COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe/Simvastatine Genepharm 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg, tablets

(ezetimibe/simvastatin)

NL/H/4415/001-004/DC

Date: 22 August 2019

This module reflects the scientific discussion for the approval of Ezetimibe/Simvastatine Genepharm. The procedure was finalised at 22 May 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ezetimibe/Simvastatine Genepharm 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg, tablets from Genepharm S.A.

The following indications are approved:

Prevention of Cardiovascular Events
Ezetimibe/Simvastatine Genepharm is indicated to reduce the risk of cardiovascular events (see SmPC section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Hypercholesterolaemia
Ezetimibe/Simvastatine Genepharm is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:

- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetimibe/Simvastatine Genepharm is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis)

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Inegy 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, tablets (NL License RVG 30927-30930) which has been registered in the Netherlands by Merck Sharp & Dohme B.V. since 22 November 2004 through mutual recognition procedure DE/H/0496/001-004/MR.

The concerned member state (CMS) involved in this procedure was Greece.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Simvastatine Genepharm is a white to off white capsule-shaped uncoated tablet debossed with "G" on one side in four strengths:
10 mg/10 mg - is debossed with "321" on other side
10 mg/20 mg – is debossed with "322" on other side
10 mg/40 mg – is debossed with "323" on other side
10 mg/80 mg – is debossed with"324" on other side

Each tablet contains 10 mg ezetimibe and 10 mg, 20 mg, 40 mg or 80 mg of simvastatin.

The tablets are packed in HDPE bottles with polypropylene cap and heat seal liner and PVC-Aluminium-OPA/Aluminium blisters.

The excipients are lactose monohydrate, microcrystalline cellulose (E 460), hypromellose, croscarmellose sodium (E468), propyl gallate (E310), butyl hydroxyl anisole (E320), citric acid monohydrate (E330), sodium lauryl sulphate and magnesium stearate (E470b).

The composition of the four different strengths is dose proportional, with the exception of ezetimibe (10 mg in all tablets), for which the amount of filler is compensated.

II.2 Drug Substances

Ezetimibe
The active substance is ezetimibe, an established active substance that is not described in the European, British or United States Pharmacopoeia (Ph.Eur., BP, USP). Ezetimibe is a white to off-white crystalline powder, which is freely soluble in ethanol and methanol but practically insoluble in water. Ezetimibe contains three asymmetric carbon atoms and therefore exhibits optical isomerism. It is shown that the anhydrous crystalline form is consistently obtained through the manufacturing process.

The Active Substance Master File (ASMF) procedure is used by both manufacturers for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The syntheses descriptions are in sufficient detail and sufficient chemistry is part of the regulatory synthesis route. Specifications of starting materials and intermediates are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance

Manufacturer-I - The retest period is 30 months, based on stability data of three commercial scale batches stored at long-term conditions up to 18 months and accelerated conditions up to six months.

Manufacturer-II - The retest period is 48 months, based on stability data of three lower scale and three higher scale validation batches stored at long-term conditions up to 60 months and accelerated conditions up to six months.

Simvastatin

The active substance simvastatin is an established active substance described in the Ph.Eur. The active substance is a white or almost white, crystalline powder. It is practically insoluble in water, very soluble in methylene chloride and freely soluble in ethanol (96%). No polymorphism is observed.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance

The active substance is stable for three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, formulation development, dissolution method development, manufacturing process development and the performance of comparative dissolution studies complementary to the bioequivalence study with the 10 mg/10 mg and 10 mg/80 mg strength. Similarity of the dissolution profiles between the bioequivalence study test and reference batches has been studied in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer and QC dissolution medium (pH 7.0 Phosphate Buffer with 0.5 % SLS).

Based on bioequivalence studies carried out on highest strength 10 mg/80 mg of ezetimibe and simvastatin tablets, a biowaiver is requested for lower strength 10 mg/40 mg. Additionally, in accordance with a bracketing approach, a biowaiver for 10 mg/20 mg strength is requested considering bioequivalence studies carried out on highest strength 10 mg/80 mg and lowest strength 10 mg/ 10 mg of ezetimibe and simvastatin tablets.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three exhibit batches of each strength containing ezetimibe from manufacturer-I and two exhibit batches of each strength containing ezetimibe from manufacturer-II in accordance with the relevant European guidelines.

Control of excipients

All excipients ae controlled conform Ph.Eur. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, dissolution, uniformity of dosage units, related substances, assay, butylated hydroxyl anisole, propyl gallate, residual solvents, water content, microbial enumeration tests, and tests for specified microorganisms. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three exhibit batches of each strength containing ezetimibe from manufacturer-I and two exhibit batches of each strength containing ezetimibe from manufacturer-II have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data from accelerated (40°C/75% RH, up to six months), intermediate (30°C/65%

RH, up to 12 months) and long term conditions(25°C/60% RH, up to 24 months) are provided on at least three batches of all strengths for the proposed product. The conditions used in the stability studies are according to the ICH stability guideline.

On the basis of the data submitted, a shelf life was granted of two years with storage conditions "Do not store above 25°C, Keep the blister in the outer carton to protect from moisture, Keep the bottles tightly closed and in the outer carton in order to protect from moisture".

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the materials (except lactose monohydrate) used in the formulation are of animal and/or human origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ezetimibe/Simvastatine Genepharm has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe/Simvastatine Genepharm is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Inegy which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ezetimibe and simvastatin are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Ezetimibe/Simvastatine Genepharm (Genepharm S.A., Greece) is compared with the pharmacokinetic profile of the reference product Inegy (Merck Sharp & Dohme Ltd., United Kingdom):

- Study I - A bioequivalence study under fasting conditions with the 10 mg/80 mg strength
- Study II - A bioequivalence study under fasting conditions with the 10 mg/10 mg strength

The choice of the reference products
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH proposed a biowaiver of strengths for the 10 mg/20 mg and 10 mg/40 mg, based on the Guideline on the investigation of bioequivalence. The MAH applied a bracketing approach. The biowaiver of strengths is acceptable, as the manufacturing process and qualitative composition of all strengths is identical. Further, the deviation of quantitative proportional composition for the 10 mg/40 mg versus the 10 mg/80 mg is within limits and the 10 mg/20 mg strength quantitative proportionality deviation is also acceptable, since the MAH adequately applied a bracketing approach. All comparative dissolution tests supporting a biowaiver for the 10 mg/20 mg and 10 mg/40 mg strengths were performed in accordance with the Guideline on Investigation of Bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study

Bioequivalence study I – Ezetimibe/Simvastatine Genepharm 10 mg/80 mg strength vs Inegy 10 mg/80 mg under fasting conditions

Design

A comparative, open label, randomized, single dose, reference replicated crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects (28.9 ±5.9 years of age). Each subject received a single dose (10 mg ezetimibe and 80 mg simvastatin) of one of the two ezetimibe/simvastatin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were three dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours after administration of the products.

The study design is acceptable. The wash-out period is long enough to prevent carry-over between periods, the sampling period and sampling scheme covers the complete concentration time profile of the analytes and the fasting condition is regarded as the most sensitive to detect formulation differences. Any bioequivalence conclusion with regard to ezetimibe is based on unconjugated ezetimibe. However, total ezetimibe is presented in the report as well, for completeness.

Results

One subject discontinued due to a positive breath alcohol test, and two subjects did not report back for the 3rd period. Therefore 45 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of unconjugated ezetimibe under fasted conditions.

Treatment N=45	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	93.78 ± 36.20	99.49 ± 38.69	8.51 ± 4.89	2.0 (0.33 - 12)
Reference	89.62 ± 32.97	93.49 ± 33.20	7.53 ± 3.05	2.8 (0.59 - 9.0)
***Ratio (90% CI)**	1.05 (0.98 - 1.12)	1.06 (0.99 - 1.13)	1.08 (0.99 - 1.18)	--

$AUC_{0-\infty}$ 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
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe under fasted conditions.

Treatment N=45	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	717.0 ± 235.4	762.3 ± 245.4	108.5 ± 34.9	1.3 (0.33 – 4.5)
Reference	677.4 ± 199.9	720.4 ± 207.6	96.3 ± 32.4	1.2 (0.50 – 2.9)
***Ratio (90% CI)**	1.05 (1.00 - 1.11)	1.05 (1.00 - 1.11)	1.14 (1.07 - 1.22)	--

$AUC_{0-\infty}$ 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
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of simvastatin under fasted conditions.

Treatment N=45	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	212.33 ± 90.03	225.87 ± 94.07	50.59 ± 27.57	1.67 (0.67 – 4.50)
Reference	212.33 ± 83.87	221.92 ± 85.85	48.66 ± 20.55	1.50 (0.67 – 3.75)
***Ratio (90% CI)**	1.01 (0.94 - 1.09)	1.03 (0.96 - 1.11)	1.03 (0.93 - 1.14)	--

$AUC_{0-\infty}$ 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
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Bioequivalence study II – Ezetimibe/Simvastatine Genepharm 10 mg/10 mg vs Inegy 10 mg/10 mg under fasting conditions

Design

An open label, randomised, single dose, reference replicated crossover bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 31.7 ± 6.2 years. Each subject received a single dose (10 mg ezetimibe and 10 mg simvastatin) of one of the two ezetimibe/simvastatin formulations. The tablet was orally administered with 240 ml water after an overnight fast for at least ten hours. There were three dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours after administration of the products.

The study design is acceptable. The wash-out period is long enough to prevent carry-over between periods, the sampling period and sampling scheme covers the complete concentration time profile of the analytes and the fasting condition is regarded as the most sensitive to detect formulation differences. Any bioequivalence conclusion with regard to ezetimibe is based on unconjugated ezetimibe. However, total ezetimibe is presented in the report as well, for completeness.

Results

Two subjects discontinued the study: One subject due to positive breath alcohol, and another subject did not report to the facility for the second period check in. Therefore, 70 subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of unconjugated ezetimibe under fasted conditions.

Treatment N=70	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	70.46 ± 28.55	76.46 ± 30.42	5.01 ± 2.45	5.0 (0.3 - 12.0)
Reference	71.16 ± 31.40	77.48 ± 32.08	4.65 ± 1.88	4.8 (0.5 - 12.0)
***Ratio (90% CI)**	1.01 (0.97 - 1.06)	1.00 (0.96 - 1.05)	1.07 (1.00 - 1.14)	--
$AUC_{0-\infty}$ 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 **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**ln-transformed values*

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe under fasted conditions.

Treatment N=45	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	697.42 ± 283.17	740.73 ± 299.00	100.56 ± 36.35	1.3 (0.5 - 5.0)
Reference	703.15 ± 294.76	747.46 ± 311.65	98.46 ± 40.62	1.4 (0.6 - 4.0)
***Ratio (90% CI)**	1.00 (0.97 - 1.04)	1.00 (0.97 - 1.04)	1.04 (0.99 - 1.10)	--
$AUC_{0-\infty}$ 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 **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**ln-transformed values*

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of simvastatin under fasted conditions.

Treatment N=45	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	20.78 ± 9.96	21.32 ± 10.03	6.67 ± 2.70	1.7 (0.5 - 5.0)
Reference	22.32 ± 10.52	22.94 ± 10.63	5.97 ± 2.37	1.4 (0.8 - 3.8)
***Ratio (90% CI)**	0.94 (0.88 - 1.00)	0.94 (0.88 - 1.00)	1.15 (1.08 - 1.22)	--

$AUC_{0-\infty}$ 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
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Ezetimibe/Simvastatine Genepharm is considered bioequivalent with Inegy.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ezetimibe/Simvastatine Genepharm.

Table 7. Summary table of safety concerns as approved in RMP

Important identified risks	• Rhabdomyolysis/myopathy • Abnormal liver function • Hypersensitivity • Drug interaction with warfarin, another coumarin anticoagulant, or fluindione • Drug interaction with ciclosporin
Important potential risks	• Pancreatitis • Cholecystitis/cholelithiasis

	• Interstitial lung disease • Simvastatin hypersensitivity syndrome • New onset diabetes/impaired glucose metabolism • Haemorrhagic stroke
Missing information	• Exposure during pregnancy and lactation • Use in children (limited clinical trial experience in children 10-17 years of age. No clinical trial experience in children less than ten years of age.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Inegy. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with six participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

Furthermore a user consultation with target patient groups on the PL has been performed on the basis of a bridging report making reference to the key safety messages, design and layout of the Ezetimibe/Simvastatine Genepharm PL (NL/H/4048/001-004/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezetimibe/Simvastatine Genepharm tablets have a proven chemical-pharmaceutical quality and are a generic form of Inegy tablets. Inegy is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ezetimibe/Simvastatine Genepharm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 May 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse