COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rosuvastatine/ezetimibe EGIS 5 mg/10 mg, hard capsules

(rosuvastatin zinc/ezetimibe)

NL/H/3016/004/DC

Date: 12 September 2019

This module reflects the scientific discussion for the approval of Rosuvastatine/ezetimibe EGIS 5 mg/10 mg, hard capsules. The procedure was finalised on 8 July 2017. 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
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{72}	Area under the plasma concentration-time curve from time zero to t=72
CI	Confidence Interval
C_{max}	Maximum plasma concentration
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
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ESC	European Society of Cardiology
EU	European Union
FDC	Fixed-dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HoFH	Homozygous Familial Hypercholesterolaemia
ICH	International Conference of Harmonisation
LDL-C	Low-Density Lipoprotein Cholesterol
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
TEAE	Treatment-Emergent Adverse Events
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rosuvastatine/ezetimibe EGIS 5 mg/10 mg, hard capsules from Egis Pharmaceuticals Plc.

The product is indicated as adjunct to diet for treatment of primary hypercholesterolemia as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed-dose combination, but as separate products.

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

This decentralised procedure concerns an application is based on Article 8(3) of Directive 2001/83/EC, a full-mixed application, where the individual active substances (monocomponents) have established clinical use as well as regulatory approval.

Both active substances are approved as monotherapy in the management of (different types of) hypercholesterolaemia. The innovator products Crestor (rosuvastatin) and Ezetrol (ezetimibe) were first registered in the EU in 2002 through procedures NL/H/0343/001-004/DC and Ezetrol DE/H/0396/001/MR, respectively. The proposed product is the first rosuvastatin-ezetimibe fixed-dose combination. Co-therapy of statins and ezetimibe is currently only available as the fixed-dose combination Inegy (DE/H/0496/001-004/MR), which contains simvastatin and ezetimibe in the strengths of 10/10 mg, 20/10 mg, 40/10 mg and 80/10 mg.

The use of rosuvastatin and ezetimibe monotherapy as well as ezetimibe + statin combination therapy is supported by the guideline of the European Society of Cardiology (ESC), based on the pharmacological synergistic mechanisms of action (combining rosuvastatin with ezetimibe reduces low-density lipoprotein cholesterol by an additional 15 to 20%). Furthermore, ezetimibe is approved for combined treatment with statins as adjunct to diet for patients with homozygous familial hypercholesterolaemia (HoFH) and for patients with primary hypercholesterolaemia not sufficiently controlled on statin alone. The registered simvastatin/ezetimibe containing Inegy is indicated as adjunct to diet in the treatment of primary (familial and non-familial) hypercholesterolemia or mixed hyperlipidaemia as add-on or substation therapy and as adjunct to diet in the treatment of HoFH. This is considered a justification for the combined use of rosuvastatin and ezetimibe.
The MAH further argued that in general fixed-dose combinations could increase therapeutic adherence, and that compliance and the use of less packaging material would result in less waste production and a more protected environment.

Instead of the already in the EU approved calcium salt, the MAH has chosen zinc salt for rosuvastatin development. Rosuvastatin zinc has not yet been approved in the EU. According to Directive 2001/83/EC, as amended, products containing different salts of the same active substance may be considered essentially similar, if bioequivalence has been proven. It should further be proven that the safety profile of the new zinc salt is similar to the already approved calcium salt.

The 5 mg/10 mg strength applied for in this procedure is part of a larger range of strengths by the same company. In a previous application (NL/H/3016/001-003/DC) registration of the strengths 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg was pursued. Approval of the above mentioned products was based on the demonstration of bioequivalence with co-administration of the separate reference products Crestor and Ezetrol.

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

The marketing authorisation has been granted pursuant to Article 8(3), full-mixed application, of Directive 2001/83/EC. According to Part II of Annex I to the Directive mixed marketing authorisations shall mean: *marketing authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I*

of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis.

No dedicated studies in the target population have been performed with this product. This is however not necessary taking into account the substitution indication. No new non-clinical studies were performed in support of this application. Non-clinical evaluation of the pharmacology, pharmacokinetics and toxicology of this medicinal product was based on literature references.

In order to support the application, a bioequivalence study has been performed to compare the rate and extent of absorption of Rosuvastatine/ezetimibe EGIS 5 mg/10 mg and the active substances administered at the same time but as separate tablets. Furthermore, the MAH provided a clinical overview which was based on the clinical overviews of the previous registration procedures of the fixed-dose combinations Rosuvastatine/ezetimibe EGIS 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg hard capsules. No clinical efficacy studies with the co-administration of the two active substances have been performed by the MAH. Clinical evaluation of the rosuvastatin/ezetimibe hard capsules is based on the presented literature data relevant to each active substance and references to the combinations of statins and ezetimibe published in the scientific literature with the aim of proving the clinical benefit provided by the combination and supporting the proposed indication.

No Paediatric Investigation Plan (PIP) has been submitted. A product specific waiver has been granted by the EMA for Rosuvastatine/ezetimibe EGIS for the treatment of hypercholesterolemia in all subsets of the paediatric population, on the grounds that rosuvastatin/ezetimibe fixed-dose combination does not represent a significant therapeutic benefit over existing treatments for paediatric patients (EMEA-001447-PIP01-12, waiver decision number P/0131/2013).

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine/ezetimibe EGIS 5 mg/10 mg is an unmarked, self-closing Coni Snap type, size 0, hard gelatin capsule with yellow coloured cap and white coloured body filled with two tablets.

The capsules contain 5 mg rosuvastatin (as zinc) and 10 mg of ezetimibe.

The capsules are packed in cold OPA/AL/PVC//Al blisters.

The excipients are:
Core - silicified microcrystalline cellulose (microcrystalline cellulose (E460) and colloidal anhydrous silica (E551)), colloidal anhydrous silica (E551), magnesium stearate (E572), povidone (E1201) croscarmellose sodium (E468), microcrystalline cellulose (E460), mannitol (E421), sodium lauryl sulfate (E514), low-substituted hydroxypropyl cellulose (E463)
Capsule shell cap – titanium dioxide (E171), yellow iron oxide (E172), gelatine
Capsule shell body – titanium dioxide (E171), gelatine

II.2 Drug Substances

Rosuvastatin zinc
The active substance rosuvastatin zinc is not described in any pharmacopoeia. It is a white powder, which is freely soluble in ethanol, methylene chloride and dimethylformamide and slightly soluble in water and 2-propanol. Rosuvastatin zinc has two chiral centres, thus theoretically four diastereoisomers exist. Rosuvastatin zinc salt produced by the manufacturer has a 3R,5S geometry. Polymorphic form I is used. The substance is hygroscopic, and sensitive to light and humidity.

The Active Substance Master File (ASMF) procedure is used for rosuvastatin zinc. 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 synthesis covers several synthetic steps. Sufficient information on the manufacturers and specifications has been provided. Specifications of the intermediates, critical process parameters and in-process control tests from the starting materials have been laid down. The carry over of potential impurities and residual solvents has been adequately discussed.

Quality control of drug substance
The drug substance specification has been established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for at least three batches of rosuvastatin zinc.

Stability of drug substance
Three batches have been stored for 18 months at 25°C/60% RH and 6 months at 40°C/75% RH. Three batches have been stored for 3 months at 25°C/60% RH and 3 months at 40°C/75% RH.
The MAH has demonstrated that the polymorphic form of the drug substance does not change during storage. All stability results were in accordance with the set drug substance specification. Based on the provided stability data a re-test period of 18 months if stored in the proposed packaging at 2-8°C can be accepted.

Ezetimibe
The active substance ezetimibe is not described in any pharmacopoeia. It is a white to off-white crystalline powder which is practically insoluble in water. Ezetimibe has three chiral centres in the molecule and hence it exhibits optical isomerism. The anhydrous crystalline polymorphic form is used.
The Active Substance Master File (ASMF) procedure is used for both manufacturers of ezetimibe.

Manufacturing process
The first manufacturer produces ezetimibe in seven stages. For all steps numerous and adequate in-process controls are applied. Appropriate specifications are applied for all intermediary stages.
The process of the second manufacturer includes three chemical synthesis steps and one final purification step, which have been described in sufficient detail.

Quality control of drug substance
All proposed drug substance specifications are acceptable. For all analytical methods full descriptions and validation data have been provided. For the drug substances from both manufacturers at least three batches have been analysed, demonstrating compliance with the specification.

Stability of drug substance
For the first supplier, three lower scale batches have been stored for 5 years at 2-8°C and 6 months at 40°C/75% RH, and three larger scale batches for 4 years at 2-8°C and 6 months at 40°/75% RH. All stability results were in accordance with the set drug substance specification. Based on the provided stability data the claimed re-test period of 4 years if stored at 2-8°C in the proposed packaging can be accepted.
For the second manufacturer three batches have been stored for 60 months at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH. All stability results met the set requirements. Based on these data a re-test period of 5 years without specific storage temperature can be granted.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development for the proposed product is well-described. The aim of formulation development was to obtain a hard gelatine capsule containing two unique tablets of the two separate active ingredients in order to guarantee the rapid dissolution of ezetimibe and to ensure the best stability for both drug substances. The development of the rosuvastatin zinc 5 mg tablets and

ezetimibe 10 mg uncoated tablets has been adequately described. The MAH chose to compress both ezetimibe and rosuvastatin zinc final granule blends into tablets before inclusion into the capsules.

The bio-equivalence study between the proposed 5 mg rosuvastatin zinc/10 mg ezetimibe hard capsule product and the separate originator products (Crestor 5 mg, Ezetrol 10 mg) has been accepted. Comparative dissolution studies have been performed for the test biobatch (5 mg/10 mg hard capsule) and two separate reference bio-batches. Sufficient details on the pharmaceutical development have been provided.

Manufacturing process
Rosuvastatin zinc 5 mg tablets: The manufacturing process consists of usual steps of weighing and sieving, pre-blending, granulation, blending, sieving, final blending and compression. Batch formulae are given for batch sizes for rosuvastatin granules, rosuvastatin final blend, and rosuvastatin tablets, in accordance with the product formulae. Process validation data on the product have been presented for three pilot scaled batches for both strengths in accordance with the relevant European guidelines.
Ezetimibe 10 mg tablets: A crystalline ezetimibe suspension is prepared by precipitating an alcoholic solution of ezetimibe with an anti-solvent in the presence of a binder and a surfactant. The inner phase granules are coated with this suspension. The coated granulate is then blended. The manufacturing process for ezetimibe tablets is considered a non-standard process. The validation results from three batches showed compliance with the set acceptance criteria.

Bulk rosuvastatin 5 mg film-coated tablets and ezetimibe 10 mg tablets are subsequently packed with an automatic encapsulating machine. The proposed in-process controls are considered adequate and acceptable.

Control of excipients
Adequate specifications are applied for all excipients. The colourants used in the hard gelatin capsule, yellow iron oxide and red iron oxide, meet the specifications in Commission regulation (EU) 231/2012 and USP/NF.

Quality control of drug product
Adequate specifications are applied for the hard capsule drug product with tests on appearance of capsule, appearance of capsule filling, average mass/uniformity of mass of capsule filling, uniformity of dosage units, drug substances identification, water content, dissolution for both drug substances, related substances for both drug substances, and microbiological quality. Batch analytical data of two batches per strength have been provided, demonstrating compliance with the specification.

Stability of drug product
Three batches have been tested at 25°C/60% RH and 40°C/75% RH, for 24 respectively 6 months. Significant changes were not found either in the physical or in the chemical test characteristics of the product. Based on the stability data provided the claimed shelf-life of 36 months in the proposed blister packaging can be accepted. The restriction of the storage condition to '*Not above 30°C'* is justified in view of the requirement in the Ph. Eur. monograph on capsules. The additional storage labelling is acceptable in view of the forced degradation results, including photostability testing: '*Store in the original package in order to protect from light and moisture'.*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Valid TSE CEP versions are applicable for magnesium stearate from animal origin (only ezetimibe tablets) and all gelatin sources.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rosuvastatine/ezetimibe EGIS hard capsules have 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 Rosuvastatine/ezetimibe EGIS is intended for substitution of both active ingredients used in separate tablets, its use 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 contains two established active substances, which are available on the European market. No new non-clinical studies were provided. This is agreed, as the pharmacology of rosuvastatin and ezetimibe is well-known and also the combination of rosuvastatin and ezetimibe is well-known.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rosuvastatin and ezetimibe are well-known active substances with established efficacy and tolerability.

The clinical development program was designed to evaluate the comparative bioavailability between Rosuvastatine/ezetimibe EGIS hard capsules and tablets containing the separate active substances, taken concomitantly. For this application, the MAH has submitted a bioequivalence study, which is discussed below. The pharmacological rationale for the use of rosuvastatin and ezetimibe in combination is adequately justified in the published literature. A bibliographical data analysis regarding efficacy and safety has been presented in this application. No further studies have been performed and none are considered necessary.

IV.2 Pharmacokinetics

The pharmacokinetic (PK) properties of both active substances are well known. The clinical overview provides an elaborate overview of pharmacokinetic data on rosuvastatin, zinc, and ezetimibe.

To support the application, the MAH has submitted the report of a single dose, randomised, two-way crossover bioequivalence study comparing the test product Rosuvastatine/ezetimibe EGIS 5 mg/10 mg hard capsules (Egis Pharmaceuticals Plc., Hungary) with the reference products Crestor 5 mg film-coated tablets (AstraZeneca Ltd, UK) and Ezetrol 10 mg tablets (MSD-SP Limited, UK) taken concomitantly under fasting conditions.
The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design
Bioequivalence was investigated with a single centre, randomised, single dose, laboratory-blinded, 2-period, crossover study in 66 healthy white male subjects. Treatment 1 was a single Rosuvastatine/ezetimibe EGIS 5 mg/10 mg capsule, and treatment 2 consisted of a Crestor 5 mg film-coated tablet and a tablet of Ezetrol 10 mg taken concomitantly. After a supervised overnight fast, a single dose of the assigned formulations was orally administered in the morning. There were 2 dosing periods, separated by a washout period of 14 days.

For analysis of rosuvastatin blood samples were collected pre-dose and at 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 12.0, 16.0, 24.0, 48.0, and 72.0 hours after drug administration.

For total ezetimibe and unconjugated ezetimibe blood samples were collected pre-dose and at 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 20.0, 24.0, 48.0, and 72.0 hours after drug administration.

The design of the study is acceptable. The washout period (more than 10 elimination half-lives) was long enough to prevent from carry-over effect. The sampling schedule was adequate to characterise the pharmacokinetic profile of rosuvastatin, ezetimibe and total ezetimibe. The two active substances may be taken without reference to food intake. The bioequivalence study under fasting conditions is in accordance with the CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and 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.

Results
A total of 61 subjects completed all study periods. In accordance with the study protocol, data from all subjects who completed the study and for whom the PK profile was adequately characterised were used for PK and statistical analyses.

One subject, who was dosed in both periods, but has not completed period 1 was included in the PK and statistical analysis. Since blood samples were drawn up to 10 hours post-dose in period 1, this subject was included in the PK population for C_{max} and T_{max} only, for rosuvastatin and total ezetimibe, but excluded from the PK population for unconjugated ezetimibe. Therefore 62 subjects were included in the PK and statistical population for rosuvastatin and total ezetimibe and 61 subjects for unconjugated ezetimibe.

The 72 hour post-dose blood draw was missed in period 1 for two subjects. As per protocol, the AUC_{0-72} could not be calculated (for unconjugated and total ezetimibe) for these subjects. For rosuvastatin, the elimination rate constant for a subject could not be properly estimated. This subject was excluded from all analyses involving AUC_{0-inf}, Residual area, Kel and $T_{1/2}$ el.

Table 1: Pharmacokinetics data for rosuvastatin-ezetimibe

Rosuvastatin		
Pharmacokinetics Parameters	**Arithmetic Mean (+/-SD)**	
	Test product	**Reference product**
$AUC_{(0-t)}$ (pg·h/mL)	26782.64 (12546.73)	25112.74 (13173.11)
$AUC_{(0-\infty)}$ (pg·h/mL)	27583.03 (12317.57)	25752.94 (12815.60)
Cmax (pg/mL)	3341.32 (1573.59)	3063.42 (1440.65)
Tmax (hr) [1]	4.50 (0.500-5.00)	4.50 (2.50 -5.50)

[1] Median, (Min, Max)

Unconjugated Ezetimibe		
Pharmacokinetics Parameters	**Arithmetic Mean (+/-SD)**	
	Test product	**Reference product**
$AUC_{(0-72)}$ (pg·h/mL)	65037.02 (20451.73)	68410.67 (22484.00)
Cmax (pg/mL)	3923.78 (1968.95)	3875.49 (1576.80)
Tmax (hr) [1]	5.00 (0.500-24.0)	5.00 (0.500-48.1)

[1] Median, (Min, Max)

Total Ezetimibe		
Pharmacokinetics Parameters	**Arithmetic Mean (+/-SD)**	
	Test product	**Reference product**
$AUC_{(0-72)}$ (pg·h/mL)	634.16 (241.12)	648.42 (199.55)
Cmax (pg/mL)	57.83 (19.43)	73.22 (26.88)
Tmax (hr) [1]	1.50 (0.750-5.50)	1.00 (0.500-5.00)

[1] Median, (Min, Max)

Table 2: Bioequivalence evaluation of rosuvastatin and unconjugated ezetimibe

Rosuvastatin			
Pharmacokinetics parameter	**Geometric Mean Ratio Test/Ref**[1]	**Confidence Intervals**	**CV%**[2]
$AUC_{(0-t)}$ (pg·h/mL)	108.45%	101.84% to 115.49%	20.98%
$AUC_{(0-\infty)}$ (pg·h/mL)	108.43%	102.04% to 115.23%	20.07%
Cmax (pg/mL)	109.69%	101.57% to 118.47%	26.02%

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Unconjugated Ezetimibe			
Pharmacokinetics parameter	**Geometric Mean Ratio Test/Ref**[1]	**Confidence Intervals**	**CV%**[2]
$AUC_{(0-72)}$ (pg·h/mL)	96.12%	92.40% to 99.98%	12.84%
Cmax (pg/mL)	97.99%	89.57% to 107.21%	30.32%

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Table 3: Comparative bioavailability data of total ezetimibe

Total Ezetimibe			
Pharmacokinetics parameter	**Geometric Mean Ratio Test/Ref[1]**	**Confidence Intervals**	**CV%[2]**
$AUC_{(0-72)}$ (pg·h/mL)	96.11%	92.81% to 99.54%	11.39%
Cmax (pg/mL)	79.00%	73.28% to 85.16%	25.36%

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Conclusion on bioequivalence study
The bioequivalence is shown appropriately based on unconjugated ezetimibe and rosuvastatin.
The 90% CI for the Test/Reference ratios of geometric means for $AUC_{(0-72)}$ (92.40 - 99.98%) and C_{max} (89.57% - 107.21%) of unconjugated ezetimibe, and AUC_T (101.84% - 115.49%) and C_{max} (101.57% - 118.47%) of rosuvastatin are completely contained within the acceptance range of 80.00-125.00%. Bioequivalence is established for the product

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 Clinical efficacy

The Rosuvastatine/ezetimibe EGIS combination capsule was submitted to register a new strength of Rosuvastatine/ezetimibe EGIS, namely 5 mg rosuvastatin/10 mg ezetimibe, based on the approved documentation of the rosuvastatin and ezetimibe 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg hard capsules. No clinical efficacy studies with the co-administration of the two mono-components have been performed by the MAH. Therefore, clinical evaluation of rosuvastatin/ezetimibe hard capsules is based on literature data relevant to each active substance and references to the combinations of statins and ezetimibe published in the scientific literature with the aim of proving the clinical benefit provided by the combination.

Justification of the pharmacological and clinical rationale
The advantage of this combination for substitution of the mono-components is simplification of therapy by decreasing the number of individual dose units to be taken by the patient, which may lead to improved compliance to long-term therapy. The rationale of combining both components is evident, as both components provide low-density lipoprotein cholesterol (LDL-C) lowering effects by different mechanisms of action. Current guidelines (such as the ESC/EAS guideline[1]) recommend combinations of statins with other lipid lowering drugs for combination therapy including the combination of a statin and ezetimibe. Also, the concomitant use of ezetimibe with statins is already reflected in the indication of ezetimibe.

Relevant contribution of all components to the desired therapeutic effect
The MAH has discussed studies to support the beneficial lipid lowering effect of this specific combination. The ACTE study performed by Bays et al.[2] showed additional LDL-C lowering effect of ezetimibe as add-on therapy to 5 mg rosuvastatin compared to uptitration of monotherapy of rosuvastatin. A prospective randomized open-label study performed by Masuda et al.[3], resulted in a

1 European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011 Jul;32(14):1769-818
2 Bays HE, Davidson MH, Massaad R, et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). Am J Cardiol. 2011 Aug 15;108(4):523-30
3 Masuda J1, Tanigawa T, Yamada T, et al. Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease. Int Heart J. 2015 May 13;56(3):278-85

significant reduction in coronary plaques compared with the same 5 mg dose rosuvastatin monotherapy. Also, additional LDL-C lowering effect of the combination was shown in this study.

Overall, the MEB considers that the provided data is sufficient in terms of fulfilling the first two requirements for a 5 mg rosuvastatin and 10 mg ezetimibe combination intended for a substitution indication. However, the MEB considers that the need for such a combination therapy may be less certain than for the other dose strengths considering that the prescription data in support of the real life use for this new lower strength of 5 mg rosuvastatin/10 mg ezetimibe is limited, likely considering that most patients have been up-titrated already from the 5 mg starting dose of rosuvastatin to higher doses (with subsequent addition of ezetimibe). These prescription data indicate that the percentage of 5 mg rosuvastatin co-prescribed with ezetimibe 10 mg is limited to 0.3 % - 3.5% in the different countries, which is much lower compared to the percentage of the higher strengths of rosuvastatin co-prescribed with ezetimibe (up to 25.6%). Although this limitation we are willing to accept this combination also considering that other combinations with a starting dose of statin have been approved e.g. for simvastatin and atorvastatin.

IV.4 Clinical safety

Both components are well known with respect to their safety profile. The safety of rosuvastatin and ezetimibe has already been established during the clinical development of each substance. In the clinical development of ezetimibe, ezetimibe was also routinely administered in combination with statins with no evidence of safety concerns.

Bioequivalence study
In order to support the present application, a bioequivalence study of rosuvastatin/ezetimibe 5 mg/10 mg capsule and Crestor 5 mg film-coated tablet co-administered with Ezetrol 10 mg tablet has been performed. 66 healthy males were randomised and dosed; they were evaluated as the safety population of the study. A total of 26 treatment-emergent adverse events (TEAEs) were reported by 17 of the 66 subjects who received at least one dose of the study medication. The breakdown by treatment group is as follows: 16 TEAEs reported by 16.7% (n=11) of the 66 subjects who received Treatment A (Test) and 10 TEAEs reported by 12.9% (n=8) of the 62 subjects who received Treatment B (Reference). The most commonly reported TEAE was “Headache” reported by 10.6% (n=7) of subjects who constituted the safety population. This TEAE was only reported by subjects following the administration of Treatment B. However, there is no safety concern as headache is expected with the use of Crestor and Ezetrol.

Of the 26 TEAEs reported, 18 were graded as mild, 6 were graded as moderate, and 2 were graded as severe in severity. Of the 26 TEAEs reported, the relationship of 1 was judged as probable, 10 was judged as possible, 4 as unlikely, and 11 as unrelated.
No deaths or other serious adverse events were reported during this study. Six subjects experienced the following significant TEAEs: Drug-induced liver injury, Pharyngitis bacterial, Lymphangitis, Gastroenteritis, Bronchitis, Sinusitis, Diarrhoea, and Gastroenteritis (twice).

Conclusion safety profile
The adverse reactions seen with rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse reactions.
In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2396 patients, or with a statin in 11,308 patients or with fenofibrate in 185 patients.
Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.
As reported in the published literature, the most frequent common adverse events related to rosuvastatin-ezetimibe combination treatment in hypercholesterolemic patients are increased hepatic transaminases, gastrointestinal problems and muscle pain. These are known undesirable effects of the active substances.

Both mono-components are well known with respect to their safety profile. Additionally, safety data from the bioequivalence study in healthy volunteers does not suggest a different safety profile with the combination of 5 mg rosuvastatin and 10 mg ezetimibe compared with the safety profile of the mono-components, although data are limited. Moreover, the safety data on the combined use of rosuvastatin

with ezetimibe has already been assessed during the registration of the higher strengths of Rosuvastatine/ezetimibe EGIS and deemed to be acceptable.

IV.5 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 Rosuvastatine/ezetimibe EGIS.

- **Summary table of safety concerns as approved in RMP (version 10.0 - 17 December 2018)**

Important identified risks	• Muscle injury (Rhabdomyolysis/myopathy) • Abnormal liver function
Important potential risks	None
Missing information	• Use in children less than 18 years of age • Use in patients with moderate or severe liver problems

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

IV.6 Discussion on the clinical aspects

The combined use of rosuvastatin and ezetimibe is well-established. The literature data submitted by the MAH support the use of the combination. The bioequivalence study shows satisfactory results: a single capsule of Rosuvastatine/ezetimibe EGIS 5 mg/10 mg can be used instead of co-administration of the separate products Crestor 5 mg and Ezetrol 10 mg tablets. Risk management is adequately addressed.

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 preliminary round of testing with 4 participants, followed by two rounds of testing with 10 participants each. Fifteen questions were prepared to test for traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine/ezetimibe EGIS 5 mg/10 mg, hard capsules have a proven chemical-pharmaceutical quality and are considered an acceptable new formulation. Both rosuvastatin and ezetimibe are well known, established substances which are used as a combination in clinical practice.

The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate reference products Crestor and Ezetrol. The efficacy and safety profile is considered the same as for the mono-components.

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 this fixed-dose combination is approvable, since bioequivalence has been demonstrated with the innovator products of the individual components. The decentralised procedure was finalised with a positive outcome on 8 July 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Minor changes to an approved change management protocol that do not change the strategy defined in the protocol	NL/H/3016/ 004/IB/013	IB	26-10-2017	25-11-2017	Approved	No
The API manufacturer of ezetimibe has released a new (updated) ASMF version.	NL/H/3016/ 1-4/II/011	II	07-11-2017	06-01-2018	Approved	Yes
Change in the (invented) name of the medicinal product; for nationally authorised roducts	NL/H/3016/ 1-4/IB/015	IB	22-01-2018	21-02-2018	Approved	No
Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product; introduction of a new route of synthesis for the active substance Rosuvastatin zinc, supported by a new ASMF, in addition to the already approved routes of synthesis, by existing ASMF's	NL/H/3016/ 1-4/II/010	II	05-10-2017	13-04-2018	Approved	Yes
Implementation of changes foreseen in an approved change management protocol; the implementation of the change requires further supportive data	NL/H/3016/ 004/IB/016	IB	21-05-2018	02-07-2018	Approved	No
Change(s) in the SmPC, Labelling or PL of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006	NL/H/3016/ 1-6/IA/019	IA	16-07-2018	14-08-2018	Approved	No
- Changes in the manufacturing process of the active substance - Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance - Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance - Extension or introduction of a re-test period/storage period supported by real time data	NL/H/3007/ IB/018/G	IB	25-06-2018	05-09-2018	Approved	No
Change(s) in the SmPC, Labelling or PL of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006	NL/H/3016/ 1-6/IA/020	IA	03-12-2018	02-01-2019	Approved	No
Renewal; Introduction of new Summary table of safety concerns as approved in RMP	NL/H/3016/ 004/R/001	Renewal	24-10-2018	07-03-2019	Approved	Yes
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to	NL/H/3016/ 1-6/IB/021	IB	28-05-2019	27-06-2019	Approved	No

implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006						