CBG MEB

Public Assessment Report

Scientific discussion

Ezetimibe/Simvastatine SUN 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets

(ezetimibe and simvastatin)

NL/H/3369/001-004/DC

Date: 18 April 2017

This module reflects the scientific discussion for the approval of Ezetimibe/Simvastatine SUN 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets. The procedure was finalised on 13 May 2016. 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
BP	British Pharmacopoeia
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ezetimibe/Simvastatine SUN 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg tablets from Sun Pharmaceutical Industries Europe B.V.

The following indications are approved:

Prevention of cardiovascular events
Ezetimibe/Simvastatine SUN 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 SUN tablets are 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 SUN tablets are 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.

The concerned member states (CMS) involved in this procedure were:
10 mg/10 mg - Czech Republic, Germany, Greece, France, Poland and the Slovak Republic
10 mg/20 mg - Czech Republic, Germany, Greece, Spain, France, Poland and the Slovak Republic
10 mg/40 mg - Czech Republic, Germany, Greece, Spain, France, Poland and the Slovak Republic
10 mg/80 mg - Germany

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

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Simvastatine SUN is a white to off white capsule-shaped uncoated tablet in four strengths:
10 mg/10 mg - debossed with “L” on one side and plain on the other side
10 mg/20 mg - debossed with “I” on one side and plain on other side
10 mg/40 mg - debossed with “F” on one side and plain on the other side
10 mg/80 mg - debossed with “F” on one side and plain on the other side (the tablets can be distinguished from the 10 mg/40 mg strength by size)

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

The tablets are packed in OPA/Al/PVC/Al blisters.

The excipients are butylated hydroxyanisole (E320), citric acid monohydrate (E330), croscarmellose sodium (E468), hypromellose (E464), lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E461) and propyl gallate (E310).

The composition of the 4 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 ezetimibe is an established active substance not described in the European, British or United States Pharmacopoeia (Ph.Eur., BP, USP). The drug substance is a white to off-white crystalline powder, practically insoluble in water and soluble in methanol. Ezetimibe has three chiral centres, consequently it 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 for this 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 manufacturing process consisting of 7 steps is described in sufficient detail. The proposed starting material is acceptable, intermediate stages are adequately controlled and the active substance is sufficiently characterised.

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 3 batches.

Stability of drug substance
Three lower scale batches have been stored for 5 years at 2-8°C and 6 months at 40°C/75% RH, and three higher scale batches for 4 years at 2-8°C and 6 months at 40°C/75% RH. All stability results were in accordance with the set drug substance specification. Based on the provided stability data the claimed retest period of 4 years if stored at 2-8°C in the proposed packaging can be accepted.

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. It is an optically active compound.

The CEP procedure is used for this 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 and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 5 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. All excipients used are well-known and are considered safe in the proposed concentrations. The Alu-Alu blister packaging is usual and acceptable. The simvastatin content during manufacture is optimised.

Two bioequivalence studies have been performed using the 10 mg/10 mg and 10 mg/80 mg strength of the test and reference product. All comparative dissolution testing results between the test and reference bio-batches are >85% in 15 min at pH 7.0 medium including 0.5% Sodium Lauryl Sulphate (SLS). The dissolution profiles for test and reference products in the recommended dissolution test media without SLS (pH 1.2, pH 4.5 and pH 6.8) were similar but very low (<10% in 30 min at all 3 pH values). This is accepted as poor solubility is related to both drug substances rather than the formulation.

Based on bracketing approach the Ezetimibe/Simvastatine SUN tablets satisfy the conditions for a waiver of separate bioequivalence study with the other strengths (10 mg/20 mg and 10 mg/40 mg) of the formulation.

Manufacturing process
The manufacture comprises steps of sifting of the main excipients, preparation of the drug dispersion, top spray granulation and drying, spraying of the antioxidants solution on the granules, dry screening, blending and lubrication, and compression. It is considered a non-standard process in view of the relatively low ezetimibe content in the 10 mg/80 mg strength. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches per strength in accordance with the relevant European guidelines.

Control of excipients
All excipients used comply with the respective Ph.Eur. monograph specifications. 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 of ezetimibe and simvastatin, identification of antioxidant, identification of propyl gallate, identification of citric acid monohydrate, uniformity of dosage units, loss on drying, dissolution, microbial enumeration test and microbial test for specified organisms, content of antioxidant, content of propyl gallate, content of citric acid monohydrate, assay, related substances and residual solvents. 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 3 batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
The stability studies are based on 3 stability batches per strength, and stability data are available at 40°C/75% RH (6 months), 30°C/65% RH (12 months) and 25°C/60% RH (18 months). After 18 months long-term conditions, a decrease of simvastatin is observed in all strengths. After 12 months intermediate conditions in general moderate simvastatin decreases are observed. The MAH attributes the simvastatin assay losses to thermal degradation of simvastatin in the presence of oxygen. The product is photostable. Based on the available stability data the shelf-life accepted is 18 months if stored in aluminum-aluminum blisters not above 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate used in the formulation is of animal 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 SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe/Simvastatine SUN 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 a 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 SUN (Sun Pharmaceutical Industries Europe B.V, the Netherlands) 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

Biowaiver

The amount of ezetimibe in the lowest strength (10 mg/10 mg) is disproportional to the higher strengths and the amount is 10% of the weight of the core tablet. Therefore, the MAH submitted a bioequivalence study with the highest (10 mg/80 mg) and the lowest (10 mg/10 mg) strength considering a bracketing approach as per current applicable CHMP "Guidelines on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, January 2010)", section 4.1.6: *strength to be investigated; bracketing approach; page no. 13/27 "Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies".* Based on the bracketing approach, the test products satisfy the conditions for waivers of separate bioequivalence studies with the other strengths (10 mg/20 mg and 10 mg/40 mg) of the formulation. Any differences in composition in the remaining strengths are covered by the two conducted studies.

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

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

Bioequivalence studies

Bioequivalence study I – Ezetimibe/Simvastatine SUN 10 mg/80 mg vs Inegy 10 mg/80 mg under fasting conditions
Design
The study was conducted in two groups:

- Group 1 carried out a conventional 2 way crossover design under fasted conditions; 54 healthy subjects, aged 19-43 years were dosed for the evaluation of free ezetimibe. Each subject received a single dose (10 mg ezetimibe and 80 mg simvastatin) of one of the 2 fixed dose formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.
- Group 2 conducted a replicate design to assess the bioequivalence of simvastatin. The study was carried out under fasted conditions in 50 healthy subjects, aged 19-43 years. Each subject received a single dose (10 mg ezetimibe and 80 mg simvastatin) of one of the 2 fixed dose formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 4 dosing periods, separated by a washout period of 14 days.

Blood samples of group 1 were collected pre-dose and at 0.167, 0.33, 0.5, 0.67, 0.83, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 16, 24, 36, 48 and 72 hours after administration of the products.
For group 2, samples were drawn pre-dose and at 0.167, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 11, 16, 24, 36 and 48 hours post dose.

This non-standard approach using 2 groups for the design of the study is acceptable. The simvastatin evaluation was performed using a full replicate design, which is common for highly variable drug products like simvastatin. The intra-subject variability was high (>30%) for the reference product. Therefore, as predefined in the protocol, the full replicate design allows the bioequivalence acceptance interval for C_{max} to be widened. Sampling schemes for both ezetimibe (up to 72 hours) and simvastatin (up to 48 hours) are adequate. As the drug can be taken with or without food, a study under fasting conditions is appropriate.

Results
In group 1, a total of 5 subjects were withdrawn and 1 subject dropped-out due to personal reasons. Therefore 48 subjects were eligible for pharmacokinetic analysis.

In group 2, there were 6 drop-outs due to personal reasons, and 6 subjects were withdrawn. 38 subjects completed all periods of the study. 43 subjects completed at least 2 periods of the study and were eligible for pharmacokinetic and statistical analyses of simvastatin.

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

Treatment N=48	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	67.7 ± 31.6	70.1 ± 33.6	6.2 ± 3.6	1.5 (0.33 - 12.0)
Reference	68.1 ± 35.2	69.6 ± 36.7	6.3 ± 3.0	0.9 (0.33 - 9.0)
***Ratio (90% CI)**	1.00 (0.92 - 1.08)	0.99 (0.91 - 1.08)	0.96 (0.85 - 1.09)	--
$AUC_{0-\infty}$ 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 under fasted conditions.

Treatment N=38	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test (1st time)	176 ± 114	181 ± 115	56.1 ± 38.2	4.5 (2.0 - 5.0)
Test (2nd time)	160 ± 77.7	164 ± 77.7	57.2 ± 33.5	4.5 (0.83 - 6.0)
Reference (1st time)	183 ± 88.6	190 ± 90	49.2 ± 27.3	4.5 (3.5 - 8.0)
Reference (2nd time)	184 ± 92.9	190 ± 93.7	52.2 ± 36.8	4.5 (1.25 - 5.0)
***Ratio (90% CI)**	0.89 (0.82 - 0.96)	0.82 (0.82 - 0.96)	1.09 (0.99 – 1.20)	--
$AUC_{0-\infty}$ 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 SUN 10 mg/10 mg vs Inegy 10 mg/10 mg under fasting conditions

Design

An open label, balanced, randomised, two treatment, two sequence, four period, single dose fully replicate crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 20-42 years. Each subject received a single dose (10 mg ezetimibe and 10 mg simvastatin) of one of the 2 fixed dose formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 4 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.66, 0.83, 1.0, 1.33, 1.66, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The study design is acceptable; the wash-out period is long enough, the sampling period long enough and sampling scheme is adequate to estimate pharmacokinetic parameters. The choice of a replicate

design study was based on the high intra individual variability in the absorption rate of simvastatin which was found in earlier studies.

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

Treatment N=45	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h
Test (1st time)	81822.55 ± 45749.77	86187.28 ± 49974.06	5216.36 ± 2905.97	4.50 (0.33 – 12.00)
Test (2nd time)	83122.52 ± 45663.98	86402.23 ± 48497.29	5376.88 ± 2853.13	5.00 (0.33 – 12.00)
Reference (1st time)	81486.71 ± 47442.39	85934.77 ± 50161.93	5752.85 ± 3018.67	4.50 (0.33 – 11.00)
Reference (2nd time)	77341.61 ± 48435.50	80201.08 ± 53429.47	5420.10 ± 3778.67	5.00 (0.50 – 36.00)
***Ratio (90% CI)**	1.05 (0.99 – 1.12)	1.06 (0.99 – 1.14)	0.97 (0.90 – 1.04)	--
CV (%)	24.18	26.79	28.27	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 4. 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 (1st time)	16.97 ± 9.44	17.90 ± 9.57	7.68 ± 3.93	0.83 (0.50 – 4.50)
Test (2nd time)	18.32 ± 10.55	19.23 ± 10.82	8.72 ± 6.15	1.00 (0.33 – 3.00)
Reference (1st time)	17.79 ± 10.75	19.10 ± 11.60	7.2 ± 4.25	1.00 (0.50 – 3.50)
Reference (2nd time)	18.18 ± 10.20	19.37 ± 10.45	7.08 ± 5.15	1.00 (0.55 – 3.00)
***Ratio (90% CI)**	0.98 (0.91 – 1.06)	0.97 (0.90 – 1.05)	1.16 (1.05 – 1.27)	--
CV (%)	32.77	31.52	41.33	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The reference product Inegy was found to be highly variable for simvastatin C_{max} with an intra-subject variability exceeding 30% in both studies. Widening of the acceptance intervals was allowed but, based on the study results, proved not to be necessary. 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 both active substances. Based on the submitted bioequivalence studies Ezetimibe/Simvastatine SUN tablets are considered bioequivalent with Inegy tablets.

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 SUN.

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 cyclosporin
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 10 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 4 participants, followed by two rounds with 10 participants each. The participants were men and women over 18 years of age. The test was performed in English. There were sufficient questions about critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. Three additional questions were formulated with regards to positive, negative and stylistic feedback about the readability of the PL.
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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezetimibe/Simvastatine SUN tablets have a proven chemical-pharmaceutical quality and are generic forms 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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 May 2016.

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
NL/H/3369/001-003/DC	Change name in PL	PL	23-11-2016	Approval	--