COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rozesta 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg film-coated tablets

(rosuvastatin calcium/ezetimibe)

NL/H/4758/001-004/DC

Date: 10 June 2021

This module reflects the scientific discussion for the approval of Rozesta. The procedure was finalised at 4 February 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
ASMF	Active Substance Master File
AST	Aspartate Aminotransferase
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
EZE	Ezetimibe
FDC	Fixed Dose Concentration product
ICH	International Conference of Harmonisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RSV	Rosuvastatin
SmPC	Summary of Product Characteristics
SAE	Serious Adverse Event
TSE	Transmissible Spongiform Encephalopathy
ULN	Upper Limit of Normal value
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 Rozesta 5 mg/10 mg; 10 mg/10 mg; 20 mg/10 mg and 40 mg/10 mg film-coated tablets from Zentiva k.s.

The product is indicated as adjunct to diet for treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia as substitution therapy in adult patients, who are adequately controlled with rosuvastatin and ezetimibe given concurrently at the same dose level as in the fixed dose combination product (FDC), but as separate products.

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

The current application combines two active substances which have well-established clinical use and well-known safety and efficacy profiles when prescribed individually as well as concomitantly. Apart from this well-established use, there is a further rationale for the development of this product. Hence there is a large number of patients that do not reach target lipid goals and a fixed combination product may improve adherence to medication.

FDCs of ezetimibe with other statins are authorised within the EU, such as Inegy (ezetimibe/simvastatin combination) with procedure number DE/H/0496/001 and, very recently, Atozet (ezetimibe/ atorvastatin) with procedure number DE/H/3895/001, both authorised by Merck Sharp & Dohme B.V. A 'formal' reference product does not exist within the EU for the specific rosuvastatin/ezetimibe combination but similar combination products have been already authorised in EU recently (Rosuvastatin/Ezetimibe egis with procedure number NL/H/3016/001 , Rosuvastatin /Ezetimibe zentiva Rosuvastatin/Ezetimibe adamed), claiming a substitution indication.

This decentralised procedure concerns a FDC of rosuvastatin as calcium salt and ezetimibe. Rosuvastatin and ezetimibe are both approved medicinal products, marketed worldwide for many years. The innovator product Crestor film-coated tablets (rosuvastatin) was first registered in the Netherlands by AstraZeneca BV (NL Licence RVG 26873) through a national procedure on 6 November 2002. Crestor is currently registered through mutual recognition procedure NL/H/0343/MR since 7 March 2003. Ezetrol 10 mg tablets (ezetimibe) is registered in the Netherlands by Merck Sharp & Dohme Ltd. since 18 April 2003 (NL Licence RVG 28626) through mutual recognition procedure DE/H/0396/001.

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Latvia, Estonia, Poland, Portugal and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

- Rozesta 5 mg/10 mg are light yellow, round, biconvex film-coated tablets with “EL5” embossed on one side
- Rozesta 10 mg/10 mg are beige, round, biconvex film-coated tablets with “EL4” embossed on one side.
- Rozesta 20 mg/10 mg are yellow, round, biconvex film-coated tablets with “EL3” embossed on one side.
- Rozesta 40 mg/10 mg are white, round, biconvex film-coated tablets with “EL2” embossed on one side.

Each film-coated tablet contains as active substances 5.20 mg, 10.40 mg, 20.80 mg or 41.60 mg of rosuvastatin, being equivalent to 5 mg, 10 mg, 20 mg and 40 mg of rosuvastatin as rosuvastatin calcium, and 10 mg of ezetimibe.

The film-coated tablets are packed in cold blisters (OPA/AL/PVC/Al).

The excipients for Rozesta 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg are:

Tablet core - cellulose microcrystalline (E460), colloidal anhydrous silica (E551), magnesium stearate (E572), povidone K 30 (E1201), croscarmellose sodium (E468), sodium laurilsulfate (E514), lactose monohydrate and hypromellose 2910.

Tablet coating
Rozesta 5 mg/10 mg - hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521), iron oxide yellow (E172), talc (E553b) and iron oxide red (E172).

Rozesta 10 mg/10 mg - hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521), iron oxide yellow (E172) and talc (E553b).

Rozesta 20 mg/10 mg - hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521) and ferric oxide yellow (E172).

Rozesta 40 mg/10 mg - hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521) and lactose monohydrate.

II.2 Drug Substances

Rosuvastatin Calcium

The first active substance rosuvastatin calcium is an established active substance described in the Ph. Eur. Rosuvastatin calcium is slightly soluble in water and practically insoluble in anhydrous ethanol. Rosuvastatin calcium exhibits polymorphism and exists in its amorphous form.

For rosuvastatin calcium the CEP procedure is used. Rosuvastatin calcium is supplied by two different suppliers. 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./CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches. For analytical procedures reference is given to the Ph. Eur. monograph and CEP. This is acceptable. For the in-house test method for particle size distribution sufficient description and adequate data on validation have been provided. Batch analysis data of three batches complying with the proposed specification is included for both suppliers.

Stability of drug substance

manufacturer I

Stability data on the active substance have been provided for five batches in accordance with applicable European guidelines demonstrating the stability of the active substance stored at long term conditions up to 48 months and accelerated conditions up to six months. Based on the data submitted, a retest period could be granted of 24 months when stored in an airtight container, protected from light, at a temperature of 2°C to 8°C.

manufacturer II

Stability data on the active substance have been provided for at least three batches in accordance with applicable European guidelines demonstrating the stability of the active substance stored at long term conditions up to 18 months and accelerated conditions up to six months. Based on the data submitted, a retest period could be granted of 36 months when stored in an airtight container, protected from light, at a temperature of 2°C to 8°C.

Ezetimibe

The second active substance is Ezetimibe, an established active substance not described in any Pharmacopoeia (Ph.Eur.). Ezetimibe is a white to off-white crystalline powder, which is freely soluble in ethanol and methanol but practically insoluble in water. Ezetimibe contains three asymmetric carbon atoms and therefore exhibits optical isomerism. The R,S,S isomer is used. Ezetimibe exhibits polymorphism. Based on X-Ray diffraction studies, it is concluded that the manufacturing process for ezetimibe consistently produces the anhydrous crystalline form.

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 MAH 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 consists of six chemical steps and one purification step. The synthesis description is sufficiently detailed and sufficient chemistry is part of the regulatory synthesis route. Specifications of starting materials and intermediates are acceptable. The drug substance is sufficiently characterised with regard to the chemical structure and regarding polymorphic form.

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./USP. The test methods covered by these monographs are also covered by the ASMF. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The MAH claims that the retest period and storage conditions are identical to the re-test period and storage conditions stated by the drug substance manufacturer in the ASMF, which is acceptable. The re-test period is 48 months, based on stability data of three lower scale- and three higher scale- validation batches stored at long-term conditions (25°C/60% RH) up to 60 months and accelerated conditions (40 °C/75 %RH) up to six months. No special temperature storage conditions are required. Stability data on the active substance has been provided for six batches stored at 25°C/60% RH (60 months) and 40 °C/75 % RH (six months) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 48 months with no special temperature storage conditions being required

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, formulation development, dissolution methods development, manufacturing process development and the performance of comparative dissolution studies complementary to the bioequivalence studies with the 40 mg/10 mg and 5 mg/10 mg strengths. In general, all those parts of the drug development were appropriately performed and described.

Bioequivalence studies were carried out on the highest strength (40 mg/10 mg) and the lowest strength (5 mg/10 mg) of the product applied for. A biowaiver is requested for the additional 10/10 mg and 20/10 mg strengths. Since the provided *in vitro* dissolution data support the requested biowaiver, the biowaiver of strengths is considered acceptable from the chemical pharmaceutical point of view.

Manufacturing process

The manufacturing processes consists of sieving, mixing, granulation liquid preparation, wet granulation, drying, milling, lubrication, tableting, coating suspension preparation, coating and blistering. For the 10 mg/10 mg, 20 mg/10 mg, 40 mg/10mg (rosuvastatin/ezetimibe) strengths the manufacturing process is considered to be a standard process. However, as the drug load of rosuvastatin in the 5 mg/10 mg strength is low, this does not correspond to a standard process. The manufacturing process has generally been described in sufficient detail. Validation has been performed on three batches of each strengths of the product applied for and is considered to be adequately validated.

Control of excipients

Specifications for all excipients have been provided and are in line with Ph.Eur. (except for the coating agents) and additional testing for some excipients have been performed. The specifications proposed for the excipients are considered acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is acceptable based on batch analysis results, available stability results and European guidance and includes tests for appearance, uniformity of dosage units, water, disintegration, mean weight, identification of rosuvastatin and ezetimibe, assay, related substances, dissolution, microbiological tests and identification of colourants. 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 12 registration batches, three batches of each strength of the product applied for from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production batches per product strength with an exception of 40 mg/10 mg (rosuvastatin/ezetimibe) strength where a fourth batch was placed in stability in accordance with applicable European guidelines for 24 months under long term (25 ˚C/60 RH), 24 months under intermediate (30 ± 2 ºC/75 ± 5% RH) and six months under accelerated (40 ± 2 ºC/75 ± 5% RH) conditions. On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are: "No special temperature storage conditions" and an additional storage statement "Keep the drug product in the original package in order to protect from moisture and light".

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

None of the materials (except lactose monohydrate) used in the formulation of the product applied for is of animal and/or human origin. TSE/BSE declarations obtained from the drug substance manufacturer and excipients manufacturers have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rozesta is intended to be a FDC product, 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 FDC product of rosuvastatin and ezetimibe based on Crestor and Ezetrol which are available on the European market. Reference is made to the preclinical data obtained with Crestor and Ezetrol. 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

For this FDC product application, the MAH has submitted two bioequivalence studies which are discussed below. Furthermore, the MAH has submitted an extensive literature review, making reference to scientific studies relevant to this fixed combination product.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies:

- Study I: single dose study with the 40/10 mg tablet under fasting conditions.
- Study II: single dose study with the 5/10 mg tablet under fasting conditions.

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Rosuvastatin/Ezetimibe 40 mg/10 mg and 5 mg/10 mg tablets (Elpen S.A. Pharmaceutical Industry, Greece) are compared with the pharmacokinetic profile of the reference products Ezetrol 10 mg tablets (MSD Greece for study II, Schering-Plough Labo N.V., Belgium for study I) and Crestor 5 mg and 40 mg tablets (AstraZeneca Osterreich GmbH for study II, AstraZeneca GmbH, Germany for study I).

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

The design of the studies is acceptable.

<u>Biowaiver</u>
Two bioequivalence studies have been carried, one with the lowest strength and one with the highest strength. The formulations can be considered proportional, based upon the 5% rule and the fixed formulation rule, in which in this case ezetimibe can be considered as an inert excipient. Considering the linear pharmacokinetics of rosuvastatin, in principle one bioequivalence study would have been sufficient. Dissolution data at pH 1.2, 4.5 and 6.8 showed comparable dissolution between the 5mg/10mg, 10mg/10mg, 20mg/10mg, 40mg/10mg tablets. Therefore, the conclusions of the bioequivalence studies with the rosuvastatin/ezetimibe 40/10 and 5/10 mg strengths can be extrapolated to the intermediate 10/10mg and 20/10 mg tablet strengths.

<u>Bioequivalence studies</u>
Study I: single dose study with the 40/10 mg tablet under fasting conditions.
Design
An open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 62 healthy male subjects, aged 18-44 years. Each subject received a single dose (40/10 mg: 1 x 40/10 mg tablet or 1 x 40

mg tablet + 1 x 10 mg tablet) of both the test and the reference rosuvastatin and ezetimibe formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

Out of a total of 62, 58 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn due to an adverse event following period one (accident, physical injury), one subject was found positive in alcohol breath test during admission of period two and two subjects did not report to the facility during admission of period two.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe of the test and reference product under fasting conditions

Treatment N=58	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test: Rozesta 40/10 mg tablet	1192 ± 553	1291 ± 633	169 ± 91	1.0 (0.33 – 5.0)
Reference: Ezetrol 10 mg tablet	1211 ± 494	1294 ± 520	169 ± 79	1.0 (0.67 – 4.0)
***Ratio (90% CI)**	0.97 (0.92 – 1.03)	--	0.98 (0.91 - 1.06)	--
CV (%)	17.6	--	25.0	--

$AUC_{0-\infty}$ 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 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total rosuvastatin of the test and reference product under fasting conditions

Treatment N=58	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test: Rozesta 40/10 mg tablet	414 ± 184	427 ± 185	49 ± 25	3.67 (0.67 – 4.67)
Reference: Crestor 40 mg tablet	432 ± 209	445 ± 209	52 ± 30	2.5 (0.67 – 6.0)
***Ratio (90% CI)**	0.98 (0.93 – 1.03)	--	1.00 (0.92 - 1.09)	--
CV (%)	17.8	--	27.9	--

$AUC_{0-\infty}$	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*

Study II: single dose study with the 5/10 mg tablet under fasting conditions.

Design

An open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 62 healthy male subjects, aged 18-44 years. Each subject received a single dose (5/10 mg: 1 x 5/10 mg tablet or 1 x 5 mg tablet + 1 x 10 mg tablet) of both the test and the reference rosuvastatin and ezetimibe formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

Out of a total of 62, 62 subjects were eligible for pharmacokinetic analysis. One subject withdrew its consent before study initiation and was therefore replaced by the reserve subject.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total rosuvastatin of the test and reference product under fasting conditions

Treatment N=62	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test: Rozesta 5/10 mg tablet	58 ± 24	61 ± 25	6.6 ± 3.0	4.33 (0.67 – 5.0)
Reference: Crestor 10 mg tablet	63 ± 27	66 ± 27	6.8 ± 3.2	4.33 (0.67 – 6.0)
***Ratio (90% CI)**	0.93 (0.88 – 0.98)	--	0.97 (0.91 - 1.04)	--
CV (%)	17.6	--	23.1	--

$AUC_{0-\infty}$	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 total rosuvastatin of the test and reference product under fasting conditions

Treatment N=62	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test: Rozesta 5/10 mg tablet	1049 ± 466	1101 ± 499	168 ± 65	0.67 (0.33 – 2)
Reference: Ezetrol 5 mg tablet	1041 ± 427	1107 ± 463	154 ± 73	0.68 (0.67 – 2.7)
***Ratio (90% CI)**	1.00 (0.95 – 1.04)	--	1.11 (1.04 – 1.19)	--
CV (%)	15.0	--	21.6	--

$AUC_{0-\infty}$	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 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rozesta is considered bioequivalent with Crestor and Ezetrol.

The results of the bioequivalence studies with the 40 mg/10 mg and 5 mg/10 mg formulations respectively, can be extrapolated to the additional strengths of 10 mg/10 mg and 20 mg/10 mg as all the requirements in the bioequivalence study guideline (Doc. Ref.:CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 2010) for granting such a biowaiver are fulfilled.

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 Pharmacodynamics

Rosuvastatin

Rosuvastatin belongs to the pharmacotherapeutic group of lipid modifying agents and HMGCoA –reductase inhibitors (statins). This active substance is a selective and competitive inhibitor of HMG-CoA reductase which lowers the intracellular cholesterol level, converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol and upregulates the LDL receptors, resulting in increased clearance of LDL from the circulation.
Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see table 5). It also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios (AstraZeneca, 2017; AstraZeneca UK Limited, 2016; MHRA, 2017b).

Table 5. dose response to rosuvastatin 5, 10, 20 and 40 mg in patients with hypercholesterolemia.

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	Apo B	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

Ezetimibe

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine [by interaction with the Niemann- Pick C1-like protein 1 (NPC1L1)], ezetimibe reduces the amount of cholesterol delivered to the liver. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-

reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols) (Merck Sharp & Dohme Limited, 2016; MHRA, 2017a; Sandoz Canada Inc., 2013). Ezetimibe has been shown to reduce LDL concentrations by 20%, but in adults it is used in combination with statins (Merck Sharp & Dohme Limited, 2016; MHRA, 2017a; Sandoz Canada Inc., 2013).

IV.4 Clinical efficacy

According to the guideline on clinical development of FDC products [EMA/CHMP/158268/2017] the requirements 1, 2 and 3 have to be fulfilled, i.e. justification of the medical rationale of the combination, establishment of the evidence base for the relevant contribution of all active substances to the desired therapeutic effect and demonstration that the evidence presented, if based on combined administration of separate active substances, is relevant to the FDC product for which the application is made.

a. Justification of the medical rationale of the combination
The combination of statin with ezetimibe is a widely used double combination for the treatment of hypercholesterolemia. The addition of ezetimibe in statin therapy (e.g. rosuvastatin) is recommended from the relevant guidelines and their therapeutic benefit and their clinical use have been demonstrated through a series of clinical studies.
The combination of ezetimibe plus a statin has the potential to effectively lower LDL-C levels by two independent and complementary pathways: inhibition of cholesterol absorption and inhibition of cholesterol synthesis. The specific combination has not only synergistic effects on the lowering of LDL-C levels and decreasing cholesterol absorption compared with a statin administered alone (Bays et al., 2011; Catapano et al., 2005; Daskalopoulou and Mikhailidis, 2004) but also this combination has a positive influence on the reduction of adverse events (Catapano et al., 2005; Daskalopoulou and Mikhailidis, 2004). In addition, some studies report that a greater proportion of patients reached their target LDL level with rosuvastatin and ezetimibe than those with up-titration of rosuvastatin alone (Ballantyne et al., 2007; Bays et al., 2011). Moreover, a FDC is expected to improve medication compliance in patients with chronic diseases such as hypercholesterolemia (Bangalore et al., 2007). Based on a study conducted by Kosoglou and his co-scientists, there is no clinically significant interaction between the two active substances (Kosoglou et al., 2004b). Therefore, a FDC tablet of rosuvastatin/ezetimibe has been developed aimed to improve patient compliance and clinical outcomes.

b. Relevant contribution of all active substances to the desired therapeutic effect
The claimed therapeutic indication for the rosuvastatin/ezetimibe combination is a substitution indication for patients that are already used to be on dual concurrent therapy of the two mono components at the same dose level as in the FDC, since mono – or double treatment was not effective in the control of the disease.
The FDC product is intended to be used in patients who are already stabilised on an optimal dose of the mono-components, where the monocomponents will be discontinued and the FDC product started. It may be possible that those components belong to different therapeutic classes. The clinical use of statin (rosuvastatin) and cholesterol absorption inhibitors

(ezetimibe) concurrently is recommended in the relative guidelines for the management of hypercholesterolemia and for prevention of cardiovascular disease.
The MAH has presented studies on the combined use of statins (including rosuvastatin) with ezetimibe including the EASE study of Sweeney and Johnson, 2007, a study of Hamilton-Craig et al., 2010, a study of Morrone et al., 2012, a pooled analysis of Ambegaonkar et al., 2014, a study specifically in HeFH of Pitsavos et al., 2009, a publication of Foody et al., 2013, a study of Inoue et al., 2010, and a study of Okada et al., 2012.

Moreover, the MAH has presented studies on the specific combined use of rosuvastatin with ezetimibe. These included the following studies:

- I-ROSETTE (Ildong ROSuvastatin & ezETimibe for hypercholesTErolemia) was an eight-week, double-blind, multicentre, Phase III randomised controlled trial conducted at 20 hospitals. Patients were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg in a 1:1:1:1:1:1 ratio (Hong et al., 2018).
- A 12-week, randomised, double-blind, placebo-controlled, multicentre study in 245 patients with high cardiovascular risk. Patients received one of six regimens for eight weeks as follows: (1) rosuvastatin 5 mg, (2) rosuvastatin 5 mg/ezetimibe 10 mg, (3) rosuvastatin 10 mg, (4) rosuvastatin 10 mg/ ezetimibe 10 mg, (5) rosuvastatin 20 mg, or (6) rosuvastatin 20 mg/ezetimibe 10 mg (Yang et al., 2017).
- A study in 135 patients who were enrolled within 24 hours of Acute Myocardial Infarction (AMI), and were randomised to receive 10 mg rosuvastatin or 10 mg rosuvastatin plus 10 mg ezetimibe daily. HsCRP, Lp- PLA2, total cholesterol (TC), triglycerides (TG), LDL-C and high-density lipoprotein cholesterol (HDL-C) were determined at baseline and after one, three, six and 12 months of treatment (Ren et al., 2017).
- A clinical study in which 60 eligible patients were randomly assigned into 3 groups (20 subjects in each) and were treated for a period of 14 days with rosuvastatin 10 mg/d (R group), ezetimibe 10 mg/d (E group), and rosuvastatin 10 mg/d plus ezetimibe 10 mg/d (R+E group), respectively (Zhang et al., 2017).
- A study in which a total of 125 patients were randomly assigned to an intermediate intensity rosuvastatin group (rosuvastatin 10 mg/d, n = 42), high-dose rosuvastatin group (rosuvastatin 20 mg/d, n = 41) or combination therapy group (ezetimibe 10 mg/d and rosuvastatin 10 mg/d, n = 42) with a 12-week follow-up (Ran et al., 2017).
- A multicentre eight-week randomised double-blind phase III study (MRSROZE_ Multicenter Randomised Study of ROsuvastatin and eZEtmibe) which evaluated the efficacy of fixed-dose combinations of ezetimibe 10 mg plus rosuvastatin, compared with rosuvastatin alone in patents with primary hypercholesterolemia in 407 patients with primary hypercholesterolemia (Kim et al., 2016).
- A study including 106 patients with coronary atherosclerotic heart disease and hyperlipidaemia who were randomly assigned to one of two groups: (1) ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n = 55) or (2) rosuvastatin alone (10 mg, once a night) (n = 51) for 12 months (Wang et al., 2016).

- In a 12-week, prospective, randomised, open-label clinical study, Saeedi et al examined the efficacy of combination treatment with rosuvastatin and the cholesterol transport blocker, ezetimibe, vs. monotherapy with rosuvastatin in patients not achieving lipid goal (Saeedi et al., 2015).
- In a prospective randomised open-label study, a total of 51 patients with stable coronary artery disease requiring percutaneous coronary intervention were enrolled, and assigned to a combination group (n = 26, rosuvastatin 5 mg/day + ezetimibe 10 mg/day) or a monotherapy group (n = 25, rosuvastatin 5 mg/day) (Masuda et al., 2015).
- In a randomised clinical study (GRAVITY study), adult patients (n = 833) were randomised to rosuvastatin (RSV)10 mg/ezetimibe (EZE)10 mg, RSV20 mg/EZE10 mg, SIM40 mg/EZE10 mg or SIM80 mg/EZE10 mg for 12 weeks (Ballantyne et al., 2014)
- In a randomised open-label study, diabetic patients under treatment with rosuvastatin (2.5 mg daily), who had LDL-C levels ≥80 mg/dL (n = 79) were randomly allocated to two groups: the add-on ezetimibe group (combination group) that received 2.5 mg/day of rosuvastatin and 10 mg/day of ezetimibe (n = 40), and the rosuvastatin dose escalation group that received 5 mg/day of rosuvastatin (n = 39) for 12 weeks (Torimoto et al., 2013).
- A prospective randomised, open-label study for a 12-month prognosis after vascular surgery. Patients were randomly assigned to receive rosuvastatin (RSV) 10 mg/d or rosuvastatin 10 mg/d plus ezetimibe (RSV/EZT) 10 mg/d, starting prior to scheduled surgical procedure (Kouvelos et al., 2013).
- A prospective open randomised study, in which 17 patients with heterozygous familial hypercholesterolemia and single LDL receptor gene mutations were enrolled. Study subjects were divided into two groups: rosuvastatin 20 mg/day (group 1) versus rosuvastatin 10 mg/day coadministered with ezetimibe 10 mg/day (group 2) (Kawashiri et al., 2012).
- A multicentre, six-week, randomised, double-blind, parallel-group, clinical trial (ACTE study) evaluated the efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus uptitration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg. The study population included 440 subjects at moderately high/high risk of coronary heart disease with low-density lipoprotein (LDL) (Bays et al., 2011).
- In a prospective study one group of patients (n=33) were administered with ezetimibe 10 mg/day alone for 12 weeks. In the other two groups, ezetimibe was given with an HMG-CoA reductase inhibitor (statin) to 13 patients for 12 weeks: pravastatin 10 mg/day (n = 7) or rosuvastatin 2.5 mg/day (n = 6) for 12 weeks. (Sawayama et al., 2010)
- In an open-label, 12-week sub study within a larger trial, ezetimibe 10 mg was added to stable therapy with rosuvastatin 40 mg (± bile acid sequestrant/niacin) in 107 patients with severe hypercholesterolemia (Stein et al., 2007).
- Another clinical study (EXPLORER study) aimed to investigate the efficacy of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg. Four hundred sixty-nine patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for six weeks (Ballantyne et al., 2007).

Furthermore, the MAH mentions that a more pronounced LDL-C reduction when adding ezetimibe to a statin should reduce the risk for major cardiovascular events which has been

shown in the IMPROVE-IT trial (Cannon et al., 2015). When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. In various other studies, add-on ezetimibe was significantly more effective in reducing LDL-C levels than doubling the statin dose, enabling more patients to achieve LDL-C goals (Mikhailidis et al., 2011). Further, reference is made to the JUPITER study.

c. Demonstration that the evidence presented - if based on combined administration of separate active substances - is relevant to the FDC product for which the application is made
Bridging studies comparing pharmacokinetic data between the FDC product and authorised active substances taken simultaneously is essential and bioequivalence should be demonstrated. Bioequivalence of the FDC product is in general required to bridge existing clinical data obtained from the combined use of mono-components with those from the FDC formulation. In order to support the clinical equivalence of the product, bioequivalence studies have been performed on the highest strength of the current application, 40 mg/10 mg (Rosuvastatin/Ezetimibe) versus Crestor (Rosuvastatin) film-coated tablets of AstraZeneca B.V Netherlands and Ezetrol (Ezetimibe) 10 mg Tablets of Merck Sharp & Dohme Ltd. Greece). In addition, two pilot bioequivalence studies in the same strength (40 mg/10 mg) were conducted, in order to decide the design and sample size for the pivotal study.

IV.5 Clinical safety

Rosuvastatin
Data has been presented based on information in the SmPC of AstraZeneca, 2017; AstraZeneca UK Limited, 2016; MHRA, 2017b. Safety information based on publication has also been presented.

Ezetimibe
Data has been presented based on information in the SmPC of Merck Sharp & Dohme Limited, 2016; MHRA, 2017a. Safety information based on publication has also been presented.

Rosuvastatin and ezetimibe
Several studies have been presented. These studies have also been included in the efficacy section. The largest studies are mentioned below:

- In an eight-week, double-blind, multicentre, Phase III randomised controlled trial (IROSETTE) conducted at 20 hospitals, patients with hypercholesterolemia were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg in a 1:1:1:1:1:1 ratio. Among the 392 patients in the safety profile set, 44 (11.2%) experienced at least one adverse event (AE) after randomization. The most common AEs were gastrointestinal disorders, followed by investigations and musculoskeletal and connective tissue disorders. There were no significant differences in the overall incidence of AEs, adverse drug reactions (ADRs), or serious AEs. The observed AEs and frequency of drug-related AEs experienced by ≥2% of patients are the following ones (Hong et al., 2018).

- A multicentre eight-week randomised double-blind phase III study evaluated the safety of fixed-dose combinations of ezetimibe 10 mg plus rosuvastatin, compared with rosuvastatin alone in patents with primary hypercholesterolemia. 407 patients with primary hypercholesterolemia who required lipid-lowering treatment according to the ATP III guideline were randomised to one of the following six treatments for eight weeks: fixed dose combinations with ezetimibe 10 mg daily plus rosuvastatin (5, 10, or 20 mg daily) or rosuvastatin alone (5, 10, or 20 mg daily). No serious drug-related AEs were reported. There were three serious AEs, including one in the monotherapy group (breast cancer) and two in the combo therapy group (left ulnar fracture and epigastric pain), although these were not considered drug-related AEs by the investigators. The incidence of prespecified AEs was generally comparable between the two groups, with no clinically meaningful differences or statistical significance. Consecutive elevations ≥three times the upper normal limits in alanine aminotransferase or aspartate aminotransferase occurred in one (0.5%) of 204 patients receiving monotherapy and one (0.5%) of 206 patients receiving combo therapy. Elevations ≥five-times the upper normal limits in creatine kinase occurred only in one (0.5%) of 204 patents receiving combo therapy, with no significant differences between the groups (Kim et al., 2016).
- In a 12-week, randomised, double-blind, placebo-controlled, multicentre study, a total of 337 patients were screened. After a four-week run-in period, 245 of these patients with high or moderately high risk as defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines were randomly assigned. Patients received one of six regimens for eight weeks as follows: (1) rosuvastatin 5 mg, (2) rosuvastatin 5 mg/ezetimibe 10 mg, (3) rosuvastatin 10 mg, (4) rosuvastatin 10 mg/ ezetimibe 10 mg, (5) rosuvastatin 20 mg, or (6) rosuvastatin 20 mg/ezetimibe 10 mg. The proportions of patients who experienced any AE in the rosuvastatin monotherapy and the rosuvastatin/ezetimibe combination groups were similar (26 patients [21.5%] and 26 patients [21.1%], respectively). Patients with serious AEs or discontinued drugs for AEs were not common in either group. No individuals reported rhabdomyolysis, liver enzyme elevation, or muscle enzyme elevation above predefined levels (Yang et al., 2017).
- A study conducted by Ballantyne investigated the safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease. 469 patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks. Both treatments were well tolerated, and the overall frequency and type of AEs were similar between treatment groups. Adverse events were experienced by 31.5% and 33.5% of patients receiving combination therapy or monotherapy, respectively. Frequencies of liver, muscle, and renal AEs were low in both groups. Myalgia was the most frequently reported AE in both treatment groups. Most AEs were mild to moderate in intensity. The most frequently reported treatment-related AE was increased ALT in the combination therapy group (n = 6 [2.5%]) and myalgia in the monotherapy group (n=5 [2.2%]) (Ballantyne et al., 2007).
- Adult patients (n= 833) were randomised to rosuvastatin (RSV) 10 mg/ezetimibe (EZE) 10 mg, RSV20/EZE10, SIM40/EZE10 or SIM80/EZE10. Following a six-week dietary lead-in, patients received six weeks' statin monotherapy followed by same statin dose plus

ezetimibe for six more weeks. AEs were experienced by 32.7% and 31.4% of patients overall during monotherapy and combination therapy, respectively. Overall incidence of liver, muscle and renal AEs was low in all treatment groups during monotherapy and combination therapy: one case of myopathy was reported in the rosuvastatin 10 mg group; one case of myopathy was reported in the rosuvastatin 20 mg/ezetimibe 10 mg group during combination therapy. No cases of rhabdomyolysis were reported. 19 patients discontinued due to an AE during monotherapy. The most common AE leading to withdrawal was myalgia, occurring in one patient each in the rosuvastatin 10 mg and simvastatin 40 mg groups and three patients in the rosuvastatin 20 mg group. Twelve patients discontinued due to an AE during combination therapy. The most frequent AEs leading to withdrawal were fatigue, muscle spasms and dizziness, with each occurring in no more than one patient in any group and no notable differences in the frequency of AEs between groups. During monotherapy, 12 patients (1.4%), distributed across all groups, experienced serious adverse events (SAEs). Two patients in the rosuvastatin 20 mg group experienced a cerebrovascular accident, and all other SAEs occurred in no more than one patient. 16 patients (2.1%) experienced an SAE during combination therapy. The most frequent SAE was unstable angina occurring in two patients receiving rosuvastatin 10 mg plus ezetimibe and three patients receiving simvastatin 40 mg plus ezetimibe. All other SAEs were isolated reports. No deaths occurred during the study (Ballantyne et al., 2014).

- A multicentre, six-week, randomised, double-blind, parallel-group, clinical trial evaluated the safety of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg. The study population included 440 subjects at moderately high/high risk of coronary heart disease with low-density lipoprotein (LDL) cholesterol levels higher than the National Cholesterol Education Program Adult Treatment Panel III recommendations. All doses of rosuvastatin (10, 20 mg) and rosuvastatin (5, 10 mg) plus ezetimibe 10 mg add-on were generally well tolerated during the six-week study. Analysis of the pooled rosuvastatin (5 mg and 10 mg) plus ezetimibe add-on and pooled rosuvastatin up-titration (10 and 20 mg) showed a similar incidence of one AE, drug related AE, and serious AE. No serious drug-related AEs were observed during the present study. Drug-related discontinuations that occurred during rosuvastatin plus ezetimibe add-on therapy included mild or moderate arthralgia, constipation, myalgia, dermatitis allergic, or eczema. The incidence of prespecified AEs of special interest was low, with no significant differences seen between the pooled groups. Only one subject in the rosuvastatin 5- mg plus ezetimibe 10-mg group experienced an elevation in alanine aminotransferase of three times the upper limit of normal, but it was not related to treatment. No patient experienced elevations in aspartate aminotransferase of three times the upper limit of normal. Only one subject in the rosuvastatin 20 mg group experienced an asymptomatic elevation in creatine kinase of 10 times the upper limit of normal. It was judged by the site investigator to not be related to drug therapy. The most common AE was gastrointestinal related. Ten subjects experienced the following drug-related clinical AEs while receiving ezetimibe added to rosuvastatin 5 mg or 10 mg: abdominal distension in one, abdominal pain in one, constipation in two, dry mouth in one, nausea in one, arthralgia in one, myalgia in two, dermatitis in one, and

eczema in one patient. Six subjects who received rosuvastatin up-titrated to 10 or 20 mg experienced the following drug-related clinical AEs: constipation in two, asthenia in one, fatigue in one, myalgia in one, and skin exfoliation in one patient. The safety endpoints are presented in the following tables (Bays et al., 2011).

- Ran and his co-researchers randomly assigned 125 patients to an intermediate intensity rosuvastatin group (rosuvastatin 10 mg/d, n = 42), high-dose rosuvastatin group (rosuvastatin 20 mg/d, n = 41) or combination therapy group (ezetimibe 10 mg/d and rosuvastatin 10 mg/d, n = 42) with a 12-week follow-up. The incidence of drug-related adverse events was much higher in the rosuvastatin 20 mg group than the rosuvastatin 10 mg group and the combination therapy group (17.0% vs 2.4% vs 4.8%, P < 0.05). A total of ten patients experienced ADRs during the 12-week follow-up period. One patient in the rosuvastatin 20 mg group withdrew from our trial due to an elevated CK ≥five times the upper limit of normal values (ULN) on day five after the initiation of therapy. Patients in the rosuvastatin/ ezetimibe group and the rosuvastatin 10 mg group tolerated the treatments well and completed the study. One patient in the rosuvastatin 10 mg group experienced muscle pain. Seven patients in the rosuvastatin 20 mg group experienced adverse effects (one patient developed a rash and five patients had muscle pain), and two patients in the rosuvastatin/ezetimibe group reported AEs (one patient had muscle pain, and the other patient experienced gastrointestinal discomfort). No patients experienced rhabdomyolysis or obvious liver enzymes elevation. The total percent of ADRs in the rosuvastatin 20 mg group was significantly higher than those in the rosuvastatin 10 mg group and the rosuvastatin/ezetimibe group (17.0% vs. 2.4% vs. 4.8%, P< 0.05) (Ran et al., 2017).
- In a clinical study by Wang et al comprised of a study group with 106 patients with coronary atherosclerotic heart disease and hyperlipidaemia. Each patient was randomly assigned to one of two groups: (1) Ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n = 55) or (2) Rosuvastatin alone (10 mg, once a night) (n = 51). The primary endpoint was new or recurrent myocardial infarction, unstable angina pectoris, cardiac death, and stroke. In the rosuvastatin group, one patient was withdrawn due to AEs, one patient was withdrawn because of poor compliance and one patient was lost to follow-up. In the combination of ezetimibe plus rosuvastatin group, two patients were withdrawn due to AEs, one patient was withdrawn because of poor compliance and two patients were lost to follow-up. The major AEs were recorded during 12 months. AEs occurred in two groups: One case of abnormality of laboratory value Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) > three times ULN; one case of myalgia in the rosuvastatin group; two cases of abnormality of laboratory value AST or ALT > three times ULN, one case of myalgia in the ezetimibe plus rosuvastatin group. Two cases of myalgia in the two groups occurred in older patients (Wang et al., 2016).

IV.6 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 Rozesta.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	• Muscle injury (Rhabdomyolysis/myopathy) • Abnormal liver function
Important potential risks	None
Missing information	None

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

IV.7 Discussion on the clinical aspects

This decentralised procedure concerns a FDC application for for Rozesta 5 mg/10 mg; 10 mg/10 mg; 20 mg/10 mg and 40 mg/10 mg film-coated tablets, with Crestor 40 mg + Ezetrol 10 mg and Crestor 5 mg + Ezetrol 10 mg tablets as reference products. Two bioequivalence studies, one with the 40 mg/10 mg and one with the 5 mg/10 mg strength, were submitted. The results of the studies showed bioequivalence with respect to the rate and extent of absorption of rosuvastatin and ezetimibe between the test formulation and the respective individual reference formulations under fasting conditions.

Clinical Efficacy/Safety

For development of fixed combination medicinal products" [EMA/CHMP/158268/2017], a Marketing Authorisation Application (MAA) for a new FDC has to comply with the following requirements:

1. There has to be a justification of the pharmacological and clinical rationale for the combination
2. Establishment of the evidence base for a relevant contribution of all active substances to the desired therapeutic effect and a positive risk-benefit for the combination in the targeted population
3. Demonstration that the evidence presented - if based on combined administration of separate active substances - is relevant to the fixed combination medicinal product for which the application is made.

Justification of the pharmacological and clinical rationale

The MAH has provided a justification of the use of the combination of rosuvastatin and ezetimibe as already outlined in the introduction. Rosuvastatin and ezetimibe have different pharmacologic mechanisms. These pharmacological effects are considered to be synergistic in treating patient with increased lipid levels. This has been sufficiently discussed by the MAH. The use of the combination is supported by Learned Societies' guidelines (ESC/EAS. 2016). Further, combination products of rosuvastatin and ezetimibe are already approved.
For the general rationale to propose a FDC, there are some studies that indicate that a single-pill regimen would improve adherence. The MAH refers to the EMA fixed dose medicinal product guideline and publications in the relevant lipid lowering field to support this notion.

Relevant contribution of all active substances to the desired effect

The MAH provided an overview of several studies for the combination of statins with ezetimibe. These included several trials and pooled analyses of studies including several statins but also including data on the rosuvastatin/ezetimibe combination indicated the added value of lipid lowering effect in combination in patients with primary hypercholesterolemia, dyslipidaemia, and heterozygous familial hypercholesterolemia.

Moreover, specific studies combining rosuvastatin with ezetimibe have been presented. These studies were factorial design studies with several being open-label comparing (both or one of the) monocomponents to the combination for doses of 2.5 to 20 mg of rosuvastatin (mostly 10 mg) for lipid lowering as primary or one of the secondary endpoints.

The MAH further refers to studies that have investigated the combination with 40 mg rosuvastatin. Overall, these factorial designed studies can be considered to be of sufficient evidence for a substitution indication by demonstration that additional effect can be seen with addition of ezetimibe to ongoing rosuvastatin therapy.

The MAH has not specifically discussed the use of the combination in clinical practice, although, clinical practice guidelines acknowledge the combined use.

Safety data of a substantial number of patients treated with the combination have been provided based on literature data. The MAH provided data on several of the dedicated literature studies in rosuvastatin and ezetimibe as being used in combination as also presented in the efficacy section. These data do not appear to raise any concern and can be considered in line with the known safety profile of the monocomponents and that of the combination of ezetimibe with other statins.

Further, no interference on the safety profile of the components is expected, therefore, the safety profile of the individual components is also considered of importance. In this respect, the MAH has provided sufficient information based on the SmPC information, though the safety profile of the monocomponents is well known.

Overall, the combined safety data from these different sources provide an acceptable overview of the safety of the FDP of rosuvastatin and ezetimibe.

In conclusion, the data provide sufficient information for a positive benefit risk for a substitution indication.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the PL of rosuvastatin/ezetimibe Zentiva (for content, design and lay-out). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rozesta 5 mg/10 mg; 10 mg/10 mg; 20 mg/10 mg and 40 mg/10 mg film-coated tablets have a proven chemical-pharmaceutical quality and can be used as a substitute for Ezetrol and Crestor. Ezetrol and Crestor are well-known medicinal products with established favourable efficacy and safety profiles.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. Rozesta film-coated tablets were shown to be bioequivalent to the concomitant use of Crestor film-coated tablets and Ezetrol 10 mg film-coated tablets. The pharmacodynamic effects as well as the safety profile were shown to be similar. It is adequately shown that Rozesta can be used as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the FDC, but as separate products.

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 Rozesta with the reference product, and have therefore granted a marketing authorisation. The decentralised was finalised with a positive outcome on 4 February 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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

LITERATURE REFERENCES

Ambegaonkar, B.M., Tipping, D., Polis, A.B., Tomassini, J.E., Tershakovec, A.M., 2014. Achieving goal lipid levels with ezetimibe plus statin add-on or switch therapy compared with doubling the statin dose. A pooled analysis. Atherosclerosis 237, 829–837. https://doi.org/10.1016/j.atherosclerosis.2014.10.105

AstraZeneca, 2017. Product Monograph Crestor.

AstraZeneca UK Limited, 2016. SmPC Crestor.

Ballantyne, C.M., Hoogeveen, R.C., Raya, J.L., Cain, V.A., Palmer, M.K., Karlson, B.W., GRAVITY Study Investigators, 2014. 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 232, 86–93. https://doi.org/10.1016/j.atherosclerosis.2013.10.022

Ballantyne, C.M., Weiss, R., Moccetti, T., Vogt, A., Eber, B., Sosef, F., Duffield, E., EXPLORER Study Investigators, 2007. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am. J. Cardiol. 99, 673–680. https://doi.org/10.1016/j.amjcard.2006.10.022

Bangalore, S., Kamalakkannan, G., Parkar, S., Messerli, F.H., 2007. Fixed-dose combinations improve medication compliance: a meta-analysis. Am. J. Med. 120, 713–719. https://doi.org/10.1016/j.amjmed.2006.08.033

Bays, H.E., Davidson, M.H., Massaad, R., Flaim, D., Lowe, R.S., Tershakovec, A.M., Jones-Burton, C., 2011. 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. 108, 523–530. https://doi.org/10.1016/j.amjcard.2011.03.079

Catapano, A., Brady, W.E., King, T.R., Palmisano, J., 2005. Lipid altering-efficacy of ezetimibe co-administered with simvastatin compared with rosuvastatin: a meta-analysis of pooled data from 14 clinical trials. Curr. Med. Res. Opin. 21, 1123–1130. https://doi.org/10.1185/030079905X50642

Cannon, C.P., Blazing, M.A., Giugliano, R.P., McCagg, A., White, J.A., Theroux, P., Darius, H., Lewis, B.S., Ophuis, T.O., Jukema, J.W., De Ferrari, G.M., Ruzyllo, W., De Lucca, P., Im, K., Bohula, E.A., Reist, C., Wiviott, S.D., Tershakovec, A.M., Musliner, T.A., Braunwald, E., Califf, R.M., IMPROVE-IT Investigators, 2015. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N. Engl. J. Med. 372, 2387–2397. https://doi.org/10.1056/NEJMoa1410489

Daskalopoulou, S., Mikhailidis, D.P., 2004. Ezetimibe: A New Class of Cholesterol Lowering Drugs. Hellenic J Cardiol 48, 288–291.

European Society of Cardiology (ESC) and European Atherosclerosis, Society (EAS), 2016. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias.

Foody, J.M., Toth, P.P., Tomassini, J.E., Sajjan, S., Ramey, D.R., Neff, D., Tershakovec, A.M., Hu, H., Tunceli, K., 2013. Changes in LDL-C levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or rosuvastatin compared with titrating statin monotherapy. Vasc. Health Risk Manag. 9, 719–727. https://doi.org/10.2147/VHRM.S49840

Hamilton-Craig, I., Kostner, K., Colquhoun, D., Woodhouse, S., 2010. Combination therapy of statin and ezetimibe for the treatment of familial hypercholesterolemia. Vasc. Health Risk Manag. 6, 1023–1037. https://doi.org/10.2147/VHRM.S13496

Hong, S.J., Jeong, H.S., Ahn, J.C., Cha, D.-H., Won, K.H., Kim, W., Cho, S.K., Kim, S.-Y., Yoo, B.-S., Sung, K.C., Rha, S.-W., Shin, J.-H., Han, K.R., Chung, W.S., Hyon, M.S., Lee, H.C., Bae, J.-H., Rhee, M.-Y., Kwan, J., Jeon, D.W., Yoo, K.D., Kim, H.-S., 2018. A Phase III, Multicenter, Randomised, Double-blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy With Ezetimibe and Rosuvastatin Versus Rosuvastatin Monotherapy in Patients With Hypercholesterolemia: I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) Randomized Controlled Trial. Clin. Ther. 40, 226–241.e4. https://doi.org/10.1016/j.clinthera.2017.12.018

Inoue, I., Awata, T., Katayama, S., 2010. Retrospective, observation study: Quantitative and qualitative effect of ezetimibe and HMG-CoA reductase inhibitors on LDL-cholesterol: are there disappearance thresholds for small, dense LDL and IDL? Recent Pat Cardiovasc. Drug Discov. 5, 143–152. https://doi.org/10.2174/157489010791515386

Mikhailidis, D.P., Sibbring, G.C., Ballantyne, C.M., Davies, G.M., Catapano, A.L., 2007. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. Curr Med Res Opin 23, 2009–2026. https://doi.org/10.1185/030079907X210507

Kawashiri, M.-A., Nohara, A., Noguchi, T., Tada, H., Nakanishi, C., Mori, M., Konno, T., Hayashi, K., Fujino, N., Inazu, A., Kobayashi, J., Mabuchi, H., Yamagishi, M., 2012. Efficacy and safety of coadministration of rosuvastatin, ezetimibe, and colestimide in heterozygous familial hypercholesterolemia. Am. J. Cardiol. 109, 364–369. https://doi.org/10.1016/j.amjcard.2011.09.019

Kim, K.-J., Kim, S.-H., Yoon, Y.W., Rha, S.-W., Hong, S.-J., Kwak, C.-H., Kim, W., Nam, C.-W., Rhee, M.-Y., Park, T.-H., Hong, T.-J., Park, S., Ahn, Y., Lee, N., Jeon, H.-K., Jeon, D.-W., Han, K.-R., Moon, K.-W., Chae, I.-H., Kim, H.-S., 2016. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter

Randomized Study of ROsuvastatin and eZEtimibe). Cardiovasc. Ther. 34, 371–382. https://doi.org/10.1111/1755-5922.12213

Kosoglou, T., Statkevich, P., Yang, B., Suresh, R., Zhu, Y., Boutros, T., Maxwell, S.E., Tiessen, R., Cutler, D.L., 2004b. Pharmacodynamic interaction between ezetimibe and rosuvastatin. Curr Med Res Opin 20, 1185–1195. https://doi.org/10.1185/030079904125004213

Kouvelos, G.N., Arnaoutoglou, E.M., Matsagkas, M.I., Kostara, C., Gartzonika, C., Bairaktari, E.T., Milionis, H.J., 2013. 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. 18, 5–12. https://doi.org/10.1177/1074248412445506

Masuda, J., Tanigawa, T., Yamada, T., Nishimura, Y., Sasou, T., Nakata, T., Sawai, T., Fujimoto, N., Dohi, K., Miyahara, M., Nishikawa, M., Nakamura, M., Ito, M., 2015. Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease. Int. Heart J. 56, 278–285. https://doi.org/10.1536/ihj.14-311

Merck Sharp & Dohme Limited, 2016. SmPC Ezetrol.

MHRA, 2017a. Public Assessment Report_Ezetimibe.

MHRA, 2017b. Public Assessment ReportRosuvastatin tablets.

Morrone, D., Weintraub, W.S., Toth, P.P., Hanson, M.E., Lowe, R.S., Lin, J., Shah, A.K., Tershakovec, A.M., 2012. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis 223, 251–261. https://doi.org/10.1016/j.atherosclerosis.2012.02.016

Okada, K., Iwahashi, N., Endo, T., Himeno, H., Fukui, K., Kobayashi, S., Shimizu, M., Iwasawa, Y., Morita, Y., Wada, A., Shigemasa, T., Mochida, Y., Shimizu, T., Sawada, R., Uchino, K., Umemura, S., Kimura, K., 2012. Long-term effects of ezetimibe-plus-statin therapy on low-density lipoprotein cholesterol levels as compared with double-dose statin therapy in patients with coronary artery disease. Atherosclerosis 224, 454–456. https://doi.org/10.1016/j.atherosclerosis.2012.07.036

Pitsavos, C., Skoumas, I., Tousoulis, D., Metalinos, G., Masoura, C., Chrysohoou, C., Papadimitriou, L., Giotsas, N., Toutouza, M., Antoniades, C., Stefanadis, C., 2009. The impact of ezetimibe and high-dose of statin treatment on LDL levels in patients with heterozygous familial hypercholesterolemia. Int. J. Cardiol. 134, 280–281. https://doi.org/10.1016/j.ijcard.2007.12.065

Ran, D., Nie, H.-J., Gao, Y.-L., Deng, S.-B., Du, J.-L., Liu, Y.-J., Jing, X.-D., She, Q., 2017. A randomized, controlled comparison of different intensive lipid-lowering therapies in Chinese patients with non-ST-elevation acute coronary syndrome (NSTE-ACS): Ezetimibe and

rosuvastatin versus high-dose rosuvastatin. Int. J. Cardiol. 235, 49–55. https://doi.org/10.1016/j.ijcard.2017.02.099

Ren, Y., Zhu, H., Fan, Z., Gao, Y., Tian, N., 2017. Comparison of the effect of rosuvastatin versus rosuvastatin/ezetimibe on markers of inflammation in patients with acute myocardial infarction. Exp Ther Med 14, 4942–4950. https://doi.org/10.3892/etm.2017.5175

Saeedi, R., Johns, K., Frohlich, J., Bennett, M.T., Bondy, G., 2015. Lipid lowering efficacy and safety of Ezetimibe combined with rosuvastatin compared with titrating rosuvastatin monotherapy in HIV-positive patients. Lipids Health Dis 14, 57. https://doi.org/10.1186/s12944-015-0054-x

Sandoz Canada Inc., 2013. Product Monograph Sandoz Ezetimibe.

Sawayama, Y., Maeda, S., Ohnishi, H., Hayashi, S., Hayashi, J., 2010. Efficacy and safety of ezetimibe for Japanese patients with dyslipidaemia: The ESSENTIAL Study. Clin Drug Investig 30, 157–166. https://doi.org/10.2165/11531530-000000000-00000

Stein, E.A., Amerena, J., Ballantyne, C.M., Brice, E., Farnier, M., Guthrie, R.M., Harats, D., Ma, P.T.S., Le Maulf, F., Melezínková, H., Gold, A., Sager, P., 2007. Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. Am. J. Cardiol. 100, 1387–1396. https://doi.org/10.1016/j.amjcard.2007.06.029

Sweeney, M.E., Johnson, R.R., 2007. Ezetimibe: an update on the mechanism of action, pharmacokinetics and recent clinical trials. Expert Opin Drug Metab Toxicol 3, 441–450. https://doi.org/10.1517/17425255.3.3.441

Torimoto, K., Okada, Y., Mori, H., Hajime, M., Tanaka, K., Kurozumi, A., Narisawa, M., Yamamoto, S., Arao, T., Matsuoka, H., Inokuchi, N., Tanaka, Y., 2013. Efficacy of combination of Ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. Lipids Health Dis 12, 137. https://doi.org/10.1186/1476-511X-12-137

Wang, X., Zhao, X., Li, L., Yao, H., Jiang, Y., Zhang, J., 2016. Effects of Combination of Ezetimibe and Rosuvastatin on Coronary Artery Plaque in Patients with Coronary Heart Disease. Heart Lung Circ 25, 459–465. https://doi.org/10.1016/j.hlc.2015.10.012

Yang, Y.-J., Lee, S.-H., Kim, B.S., Cho, Y.-K., Cho, H.-J., Cho, K.I., Kim, S.-Y., Ryu, J.K., Cho, J.-M., Park, J.-I., Park, J.-S., Park, C.G., Chun, W.J., Kim, M.-A., Jin, D.-K., Lee, N., Kim, B.J., Koh, K.K., Suh, J., Lee, S.-H., Lee, B.-K., Oh, S.-J., Jin, H.-Y., Ahn, Y., Lee, S.-G., Bae, J.-H., Park, W.J., Lee, S.-C., Lee, H.C., Lee, J., Park, C., Lee, B., Jang, Y., 2017. Combination Therapy of Rosuvastatin and Ezetimibe in Patients with High Cardiovascular Risk. Clin Ther 39, 107–117. https://doi.org/10.1016/j.clinthera.2016.11.014

Zhang, J., Long, M., Yu, Y., 2017. The effects of additional ezetimibe treatment to baseline rosuvastatin on circulating PCSK9 among patients with stable angina. J Thorac Dis 9, 1226–1233. https://doi.org/10.21037/jtd.2017.03.186