COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rosuvastatine calcium/ezetimibe Egis 10 mg/10 mg and 20 mg/10 mg hard capsules

(rosuvastatin calcium/ezetimibe)

NL/H/3016/005-006/DC

Date: 12 September 2019

This module reflects the scientific discussion for the approval of Rosuvastatine calcium/ezetimibe Egis 10 mg/10 mg and 20 mg/10 mg hard capsules. The procedure was finalised on 2 March 2018. 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
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 calcium/ezetimibe Egis 10 mg/10 mg and 20 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.

In a previous application (NL/H/3016/001-004/DC) registration of the products Ayadont 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, containing rosuvastatin zinc, was pursued. Approval of the above mentioned fixed-dose combination 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.*

In order to support the application a bioequivalence study has been performed to compare the rate and extent of absorption of combination 20 mg rosuvastatin/ 10 mg ezetimibe and the active substances administered at the same time but as separate tablets. Furthermore, the MAH provided a clinical overview which was mostly based on the clinical overviews of the previous registration procedures of the combinations rosuvastatin (rosuvastatin zinc)/ezetimibe 10 mg/10 mg, 20 mg/10mg,

and 40 mg/ 10 mg. No clinical efficacy studies with the co-administration of the two active substances have been performed by the company. 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 Ayadont 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 calcium/ezetimibe Egis 10 mg/10 mg is an unmarked, self-closing Coni Snap type, size 0, hard gelatin capsule with yellow coloured cap and yellow coloured body filled with two tablets.
Ayadont 20 mg/10 mg is an unmarked, self-closing Coni Snap type, size 0, hard gelatin capsule with caramel coloured cap and yellow coloured body filled with two tablets.

The capsules contain 10 mg or 20 mg rosuvastatin (as calcium) 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 and body 10/10 mg: yellow iron oxide (E172), titanium dioxide (E171), gelatine
Cap 20 mg/10 mg: red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172), gelatine
Body 20 mg/10 mg: gelatine, yellow iron oxide (E172), titanium dioxide (E171)

The uncoated 10 and 20 mg rosuvastatin calcium tablets are dose-proportional.

II.2 Drug Substances

Rosuvastatin calcium
The active substance rosuvastatin calcium is described in the European Pharmacopoeia (Ph. Eur.). It is a white powder, which is freely soluble in ethanol, methylene chloride and dimethylformamide (at 37 °C) and slightly soluble in water and 2-propanol. Rosuvastatin calcium has two chiral centres, thus theoretically four diastereoisomers exist. The amorphous polymorphic form is produced by the manufacturer. The substance is hygroscopic, and sensitive to light and humidity. The Active Substance Master File (ASMF) procedure as well as the CEP procedure are used for rosuvastatin calcium.

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.

The CEP procedure also is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical

use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
The manufacturing process is adequately described. 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.
For the second manufacturer, the process is covered by the CEP.

Quality control of drug substance
Manufacturer one - 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 calcium.
Manufacturer two - The drug substance specification is in-line with the Ph.Eur monograph and the additional requirements from the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four production batches.

Stability of drug substance
Manufacturer one - The claimed re-test period is 36 months if stored under the proposed storage conditions. Three batches have been stored for 5°C (36 months), 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). During the stability studies the following parameters have been tested: identification, water content, related substances and assay. Based on the provided stability data the shelf life of 36 months can be granted.
Manufacturer two – The claimed re-test period is 36 months if stored under the proposed storage conditions. Stability data on 15 batches stored at accelerated (at 25°C) and long term stability (5°C) data are provided. The claimed re-test period is acceptable.

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 calcium 10-20 mg tablets and ezetimibe 10 mg uncoated tablets has been adequately described. The MAH chose to compress both ezetimibe and rosuvastatin calcium final granule blends into tablets before inclusion into the capsules. The bioequivalence study was performed between the proposed 20 mg rosuvastatin calcium/10 mg ezetimibe hard capsule and the separate originator products Crestor 20 mg and Ezetrol 10 mg dosed concomitantly. A biowaiver has been requested for the 10 mg/10 mg strength. Sufficient details on the pharmaceutical development have been provided.

Manufacturing process
Rosuvastatin calcium 10 mg and 20 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.

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 validation batches were meeting the set acceptance criteria

Bulk rosuvastatin 10 mg and 20 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
Four batches for each capsule strength have been tested at 25°C/60% RH and 40°C/75% RH, for 6 months so far. 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 30 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 Ayadont hard capsules have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

The following post-approval commitment was made:

- The MAH committed to validate the encapsulating process before marketing the product. The results should be available upon request.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ayadont 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

The pharmacological, pharmacokinetic and toxicological properties of rosuvastatin and ezetimibe are well known, as both substances have been in use for many years both individually and in combination. No new studies have been performed and none are considered necessary

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 Ayadont 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

To support the application, the MAH has submitted the report of a single centre, randomised, single-dose, open-label (bioanalytical laboratory blinded), two-period, two-sequence, crossover bioequivalence study comparing the test product Ayadont 20 mg/10 mg hard capsules (Egis Pharmaceuticals Plc., Hungary) with the reference products Crestor 20 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.

Biowaiver
A biowaiver was requested for the 10/10 strength. The results of the bioequivalence study apply to the Ayadont 10/10 mg hard capsules as well, because:

- Rosuvastatin has linear pharmacokinetics in the therapeutic dose range (not applicable for ezetimibe)
- The strengths were manufactured by the same manufacturer and process.

- The qualitative composition of the different strengths is the same.
- The dissolution profile for the 10/10 mg strength was demonstrated to be similar to the 20/10 mg strength.
- The ratio between amounts of each active ingredient and excipients is the same in all strengths.

The biowaiver is therefore acceptable.

Bioequivalence study

Design

Bioequivalence was investigated with a single centre, randomised, single-dose, open-label (bioanalytical laboratory blinded), two-period, two-sequence, crossover study in 66 healthy white male subjects. Treatment 1 was a single Ayadont 20 mg/10 mg capsule, and treatment 2 consisted of a Crestor 20 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 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 16, 24, 48 and 72 hours after drug administration.
For ezetimibe and ezetimibe phenyl glucuronide blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 20, 24, 48 and 72 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 characterize 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

One subject withdrew consent for personal reasons. Two subjects did not provide evaluable data for ezetimibe, one due to a meal deviation (subject left 100% of the critical supper due to an adverse event (nausea)) and one due to a gastrointestinal adverse event (diarrhoea approximately 24 hours after administration). Data of 65 subjects were considered in the pharmacokinetic analysis for rosuvastatin and 63 for ezetimibe; data of 66 subjects were considered in safety analysis.

Table 1: Pharmacokinetic Parameter Rosuvastatin

Treatment	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} ng/ml	t_{max} h
Treatment 1	107.3 (±59.9)	114.0 (±62.7)	12.8 (±8.5)	4.50 (0.50-5.00)
Treatment 2	110.5 (±65.5)	114.9 (±67.5)	12.9 (±8.9)	4.50 (0.50-5.00)
*Ratio (90% CI)	0.98 (0.91 – 1.04)	--	0.99 (0.91 – 1.07)	--
CV	23.1%	--	29.1%	--

Table 2: Pharmacokinetic Parameter Ezetimibe

Treatment	AUC_{0-72} (pg·h/mL)	$AUC_{0-\infty}$ (pg·h/mL)	C_{max} pg/ml	t_{max} h
Treatment-1	67066.1 (±25712.6)	71257.5 (±27966.5)	3466.0 (±1636.1)	5.50 (1.05-24.00)
Treatment-2	70103.5 (±27637.0)	74975.6 (±26407.8)	3693.6 (±2073.3)	5.00 (0.50-12.07)
*Ratio (90% CI)	0.96 (0.92 – 1.00)	--	0.96 (0.88 – 1.05)	--
CV	14.3%	--	30.6%	--

Table 3: Pharmacokinetic Parameter Total Ezetimibe

Treatment	AUC0-72 (ng·h/mL)	AUC0-∞ (ng·h/mL)	Cmax ng/ml	tmax h
Treatment-1	639.4 (±248.5)	715.0 (±288.2)	51.8 (±26.3)	1.50 (0.75-12.03)
Treatment-2	669.7 (±253.4)	774.4 (±305.6)	62.3 (±22.2)	1.00 (0.50-5.00)

Conclusion on bioequivalence study

Rosuvastatin

The Test-to-Reference GMR and 90% CI were within the standard acceptance interval (80.00-125.00%) for AUC_{0-t} and C_{max} of rosuvastatin. However, the C_{max} was observed in the first sampling point in four subjects. The observed C max values in these four subjects were within the same ranges of C_{max} values observed in the other subjects. These early C_{max} values may bias a reliable estimation of the C_{max}. Therefore, the company was requested to perform a sensitivity analysis excluding these four subjects to show that the bioequivalence conclusions are correct.

The sensitivity analysis of the rosuvastatin pharmacokinetic data confirms that the test product rosuvastatin-ezetimibe 20 mg/10 mg hard capsules is bioequivalent to the co-administered reference products Crestor 20mg and Ezetrol.

Ezetimibe

The Test-to-Reference GMR and 90% CI were within the standard acceptance interval (80.00-125.00%) for AUC_{0-72} and C_{max} of Ezetimibe. The t_{max} values of unconjugated ezetimibe were observed at a median time of 5 hours after administration but with a very wide range (0.5-24.00 hours). This is acceptable because the Ezetimibe PK profiles are in line with the PK profiles observed in a previous bioequivalence study that was submitted to support initial marketing authorisation and pharmacokinetic characteristics of ezetimibe reported in the literature. Ezetimibe undergoes extensive enterohepatic cycling and this enterohepatic cycling is related to bile excretion triggered by food intake. As a result of this, multiple unconjugated ezetimibe peaks are observed. The measured ezetimibe concentration is a combination of unchanged parent compound directly absorbed from the tablet and reabsorbed back-converted ezetimibe which explains the multiple peaks.

Overall, bioequivalence between Ayadont 20 mg/10 mg hard capsules and the co-administered reference products Crestor 20 mg and Ezetrol 10 mg tablet has been established.

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 application was submitted to register a rosuvastatin/ezetimibe capsule with a new salt, i.e. rosuvastatin calcium, in the strengths of 10 mg/10 mg and 20 mg /10 mg. The MAH has provided a clinical overview to support the combined use of rosuvastatin and ezetimibe as mono-components based on lipid lowering studies.

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

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

The MAH has discussed studies to support the beneficial lipid lowering effect of the rosuvastatin/ ezetimibe combination. The ACTE study performed by Bays et al[2]. showed additional LDL-C lowering effect of ezetimibe as add-on therapy to 10 mg rosuvastatin compared to uptitration of monotherapy of rosuvastatin (between-group difference of 15.2%, p<0.001). The EXPLORER study performed by Ballantyne C et al.[3] showed that the combination of 40 mg rosuvastatin and 10 mg ezetimibe reduced LDL-C significantly more than 40 mg rosuvastatin (-69.8% vs -57.1%, p<0.001). Similar results were found in the open-label study of Stein et al.[4] where addition of 10 mg ezetimibe to stable therapy with rosuvastatin 40 mg produced an additional 15% reduction in LDL-C (p<0.001). The GRAVITY trial[5] showed that the LDL-C reduction with low and high dose of rosuvastatin plus 10 mg ezetimibe was higher compared with the low and high dose of simvastatin plus ezetimibe. The prospective open-label study of Kouvelos et al.[6] showed that intensified lipid-lowering with 10 mg rosuvastatin/ 10 ezetimibe was associated with a greater decrease in LDL-C compared with 10 mg rosuvastatin alone (between-group difference of 11.3%, p=0.0004). A prospective randomized open-label study performed by Masuda et al.[7], resulted in a 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.

Proposed doses for the combination
Rosuvastatin is currently registered in the strengths: 5, 10, 20 and 40 mg. The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. A dose adjustment to the next dose level can be made after 4 weeks, if necessary. Ezetimibe is currently registered in the 10 mg strength and the recommended dose is 10 mg table daily. Both products may be given at any time of day, with or without food and are thus appropriate for a combination. The medical interest of the rosuvastatin/ezetimibe combination is confirmed by the co-prescription data from European countries. These prescription data indicate that the percentage of 10/20 mg rosuvastatin co-prescribed with ezetimibe 10 mg is 1.8-12.4% in the different countries.
Furthermore, the proposed strengths are in line with the dose recommendations statin in the product information of both products, with the exception of the 5 and 40 mg of rosuvastatin. Considering that 5 mg rosuvastatin is the starting dose, the lack of this strength is acceptable. Additionally, the co-prescription data showed that the medicinal need is limited for these strengths. Similarly, co-prescription data showed that the 40 mg rosuvastatin strength is only of importance in some countries. As such, the development of a product with only the 10/ 20 mg rosuvastatin strengths is considered acceptable.

Overall, the RMS considers that the provided data is sufficient in terms of fulfilling the first two requirements for a 10 /20 mg rosuvastatin and 10 mg ezetimibe combination intended for a substitution indication.

IV.4 Clinical safety

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

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 Ballantyne CM1, Weiss R, Moccetti T, et al. EXamination of Potential Lipidmodifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone. Am J Cardiol. 2007 Mar 1;99(5):673-80
4 Stein EA, Ose L, Retterstøl K et al. Further reduction of low-density lipoprotein cholesterol and C-reactive protein with the addition of ezetimibe to maximum-dose rosuvastatin in patients with severe hypercholesterolemia. J Clin Lipidol. 2007 Aug;1(4):280-6
5 Ballantyne CM1, Hoogeveen RC2, Raya JL, et al. Efficacy, safety and effect on biomarkers related to cholesterol and lipoprotein metabolism of rosuvastatin 10 or 20 mg plus ezetimibe 10 mg vs. simvastatin 40 or 80 mg plus ezetimibe 10 mg in high-risk patients: Results of the GRAVITY randomized study. Atherosclerosis. 2014 Jan;232(1):86-93
6 Kouvelos GN, Arnaoutoglou EM, Matsagkas MI et al. Effects of rosuvastatin with or without ezetimibe on clinical outcomes in patients undergoing elective vascular surgery: results of a pilot study. J Cardiovasc Pharmacol Ther. 2013 Jan;18(1):5-12
7 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

combination of 20 mg rosuvastatin and 10 mg ezetimibe compared with the safety profile of the mono-components. Moreover, the safety data on the combined use of rosuvastatin with ezetimibe has already been assessed, based on the similar submitted literature data, during the registration of the previous combination with rosuvastatin zinc 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 Ayadont.

- **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 Rosuvastatine calcium/ezetimibe Egis. The bioequivalence study shows satisfactory results: a single capsule of Ayadont 40 mg/10 mg can be used instead of co-administration of the separate products Crestor 40 mg and Ezetrol 10 mg tablets. A biowaiver was granted for the two lower strengths. Risk management is adequately addressed.

V. USER CONSULTATION

The MAH did not perform a user testing but submitted a bridging statement. The MAH states that as the replacement of rosuvastatin zinc by rosuvastatin calcium has no effect on the Readability Study (User Testing) performed for the original application of rosuvastatin zinc/ezetimibe hard capsules, the same is submitted for the line-extension application. The RMS agrees with the applicant that a user testing is not required. The PL for the line-extensions are essentially identical to the tested and approved PL for NL/H/3016/001-003/DC.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine calcium/ezetimibe Egis 10 mg/10 mg and 20 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 product 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 2 March 2018.

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
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
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/3007/ 006/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 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/IB/021	IB	28-05-2019	27-06-2019	Approved	No