COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

ZETIVASIM 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets (ezetimibe and simvastatin)

NL/H/5092/001-004/DC

Date: 27 January 2022

This module reflects the scientific discussion for the approval of ZETIVASIM 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets. The procedure was finalised on 15 November 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ACS	Acute coronary syndrome
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHD	Coronary heart disease
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
HofH	Homozygous Familial Hypercholesterolaemia
ICH	International Conference of Harmonisation
LDL	Low-density lipoprotein
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 ZETIVASIM 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets, from Anfarm Hellas A.E.

The products are indicated for:

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

Hypercholesterolaemia
ZETIVASIM 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)
ZETIVASIM 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 products Inegy 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets, which have been registered in Germany by Merck Sharp & Dohme Ltd since 2 April 2004 (original product). In the Netherlands, Inegy have been registered since 22 November 2004 by N.V. Organon via mutual recognition procedure DE/H/0496/001-004/MR.

The concerned member states (CMS) involved in this procedure were Cyprus and Greece.

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

II. QUALITY ASPECTS

II.1 Introduction

ZETIVASIM are white to off-white capsule shaped uncoated tablets in four strengths:

- 10 mg/10 mg - coded with “G” on one side and “321” on other side
- 10 mg/20 mg - coded with “G” on one side and “322” on other side
- 10 mg/40 mg - coded with “G” on one side and “323” on other side
- 10 mg/80 mg - coded with “G” on one side and “324” on other side

The product strengths contain as active substance 10 mg of ezetimibe and 10 mg, 20 mg, 40 mg or 80 mg of simvastatin, respectively.

The tablets of all strengths are packed in PVC-aluminium-OPA/aluminium blisters.

All tablet strengths are also packed in HDPE bottles with polypropylene cap and heat seal liner. The bottles contain a 2 g molecular sieve canister as desiccant.

The excipients are: lactose monohydrate, microcrystalline cellulose (E460), hypromellose (E464), croscarmellose sodium (E468), propyl gallate (E310), butyl hydroxyl anisole (E320), citric acid monohydrate (E330), sodium lauryl sulfate (E487) and magnesium stearate (E470b).

The four strengths are dose proportional with regard to simvastatin.

II.2 Drug Substance

II.2.1 Ezetimibe

One of the two active substances is ezetimibe, an established active substance described in the European Pharmacopoeia (Ph. Eur.). It is a white to off-white crystalline powder, which is freely soluble in ethanol and methanol but practically insoluble in water. Ezetimibe is a hygroscopic substance. The drug substance contains three asymmetric carbon atoms and therefore exhibits optical isomerism. The anhydrous crystalline form is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance ezetimibe. For ezetimibe, two ASMF-holders are involved. 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 manufacturing process of ezetimibe consists of five or seven stages, depending on the ASMF-holder. The syntheses descriptions of both ASMF-holders are in sufficient detail and sufficient chemistry is part of the regulatory synthesis route. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification for ezetimibe is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional in-house requirements. This specification applied by the MAH contains tests for appearance, solubility, identification, water content, melting range, specific optical rotation, heavy metals, related substances, assay, residual solvents, microbial enumeration test, particle size, specific impurities for material of ezetimibe manufacturer I, and a specific impurity and identification for material of ezetimibe manufacturer II.

The analytical procedures have been described in sufficient detail and are adequately validated. Batch analysis data demonstrating compliance with this specification have been provided for several batches of both ezetimibe manufacturers.

Stability of drug substance

Stability data on ezetimibe from manufacturer I have been provided for three commercial scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance up to 60 months at long-term conditions, and at accelerated conditions up to six months. Based on the data submitted, a retest period could be granted of 48 months when stored in an inner clear polyethylene bag and outer black polyethylene bag followed by triple laminated aluminium bag HDPE drum.

Stability data on ezetimibe from manufacturer II have been provided for three lower scale and three higher scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance up to 60 months at long-term conditions, and at accelerated conditions up to six months. Based on the data submitted, a retest period could be granted of 48 months when stored in a clear polyethylene bag in outer black polyethylene bag, in triple laminated bag + silica gel packs, put in a HDPE container.

II.2.2 Simvastatin

The second active substance in the products is simvastatin, an established active substance described in the European Pharmacopoeia (Ph. Eur.). This 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%). Simvastatin is a non-hygroscopic substance. No polymorphism has been reported in literature.

The CEP procedure is used for the active substance simvastatin. 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, and is in line with the Ph. Eur. and additional in-house requirements. The drug substance specifications applied by the drug product manufacturer are the same as those applied by the active substance manufacturer, these also include limits for residual solvents. The proposed limits for residual solvents are in line with ICH Q3C guideline. In addition, requirements for particle size and microbial limits are added. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for three years when stored in double polyethylene bags (outer black), with silica between the bags placed in a polyethylene container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with relevant European guidelines. The choice of excipients is justified and their functions are 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. Further, a justification has been provided for use of the drug products in the intended paediatric population (10 years and older).

The dissolution studies were conducted complementary to a 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 at three pH's. The dissolution method is demonstrated to be discriminative.

Based on bioequivalence studies carried out on the highest product strength (10 mg/80 mg; ezetimibe/simvastatin), a biowaiver is requested for the 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 processes consists of sifting, dry mixing, binder preparation, granulation, drying, blending and lubrication, compression and packaging of the product, and has been described in sufficient detail. For the 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg strengths the manufacturing process is considered to be a standard process, however, the 10 mg/80 mg strength does not correspond to a standard process as the drug load ezetimibe is below 2%.

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

Control of excipients

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

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The specifications includes tests for description, identification, average weight, dissolution, uniformity of dosage units, related substances, assay of butylated hydroxyl anisole and 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 product strength containing ezetimibe sourced from manufacturer I, and from three exhibit batches of each product strength containing ezetimibe sourced from manufacturer II from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug products

Stability information from accelerated (40°C/75% RH, up to 6 months), intermediate (30°C/65% RH, up to 12 months) and long term (25°C/60% RH, up to 24 months) is provided on at least three batches of all strengths for the proposed product packaged in the container closure systems proposed for marketing (Al/Al blisters and HDPE bottle). The conditions used in the stability studies are according to the ICH stability guideline. Based on the stability data provided, the proposed shelf life of 24 months with storage condition “Store below 25°C” with additional storage condition for the blisters: “Store in the original package in

order to protect from moisture" and for the bottles "Keep the bottles tightly closed and in the outer carton in order to protect from moisture" can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the materials, except lactose monohydrate, used in the formulation of ZETIVASIM are of animal and/or human origin. TSE / BSE declarations obtained from the drug substance manufacturer and excipients manufacturers have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that ZETIVASIM have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

The following post-approval commitments were made:
- The MAH commits to perform hold time studies on the commercial/validation batches of the product.
- The MAH commits to place first three commercial scale batches of ezetimibe and simvastatin 10 mg/10mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets and at least one batch per year (follow-up stability studies) will be tested at long term conditions to assure quality of the drug product. Additionally, the on-going stability studies at long term conditions will be continued up to the approved shelf life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since ZETIVASIM are 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

These products are generic formulations of Inegy which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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. A biowaiver was requested for the strengths of 10 mg/20 mg and 10 mg/40 mg.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products ZETIVASIM 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets (Glenmark Pharmaceuticals Ltd., India) were compared with the pharmacokinetic profiles of the reference products Inegy 10 mg/10 mg and 10 mg/80 mg (Merck Sharp & Dohme Corp., 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

Single dose bioequivalence studies under fasting conditions are considered sufficient to investigate bioequivalence of an immediate release fixed-dose formulation with systemic effect. The MAH adequately chose a study design which minimizes bias and is adequate to detect relevant differences between the two formulations. For the analysis of both ezetimibe and simvastatin, the fasting conditions are adequate as both active substances can be administered with or without food.

In both studies, analysis data were provided on unconjugated ezetimibe, total ezetimibe, simvastatin and simvastatin acid (β-hydroxy acid). This is acceptable. Ezetimibe (unconjugated) is the parent compound and ezetimibe-glucuronide (conjugated) is an active metabolite. Bioequivalence should be based on the parent compound as stated in the *Guideline on Investigation of bioequivalence*. In this public assessment report, data on total ezetimibe and simvastatin are shown.

Biowaiver of strengths

The MAH requested a biowaiver of strengths for the 10 mg/20 mg and 10 mg/40 mg strengths, based on the *Guideline on the investigation of bioequivalence*. The following criteria for a biowaiver have been met: the products are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same

and the composition of the strengths are quantitatively proportional. Furthermore, the provided *in vitro* dissolution studies were performed in accordance with the *Guideline on Investigation of Bioequivalence*. Both the 10/20 mg product and 10/40 mg product show similar drug release profiles to both the 10/10 mg and 10/80 strength.

In conclusion, conducting two bioequivalence studies using the 10/10 mg and 10/80 mg strengths is acceptable, and the results can be extrapolated to the other two strengths.

Bioequivalence studies

The choice of the reference products

The choice of the reference products in both bioequivalence studies has been justified. The formula and preparation of the bioequivalence batches are identical to the formula proposed for marketing.

Bioequivalence study I – 10 mg/80 mg strength under fasting conditions

Design

A comparative, open label, randomised, single dose, reference replicated crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-45 years. 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 washout periods of 11 days.

Blood samples were drawn 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 post dose.

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.

Results

Three subjects were withdrawn from the study due to a positive breath alcohol test (one subject) and not reporting back for the third period (two subjects). 45 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe after administration of the 10 mg/80 mg formulations 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 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of simvastatin after administration of the 10 mg/80 mg formulations 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 – 10 mg/10 mg strength under fasting conditions

Design

A comparative, open label, randomised, single dose, reference replicated crossover bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 18-45 years. 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 washout periods of 12 days.

Blood samples were drawn 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 post dose.

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.

Results

Two subjects were withdrawn from the study due to a positive breath alcohol test (one subject) and not reporting back for the second period (one subjects). 70 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe after administration of the 10 mg/80 mg formulations 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	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 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of simvastatin after administration of the 10 mg/80 mg formulations 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	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*

<u>Conclusion on bioequivalence studies</u>

For both 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 for total ezetimibe and simvastatin. Based on the submitted bioequivalence studies, ZETIVASIM 10 mg/10 mg and

10 mg/80 mg tablets are considered bioequivalent with Inegy 10 mg/10 mg and 10 mg/80 mg tablets.

The MEB has been assured that the bioequivalence study has 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 ZETIVASIM.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	• Rhabdomyolysis/myopathy • Abnormal liver function
Important potential risks	• New onset diabetes mellitus/impaired glucose metabolism
Missing information	• None

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 products Inegy. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the 10 mg/10 mg and 10 mg/80 mg products is similar to the pharmacokinetic profile of the reference products. A biowaiver has been granted for the 10 mg/20 mg and 10 mg/40 mg strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Ezetimibe/Simvastatin Glenmark 10mg/10mg, 10 mg/20mg, 10mg/40mg, 10mg/80mg tablets (NL/H/4048/001-4/DC) for content, design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

ZETIVASIM 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Inegy 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets. Inegy are well-known medicinal products with established favourable efficacy and safety profiles.

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 ZETIVASIM with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 November 2021.

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