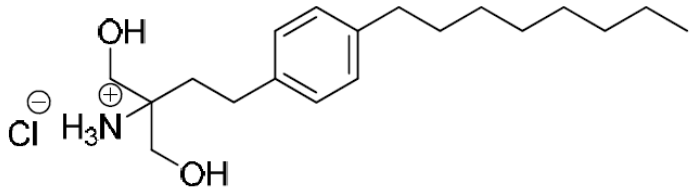


Figure 1 Active substance structure

It is a white to almost white powder. It is freely soluble in water and ethanol and practically insoluble in heptane.

The chemical structure of fingolimod hydrochloride has been confirmed by various techniques like infrared (IR) spectroscopy, ultraviolet (UV) spectroscopy, nuclear magnetic resonance (1H-NMR, 13C-NMR) and mass spectroscopy (MS).

Fingolimod hydrochloride has a non-chiral molecular structure.

Polymorphism has been observed for fingolimod hydrochloride and several crystalline forms are reported in literature. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) data provided confirms that the active substance used for Fingolimod Accord is the desired polymorphic form. This is routinely controlled in the active substance specification. Transition between crystalline forms is temperature and humidity dependant. The desired polymorphic form remains stable under the proposed long-term stability condition.

Fingolimod hydrochloride in the desired polymorphic form has been confirmed to be non-hygroscopic.

Manufacture, process controls and characterisation

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. There is one source of the active substance.

The synthesis of fingolimod hydrochloride is divided into two phases.

The synthesis of fingolimod hydrochloride consists of 6 stages, with five stages in which chemical bond formation or cleavage is involved (the last stage includes salt formation). During the synthesis five intermediates are isolated. Three starting materials are proposed in the synthesis of fingolimod hydrochloride which are all incorporated as significant structural fragments in the final API. With the proposed starting materials, enough steps are conducted under GMP to appropriately mitigate risks associated with contamination and future changes to the synthetic route or supplier of the starting material. Therefore, proposed starting materials are acceptable and adequate data for all raw materials used in the synthesis are provided.

One of the initially proposed starting materials was not considered acceptable as it was not considered to be in line with ICH Q11 guidelines on selection of starting materials. A major objection was raised in this regard. In response, the applicant redefined the starting materials an earlier stage and this was considered acceptable.

A second major objection was raised in relation the risk of formation of specific impurity during the active substance synthesis. Routine testing of the impurity in the active substance specification was considered necessary. The applicant updated the specification and the major objection was resolved.

In each stage of synthesis critical parameters have been identified and justified. Acceptance criteria and ranges are defined. Adequate in-process controls are set. Description of the analytical methods used during in-process control is provided. The specification and control methods for intermediate products, starting materials and reagents have been presented. Reprocessing has been adequately described and justified.

Specifications and analytical procedures are provided for the five intermediates and considered acceptable.

Summary of process validation on three production scale batches of the intermediate 2-acetamido-2-phenethyl propane-1,3-diyl diacetate and on final active substance is provided. Defined critical process parameters are in the specified ranges for three validation batches. Results for the validation batches, as tested per active substance specification, are within proposed limits.

Adequate data regarding possible impurities in the active substance has been provided: impurities from the synthesis, possibility of presence of Ph.Eur. impurities, inorganic impurities, residual solvents and genotoxic impurities including possibility of presence of nitroso impurities. Also, relevant carry-over studies have been conducted which indicate that the control of impurities in the active substance is adequate.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The proposed active substance specification includes tests for description, solubility (Ph. Eur.), identification (IR, XRD, Chloride), water content (KF), sulfated ash (Ph. Eur.), appearance of solution, Pd content (ICP), related substances (HPLC), assay (HPLC), residual solvents (GC, HPLC), 2-chloropropane (GC), NDEA content (LCMS), microbial examination (Ph. Eur.) and particle size.

The active substance specification is in line with the Ph.Eur. monograph for fingolimod hydrochloride (07/2019:2988). For the tests proposed as additional testing in comparison to the monograph (XRD identification, appearance of solution, Pd content, specified in-house impurities A-F, residual solvents, 2-chloropropane and microbial test) justified limits have been proposed.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated.

Specificity of the related substances method was demonstrated by spiked test preparation with known in-house impurities A-F. The applicant also demonstrated equivalency between the in-house and Ph.Eur. related substances and assay methods. In-house related substances and assay methods have the capability to detect and separate in-house and Ph.Eur. impurities, therefore the use of in-house methods for testing of assay and related substances is considered acceptable.

Satisfactory information regarding the standards used has been presented. Fingolimod hydrochloride working standard is evaluated against the Ph. Eur. chemical reference standard (CRS) while adequate data have been provided for impurities standards.

Batch analysis data from three consecutive, commercial scale batches of the active substance has been provided. The results are within the specifications and show batch to batch consistency.

The active substance is packed in a double polyethylene bag, which is placed in triple laminated bag and inserted in a high-density polyethylene (HDPE) drum. Adequate specification and test procedures of the packaging materials have been provided. Compliance of the primary packaging material with Commission regulation 10/2011 has been stated. In addition, the packaging materials comply with Ph. Eur 3.2.2 (Plastic containers and closures for pharmaceutical use) and 3.1.3 (Polyolefins).

Stability

Results of stability testing on three commercial scale batches (manufactured in 2014), packed under simulated market packs, at 25°C/60% RH (36 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months) according to the previous specification are provided. Stability results according to the specification enclosed in section S.4.1 are provided for an additional three batches manufactured in 2019 (up to 6 months at 25°C/60% RH and 40°C/75% RH).

All results for tested parameters remained within specifications at long-term conditions and accelerated conditions for the tested time period and no obvious trends or significant changes were observed.

A retest period of 24 months, in an airtight container at 25°C with excursions permitted to 15°C-30°C, protected from light, was proposed. It was demonstrated that no polymorphic form change is observed during storage at 25°C as well as up to 4 months at 30°C. Therefore, the proposed storage condition "at 25°C with excursions permitted to 15°C-30°C" for the active substance is acceptable.

The results of the forced degradation study showed that the HPLC methods for assay and for related substances are stability indicating.

Although the Applicant did not demonstrate photolytic degradation in its own study (according to ICH Q1B), storage protected from light could be accepted for the active substance.

Based on the provided results, the proposed retest-period of 24 months is acceptable since the previous specification is not critically changed (limits for impurities are tightened, equivalence between the in-house and Ph.Eur. methods is demonstrated and no stability relevant parameter is added), all results for previous batches up to 36 months are in line with updated specification, and results up to six months for

3 new commercial scale batches (tested in line with updated specification) are comparable with results for previous batches.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Fingolimod 0.5 mg capsule is a bright yellow opaque/white opaque size "3" hard gelatin capsule imprinted with "FO 0.5 mg" on the cap and two radial bands on the capsule body with yellow ink containing white to off-white powder. Each capsule is approximately 15.8 mm in length.

The qualitative finished product composition is outlined below:

- Fingolimod hydrochloride, pregelatinised starch and magnesium stearate in the capsule fill,
- gelatin, titanium dioxide (E171) and yellow iron oxide (E172) in the capsule shell,
- shellac (E904), propylene glycol (E1520), potassium hydroxide, black iron oxide (E172) and yellow iron oxide (E172) in the printing ink.

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 and black (E172) 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 formulation development was based on the composition of the reference product Gilenya. The qualitative composition of the capsule fill is similar to the composition of the reference product with a difference in diluent (mannitol, present in the reference product, is replaced with pregelatinised starch). The composition of the hard capsule and ink is similar to that of the reference product. Composition of capsule fill consists of only two excipients, for which content was optimized by dissolution studies and capsule fill weight of the reference product. Considering the very low content of active substance in the capsule fill, blend uniformity is assured by specified particle size distribution of fingolimod. Particle size distribution is also reflected in the specification of the pregelatinised starch and magnesium stearate.

The information provided in relation to control of polymorphic forms of the active substance is satisfactory.

The choice of routine dissolution method has been adequately justified. The Applicant adequately demonstrated the optimal concentration of SLS for the QC dissolution method. The discriminatory power of the method was demonstrated on a batch manufactured with active substance with a coarser particle size distribution than what is specified in the active substance specification.

A bioequivalence study was performed with relevant batches of the test and the reference 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 and the reference product have been presented in 3 media with addition of 0.2% SLS (pH 1.2, pH 4.5 and pH 6.8; basket, 100 rpm, 500 ml). In all media, more than 85% of API is dissolved in 15 min, and thus, no further calculation is required. Comparative dissolution profiles in QC medium for 2 validation batches, the test product bioequivalence batch and the reference product were also provided and found to be similar (more than 85% release is observed within 15 minutes for all batches).

The product is available in polyvinylchloride (PVC)/polyvinylidene chloride (PVdC)/aluminium blisters as follows:

- blister packs containing 7, 28 or 98 hard capsules.
- perforated unit dose blister packs containing 7 x 1, 28 x 1 or 98 x 1 hard capsule

Adequate data has been provided for the container closure system and the material complies with Ph. Eur. Monograph 3.1.11.

The following bulk storage/transportation packs are described in the dossier:

Polypropylene copolymer (PPCP) container pack comprises a low-density polyethylene (LDPE) bag which is twist tied, this LDPE bag is kept in another LDPE bag, a silica gel bag is placed in between two bags, again twist tied and placed in PPCP container & closed.

High-density polyethylene (HDPE) bottles pack comprises white opaque HDPE bottle fitted with white opaque polypropylene closure with wad having induction sealing liner.

Manufacture of the product and process controls

The finished product manufacturing process is a standard process consisting of sifting of raw materials, direct blending and encapsulation. In-process controls are adequate as well as proposed holding times of lubricated granules (30 days in stainless steel container) and bulk capsules (2 months in double PE bags with triple laminated polybag inside HDPE container).

Process validation has been carried out on three commercial size batches and the manufacturing process can therefore be considered as validated.

Product specification, analytical procedures, batch analysis

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, content, identification (HPLC, UV), loss on drying, dissolution, uniformity of dosage units (Ph. Eur.), related substances (HPLC), assay (HPLC), microbial examination (Ph. Eur.).

Identification of the active substance is controlled by two methods (HPLC and UV) in line with ICH Q6A. Limits for uniformity of dosage units and microbiological quality are in line with the relevant Ph. Eur. monographs. The proposed limits for fingolimod assay of 95-105% throughout the shelf life of the product are acceptable. Upon request, the limit for dissolution was tightened according to dissolution results for the batch used in the bioequivalence study.

The limit for single impurity is in line with ICH threshold and therefore acceptable as well as the limits for total impurities.

The Applicant has also performed a risk evaluation regarding the presence of nitrosamine impurities in the finished product. The data provided regarding the presence of nitrosamine impurities in the finished product is considered adequate.

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-MC method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective permitted daily exposure (PDE). Based on the data presented it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on control of elemental impurities is satisfactory.

Analytical methods have been adequately described and satisfactorily validated for intended purposes.

Batch analysis results were provided for of 3 validation batches which were within the specification at the time of testing. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Appropriate in-house reference standards are used. It is confirmed that the fingolimod in-house working standard is qualified against Ph.Eur. CRS.

Stability of the product

Stability data has been provided for three validation batches of commercial size packed in the proposed market pack (Alu-PVC/PVdC blister) and in bulk / transportation packs (PPCP container and HDPE bottle) in accordance with current ICH/CHMP guidelines.

For the Alu-PVC/PVdC blisters results up to 36 months at 25°C/60% RH and up to 6 months at 40°C/75% RH were provided and found within specification.

Results for finished product stored in bulk / transportation packs indicate that bulk capsules are stable for 3 years in HDPE bottles and for 2 years in PCPP container.

Based on the results of photostability study according to ICH Q1B it can be concluded that the finished product is photostable.

Considering the potential polymorphic form transition at elevated temperatures, the finished product should be stored below 25°C.

Based on the available stability data, the proposed shelf life of 3 years for finished product packed in Alu-PVC/PVdC blisters and stored below 25°C as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the hard gelatine capsule shells. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture is provided.

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

Two major objections were raised on quality aspects during the procedure. One of the initially proposed starting materials was not considered acceptable as it was not considered to be in line with ICH Q11. In response, the applicant redefined the starting materials an earlier stage and this was considered acceptable to resolve the major objection. The second major objection related to the risk of formation of a specific impurity during the synthesis of the active substance. The major objection was resolved through the introduction of routine testing of this impurity in the active substance specification.

2.2.5. Conclusions on 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 TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided.

In the initial report impurity profile was not discussed adequately and it was a point of minor concern. The updated overview written in December 2019, refers to 19 literature references dated from 2002 up to 2019. Some of the references are product information of the reference product Gilenya (Product Information, Product Monograph and Summary of product characteristics) which is acceptable in this case.

Impurity profile and excipients are discussed adequately.

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 Accord 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 be similar.

2.3.3. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of fingolimod are well known. As fingolimod is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. SmPC of the generic product is identical to the reference product.

Therefore, the CHMP agreed that no further non-clinical studies are required.

The impurity profile of applicant's fingolimod HCL is comparable to that of Gilenya. Thus, additional toxicology studies to qualify the impurity profile of the drug product are not required (please see also the recommendation in section 2.2.6).

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.3.4. Conclusion on the non-clinical aspects

The CHMP is of the opinion that the applicant has justified the absence of non-clinical studies based on the literature review and the claim that Fingolimod Accord is a generic of the reference product Gilenya. The literature data presented in the dossier is considered acceptable and sufficient for the assessment of non-clinical aspects of Fingolimod Accord in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsule, containing fingolimod hydrochloride. To support the marketing authorisation application the applicant conducted one bioequivalence study 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 product specific guideline Fingolimod capsules 0.5 mg product-specific bioequivalence guidance (EMA/CHMP/154812/2016) in their current version, are of particular relevance.

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.

Comparative dissolution profiles between the batches used in the BE study (test product batch R01869 / reference product batch S0091) in 3 different media without the addition of 0.2% SLS (0.1N HCl, pH 4.5, pH 6.8) / 500 ml, 37±0.5°C, basket apparatus at 100 rpm, have been performed. The dissolution profiles in media pH 4.5 and pH 6.8 are found similar between the batches used in the BE study. Dissimilarity of the profiles in media 0.1 HCl is not found critical, since bioequivalence was demonstrated in vivo and possible reasons for the discrepancy of the in vitro/in vivo data is addressed and justified.

Table 1 Tabular overview of clinical studies

Protocol No.	Study Title
498-14	An open label, randomized, two-treatment, single period, single oral dose, parallel, bioequivalence Study of two products of fingolimod capsules 0.5 mg (administered as 0.5 x 3 capsules) in healthy, adult, Human subjects under fasting condition

2.4.2. Pharmacokinetics

Methods

Study design

Study 498-14 was an open label, randomized, two-treatment arm, single period, single oral dose, parallel, bioequivalence study of two products of fingolimod capsules 0.5 mg (administered as 0.5 x 3 capsules) in healthy, adult, human subjects under fasting conditions. The study was conducted in two groups on 79 subjects total (40 subjects / test treatment and 39 subjects / reference treatment). Group

II was dosed after completion of clinical phase for group I and after evaluating the safety data from the first group.

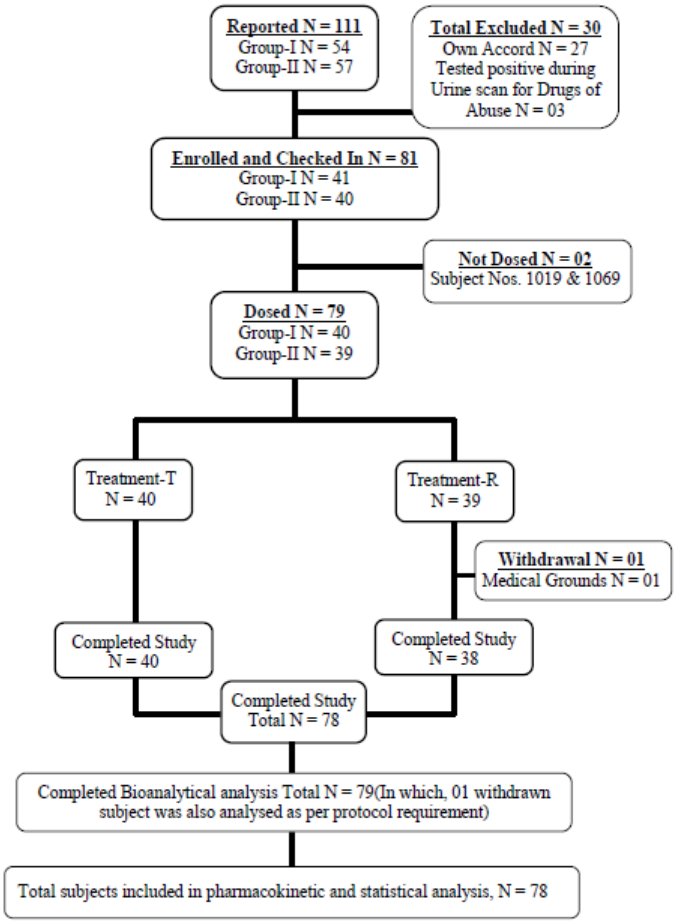
Fasting conditions were applied considering that the subjects were housed minimum 11 hours prior to drug administration. Subjects were maintained in a fasting state for at least 10 hours prior to dosing and for at least 4 hours after dosing.

As fingolimod is highly distributed in red blood cells, blood was used as matrix for the evaluation of fingolimod (parent) concentrations.

As per the protocol, a total of 27 blood samples, each of 03 mL, were to be collected from each subject at pre-dose (0 hour) and at 1, 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16,18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 40, 48 and 72 hours post-dose following drug administration.

Sampling time schedule is adequate, taking into account long t_{max} of fingolimod of around 12 - 16 hours (Gilenya SmPC).

Population(s) studied



Eighty-one non-smoker, healthy, adult, male only volunteers of Asian ethnicity between 18 to 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 to 30 kg/m^2 (both inclusive), having no significant diseases or clinically significant abnormal findings during screening, were enrolled in the study.

Two subjects were withdrawn pre-dosing (one on medical grounds and one on his own accord) and one post-dosing on medical grounds.

Seventy-eight subjects had completed the study and were included in the PK and statistical analysis.

Withdrawal of the subjects was performed according to protocol.

Analytical methods

Samples were received at the bioanalytical site on 28-SEP-2015 and 03-OCT-2015 (for Group I) and on 05-OCT-2015 and 08-OCT-2015 (for Group II).

Analysis of study samples lasted from 01-OCT-2015 to 14-OCT-2015 (including ISR and repeats).

Study samples total storage period was 57 days at -65±10°C. Validated long-term stability of drug in matrix is 265 days at -65±10°C.

Validated range was 25.037 to 3005.607 pg/mL and the assay range was 25.039 to 3000.542 pg/mL.

In-study and Pre-study:

Analyte: Fingolimod (parent)
IS: Fingolimod-d4
Matrix: human blood, anticoagulant K_2EDTA
Extraction Method: Liquid-liquid
Weighting: 1/concentration^2

Pre-study validation (MV(I)-001-13, 21-OCT-2013)

Specific LC-MS/MS method for the determination of fingolimod in human blood was developed at Bioanalytical Department of Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India.

The method was validated and met acceptance criteria with respect to: selectivity/specificity, sensitivity, linearity/calibration curve, within-run accuracy and precision, between-run accuracy and precision, robustness and ruggedness, matrix effect, IS-normalised matrix factor, stability (freeze and thaw stability, short term stability, analyte stability in matrix, solution stability) and dilution integrity.

Possibility of back-conversion of the metabolites was examined. It can be concluded that there was no interference of metabolites on fingolimod quantification and no back-conversion.

Pre-study validation was performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

In-study validation

The blood samples of subjects were analysed using a validated LC-MS/MS method for fingolimod at the Bioanalytical facility of Lambda Therapeutic Research Ltd., Ahmedabad, India.

Separately weighed stocks were used for the preparation of calibration curve standards and the quality control samples on 29-SEP-2015.

The analyte was extracted from blood by liquid-liquid extraction method using extraction solution.

Signed bioanalytical report including statement on GLP, protocol and SOP compliance (12-DEC-2015) has been provided. In-study validation was performed according to the requirements of the EMA Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/09.

All samples of one subject were analysed together in one analytical run, a minimum of two quality control samples of each QC sample concentration (LQC 74.960 pg/mL, LMQC 348.651 pg/mL, MQC 1394.602 pg/mL and HQC 2324.337 pg/mL) and eight calibration samples (25.039 to 3000.542 pg/mL) as well as blank and zero calibrants.

For the Quality control samples (LQC, LMQC, MQC and HQC), including failed QCs, global accuracy values were 99.6%, 100.6%, 99.3% and 99.2%, respectively and global precision values were 8.4%, 6.8%, 5.1% and 3.4%, respectively.

Analytical chromatograms from 16 subjects (20%) were included in the dossier.

ISR has been investigated satisfactorily. The suitability of the method validation has been confirmed. Number of QC samples is adequate.

The reasons for the repeats and the reported values are in line with the SOP LTR.BA-03-01 (for repeat analysis) and SOP LTR.BA-02 (section analytical run acceptance criteria). The original values repeat values and reported values are listed for each repeat sample.

Thirty-four individual samples were reanalysed due to significant variation in response of IS. The Applicant provided detailed clarification of the reanalysis due to afore mentioned variation as well as the possible cause of the two pre-dose study samples that were reanalysed.

Pharmacokinetic variables

The pharmacokinetic parameters were calculated from the blood concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Professional Software Version 6.4 (Certara L.P.) for fingolimod by Lambda Therapeutic Research Ltd.

Actual time points of the sample collection were used.

Primary pharmacokinetic parameters were C_{max} and AUC_{0-72} and the secondary pharmacokinetic parameter was T_{max}.

The pharmacokinetic variables are adequate and in line with the BE-Guideline and Fingolimod capsules 0.5 mg product-specific bioequivalence guidance (EMA/CHMP/154812/2016).

Statistical methods

Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out by Lambda Therapeutic Research Ltd. using statistical software package PROC MIXED of SAS® Version 9.3 (SAS Institute Inc., USA).

Analysis of variance (ANOVA) model included Group, Formulation and Group*Formulation as fixed effect.

ANOVA, power and ratio analysis for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} are computed for fingolimod.

Group*Formulation interaction term was found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72}. Hence, this interaction term (Group*formulation) was excluded from the ANOVA model and statistical analysis was re-performed for the ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72}, as per protocol.

The calculation of 90%-confidence intervals is in line with the BE-Guideline.

Results

The results are summarised in Table 2 and Table 3 below. 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 80.00-125.00%.

Concentrations for both reference and test drug in pre-dose time point were BLQ. The LLOQ of 25.037 pg/mL was sensitive enough to detect levels of 5% of the minimum C_{max}. Considering the sampling period of 72 h, and quantifiable concentrations at 72 h, $AUC_{(0-\infty)}$ and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, $AUC_{(0-72h)}$.

Table 2 Pharmacokinetic parameters for fingolimod (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$ (pg.h/mL)	100416.981	16176.6853	93289.879	16500.2311
C_{max} (pg/mL)	1818.837	300.6683	1713.346	271.6042
T_{max}* (h)	14.509	(6.000-48.000)	13.500	(9.000-36.017)
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration T_{max} time for maximum concentration (* median, range)				

Table 3 Statistical analysis for fingolimod (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$ (pg.h/mL)	107.8%	100.95% – 115.04%	17.4
C_{max} (pg/mL)	105.9%	99.38% – 112.92%	17.1
* estimated from the Residual Mean Squares			

Given that the applicant has used parallel design in the BEQ study, comparison between test and reference with respect to age, height, weight and BMI has been done and provided:

Table 4

Parameter	Statistics	Test (N=40)	Reference (N=39)	p-value*
Age	Mean	30.38	31.46	0.4692
	SD	7.182	6.030	-
BMI	Mean	21.73	23.22	0.0404
	SD	2.969	3.355	-
Height	Mean	165.90	166.70	0.4971
	SD	5.140	6.294	-
Weight	Mean	59.83	64.46	0.0263
	SD	8.883	9.284	-

* p-value using independent t-test

Based on the above table, no statistically significant difference has been observed between test and reference for Age and Height (p-value > 0.05), while statistically significant difference has been observed between test and reference for BMI and Body weight (p-value < 0.05). The applicant performed statistical analysis in ANCOVA using body weight (BW) and Body Mass Index (BMI) as covariates with formulation as fixed effect. Results showed for formulation no statistical significance for ln-transformed primary PK parameters (Cmax and AUC0-72). Additionally, the applicant performed statistical analysis for 90% CI calculation considering group and formulation as fixed effect and BW and BMI as covariates. Results showed for formulation no statistical significance for primary PK parameters (Cmax and AUC0-72). It was also showed that test to reference ratio of geometric LS means and corresponding 90% confidence interval of the Cmax and AUC0-72 were all within the acceptance range of 80.00-125.00% when BW and BMI were included as covariates.

Safety data

Safety was assessed from the screening period to the end of the study. Five (05) AEs were reported in subjects after administration of the reference product and five (05) AEs after administration of the test product. There were no deaths or serious AEs reported during the conduct of the study. Tolerability of the test product was not significantly different from that for the reference product and thus, is acceptable. One subject has withdrawn from the study on medical grounds, has received the reference product.

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

The updated Clinical Overview on the clinical pharmacology, efficacy and safety of fingolimod is adequate.

The clinical aspects of the SmPC are in line with the SmPC of the reference product. However, the innovator is approved in 0.25 mg and 0.5 mg strengths. This generic medicinal product has only been developed in the 0.5 mg strength. Therefore, the applicant adjusted the sections 4.1 and 4.2 of the SmPC according to the population for which the 0.5 mg formulation is appropriate (patients with body weight >40 kg).

2.4.6. Conclusions on clinical aspects

The application contains an adequate review of published clinical data. The bioequivalence has been shown appropriately under fasting conditions between Fingolimod Accord 0.5 mg hard capsules and Gilenya 0.5 mg hard capsules.

The treatment was well tolerated by the subjects enrolled in the study. Fingolimod Accord 0.5 mg hard capsules, and Gilenya 0.5 mg hard capsules have similar safety profiles.

2.5. Risk management plan

Safety concerns

Table 5 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 oedema • 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
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 apnea • Long-term risk of cardiovascular morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy

PML – Progressive Multifocal Leukoencephalopathy

VZV – *Varicella zoster* virus

Pharmacovigilance plan

Only routine pharmacovigilance activities have been proposed.

Risk minimisation measures

Table 6 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	Routine risk minimization measures: Sections 4.3, 4.4, 4.5 and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational materials for physicians and patients: – Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide	Additional pharmacovigilance activity: None
Hypertension	Routine risk minimization measures: Sections 4.4 and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Liver transaminase elevation	Routine risk minimization measures: Sections 4.2, 4.3, 4.4, 4.8 and 5.2 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: Educational materials for physicians and patients: – Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Posterior Reversible Encephalopathy Syndrome (PRES)	Routine risk minimization measures: Sections 4.4 and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Macular oedema	Routine risk minimization measures: Sections 4.4 and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: Educational materials for physicians and patients: – Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	Routine risk minimization measures: Sections 4.3, 4.4 and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational materials for physicians and patients: – Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide	Additional pharmacovigilance activity: None
Reproductive toxicity	Routine risk minimization measures: Sections 4.3, 4.4 and 4.6 of Fingolimod SmPC and corresponding section of PL (section 2) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: Educational materials for physicians and patients: – Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide – Pregnancy-specific patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Bronchoconstriction	Routine risk minimization measures: Sections 4.4, 4.8 and 5.1 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Routine risk minimization measures: Sections 4.3, 4.4 and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: Educational materials for physicians and patients: – Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Convulsions	Routine risk minimization measures: Sections 4.4 (pediatric patients) and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: Educational materials for physicians and patients: – Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Important Potential Risks		
Acute disseminated encephalomyelitis-like (ADEM-like) events	Routine risk minimization measures: Section 4.8 of Fingolimod SmPC and corresponding section of PL (section	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Lymphoma	Routine risk minimization measures: Sections 4.3, 4.4, 4.8 and 5.3 of Fingolimod SmPC and corresponding section of PL (sections 2 and 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Other malignant neoplasms	Routine risk minimization measures: Sections 4.3, and 4.4 of Fingolimod SmPC and corresponding section of PL (sections 2) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Thromboembolic events	Routine risk minimization measures: Section 4.8 of Fingolimod SmPC and corresponding section of PL (section	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
QT interval prolongation	Routine risk minimization measures: Sections 4.3, 4.4 and 4.9 of Fingolimod SmPC and corresponding section of PL (section 2) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Missing information		
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Routine risk minimization measures: Sections 4.2 and 5.2 of Fingolimod SmPC and corresponding section of PL (section 3) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: Educational materials for physicians and patients:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	– Physician's checklist for adult and paediatric population – Patient/Parent/Caregiver's guide	
Elderly patients (≥ 65 years)	Routine risk minimization measures: Sections 4.2 and 5.2 of Fingolimod SmPC and corresponding section of PL (section 3) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Lactating women	Routine risk minimization measures: Section 4.6 of Fingolimod SmPC and corresponding section of PL (section 2) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Patients with diabetes mellitus	Routine risk minimization measures: Sections 4.2, 4.4 and 4.8 of Fingolimod SmPC and corresponding section of PL (sections 2, 3, 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Patients with cardiovascular conditions including myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher AV block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea	Routine risk minimization measures: Sections 4.3 and 4.4 of Fingolimod SmPC and corresponding section of PL (section 2) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Long-term risk of cardiovascular morbidity/mortality	Routine risk minimization measures: *Restricted medical prescription*. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term risk of malignant neoplasms	Routine risk minimization measures: Section 4.3 of Fingolimod SmPC and corresponding section of PL (section 2) has information on this safety concern. Other routine risk minimisation measures include *Restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Unexplained death	Routine risk minimization measures: Section 4.8 of Fingolimod SmPC and corresponding section of PL (section 4) has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire has been proposed for this safety concern. Additional pharmacovigilance activity: None
Switch from other disease modifying agent	Routine risk minimization measures: Sections 4.4, 4.5 and 5.1 of Fingolimod SmPC has information on this safety concern. Other routine risk minimisation measures include *restricted medical prescription* of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 (dated 24 April 2020) 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. 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 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 nonclinical studies have been provided for this application but an adequate summary of the available nonclinical 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 as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, parallel, randomized, two-treatment, single period, single oral dose, study of two products of fingolimod capsules 0.5 mg

(administered as 0.5 x 3 capsules) in healthy, adult, human subjects under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was 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 Accord met the protocol-defined criteria for bioequivalence when compared with Gilenya. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was 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 Accord is favourable in the following indication:

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
- 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.