CBG MEB

Public Assessment Report

Scientific discussion

Rosuvastatine/Ezetimibe Althera 20 mg/10 mg, film-coated tablets

(rosuvastatin calcium/ezetimibe)

NL/H/3679/002/DC

Date: 15 October 2019

This module reflects the scientific discussion for the approval of Rosuvastatine/Ezetimibe Althera 20 mg/10 mg, film-coated tablets. The procedure was finalised on 18 May 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rosuvastatine/Ezetimibe Althera 20 mg/10 mg, film-coated tablets from Althera Laboratories Ltd.

Rosuvastatine/Ezetimibe Althera 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 a fixed dose combination of rosuvastatin (20 mg) as calcium salt and ezetimibe (10 mg). Rosuvastatin and ezetimibe are both approved medicinal products, marketed worldwide for many years. The innovator product Crestor 20 mg film-coated tablets (rosuvastatin, as rosuvastatin calcium) 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/0343/002/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 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.

The concerned member states (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC. The application concerns a line extension of the already registered strength of Rosuvastatine/Ezetimibe Althera 10 mg/10 mg (NL/H/3679/001/DC).

Paediatric Investigation Plan

No Paediatric Investigation Plan (PIP) has been submitted. A product specific waiver has been granted by the EMA, since the proposed drug product will be administered to adult patients only.

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine/Ezetimibe Althera is a pink coloured round shaped bilayer film-coated tablet plain on both sides.

Each film-coated tablet contains 20 mg rosuvastatin (as calcium) and 10 mg of ezetimibe.

Rosuvastatine/Ezetimibe Althera is packed in OPA/Al/PVC-Al blister packs.

The excipients are:
Rosuvastatin core - pregelatinised (maize) starch, microcrystalline cellulose (E460), meglumine, calcium hydrogen phosphate dihydrate (E341), crospovidone (E1202), colloidal anhydrous silica (E551) and sodium stearyl fumarate.
Ezetimibe core - mannitol (E421), butylhydroxyanisole (E320), sodium laurilsulfate (E487), croscarmellose sodium (E468), povidone (K-30) (E1201), iron oxide red (E172), magnesium stearate (E470 b) and sodium stearyl fumarate.
Tablet coating - hypromellose (E464), titanium dioxide (E171), macrogol 4000 and iron oxide red (E172).

II.2 Drug Substances

Rosuvastatin calcium
The active substance is rosuvastatin calcium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder. It is an optically active molecule, having two chiral centres. The required stereochemistry of the drug substance is 3R, 5S. Rosuvastatin calcium is amorphous in nature.

The CEP procedure 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 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., with additional requirements for residual

solvents, particle size, and polymorphic form. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Ezetimibe

The active substance is ezetimibe, an established active substance that is not described in the Ph.Eur. A United States Pharmacopoeia (USP) monograph on ezetimibe became official on 1 December 2015. Ezetimibe is a white crystalline powder. It is freely to very soluble in ethanol, methanol, acetonitrile and acetone, practically insoluble in water, and insoluble in hexane. Ezetimibe possesses three asymmetric carbons and consequently, it exhibits optical isomerism. The manufacturing process of ezetimibe results in the 3S,3R,4S isomer. Ezetimibe exhibits polymorphism. The anhydrous form is obtained by the manufacturing process.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of eight steps. Starting materials are sufficiently characterised. No metal catalysts are used. The active substance was adequately described.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. It is established in-house and includes an additional requirement for particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data have been presented for three pilot scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months) as well as for an additional 12 batches of larger batch sizes covering zero to 24 months at long term conditions and one to six months at accelerated conditions. No significant changes were observed. The drug substance does not need a temperature storage condition. It was shown to be photostable. As the drug substance is hygroscopic, the proposed storage condition 'Store in a tightly closed container to protect from moisture' is justified.

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. An alkalizer has been included to protect rosuvastatin from acid hydrolysis. Butylated hydroxyanisole as antioxidant is included to protect ezetimibe from oxidative degradation. The 20 mg/10 mg strength tablet is fully dose proportional to the already approved 10 mg/10 mg strength tablet. One bioequivalence study has been submitted. Overall, sufficient information has been provided on formulation and manufacturing process development.

Manufacturing process

The manufacturing process of the drug product can be divided in three steps: manufacture of rosuvastatin granules; manufacture of ezetimibe granules; compression into bi-layer tablets and film-coating of tablets. The process is a standard manufacturing process. Process and in process controls are described in sufficient detail. Process validation data on the product have been presented for three pilot scale batches in accordance with relevant European guidelines. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. requirements, except Opadry Pink, which complies with in-house specifications, although reference is made to usual standards for the individual components of Opadry Pink. Butylated hydroxyanisole is used as anti-oxidant; its use and the quantity have been justified. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, dimensions, identity of the active substances, colourant and of butylated hydroxyanisole, average mass, uniformity of dosage units by content uniformity, disintegration time, water content, dissolution, chromatographic purity, assay of drug substances and of butylated hydroxyanisole, residual solvents and microbiological quality. All specification limits are similar or in line with the limits approved for the 10 mg/10 mg strength, except for the limits for total impurities of rosuvastatin and the shelf-life specification for specified impurities. The wider specification is acceptable as it is in line with the Ph.Eur. monograph of rosuvastatin. The proposed limit has been adequately qualified based on non-clinical data. Tightening of the shelf-life specifications for total impurities should be re-evaluated when the additional stability data are available.

Batch analytical data from three pilot scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability studies at accelerated and long-term conditions are performed on three batches in the primary packaging material. The batches are the same as used in process validation. The provided data at long-term conditions consist of 18 months data for three batches. On the

basis of the data submitted, a shelf life was granted of 24 months when stored in the original package in order to protect from light and moisture. Hence one of the components of the product, rosuvastatin, is reported in literature as being photosensitive.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies

The materials used in rosuvastatin/ezetimibe film-coated tablets comply with Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

The non-clinical overview is adequate, providing an overview of available information on pharmacology and pharmacokinetics of the active substances. Additional non-clinical studies are not needed since all the active substances were already tested for safety and efficacy, alone or in combination in similar already marketed products.

III.2 Toxicology

To qualify a specified impurity at a specification level, the MAH has performed two in vitro genotoxicity studies with the impurity alone, and a 90-day repeated dose toxicity study in rats with ezetimibe spiked with 3% impurity. These studies are in accordance with ICH guideline Q3B. The results indicate that the impurity has no genotoxic potential and does not induce new toxicities when present at 3%. Therefore, the specification limit is toxicologically qualified.

III.3 Ecotoxicity/environmental risk assessment (ERA)

Since Rosuvastatine/Ezetimibe Althera is intended for substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.4 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of established active substances. 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

In order to support the application a bioequivalence study has been performed to compare the rate and extent of absorption of Rosuvastatin/Ezetimibe Althera 20 mg/10 mg and the active substances administered at the same time but as separate tablets. Further clinical evaluation of Rosuvastatin/Ezetimibe Althera 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.

IV.2 Pharmacokinetics

The clinical overview provides a sufficient pharmacokinetic overview of rosuvastatin and ezetimibe. Additionally the MAH provided information on the potential of pharmacokinetic interaction of rosuvastatin and ezetimibe. The MAH discussed an article (Kosoglou et al., 2004) in which no evidence could be found for a clinically relevant pharmacokinetic interaction between rosuvastatin and ezetimibe. This is confirmed by the innovator SmPC of both separate compounds.

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine/Ezetimibe Althera 20 mg/10 mg film-coated tablets (Althera Laboratories Ltd, Germany) is compared with the pharmacokinetic profile of the reference products Crestor 20 mg film-coated tablets (AstraZeneca, United Kingdom) and Ezetrol 10 mg film-coated tablets (Merck Sharp & Dohme, United Kingdom).

The choice of the reference products

The choice of the reference products in the bioequivalence study has been justified.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, pivotal bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 20-44 years. Each subject received a single dose (20 mg

rosuvastatine and 10 mg ezetimibe) of one of the two formulations (fixed dose combination or concomitant intake). A single dose of the assigned formulations were orally administered with 150 ml water in the morning after an overnight fast of at least eight hours followed by a post-dosing fast of at least five hours. Two dosing periods were conducted which were separated by a respective washout period of 14 days.

For rosuvastatin analysis one pre-dose blood sample was collected within 1 hour prior to dosing and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 7.5, 12, 16, 24, 48 and 72 hours post dose.
For ezetimibe analysis one pre-dose blood sample was collected within 1 hour prior to dosing and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6.5, 8, 10, 12, 16, 24, 48 and 72 hours post dose.

The design is acceptable, wash-out long enough, sampling period long enough, and the sampling scheme is adequate to estimate pharmacokinetic parameters. Both drugs can be taken with and without food.

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
Six subjects did not visit the facility for period two check in and one subject dropped out form the study during period two post dose due to non-health related personal emergency. Therefore 66 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=66	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	250 ± 98	254 ± 99	27.5 ± 12.9	3.0 (1.0-5.5)	12.4 ± 2.7
Reference	253 ± 103	257 ± 103	27.9 ± 12.7	3.3 (1.0-5.5)	12.0 ± 2.5
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	--	0.99 (0.93 – 1.05)	--	--
CV (%)	17.92	--	20.85	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of unconjugated ezetimibe under fasted conditions.

Treatment N=40	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	92873 ± 30011	101513 ± 37385	4531 ± 1726	6.5 (0.3-16.0)	16.9 ± 7.5
Reference	87337 ± 27367	93206 ± 30486	4659 ± 1948	6.5 (0.3-16.0)	15.0 ± 5.4
***Ratio (90% CI)**	1.06 (1.02 – 1.12)	--	1.00 (0.93 – 1.07)	--	--
CV (%)	16.13	--	22.79	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

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 study Rosuvastatine/Ezetimibe Althera 20 mg/10 mg film-coated tablets is considered bioequivalent with Crestor 20 mg film-coated tablets co-administered with Ezetrol 10 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Pharmacodynamics

The mechanism of action and main pharmacodynamic effects of rosuvastatin and ezetimibe as part of the fixed dose combination is sufficiently discussed.

Rosuvastatin

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

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. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 3: Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

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

A therapeutic effect is obtained within one week following treatment initiation and 90% of maximum response is achieved in two weeks. The maximum response is usually achieved by four weeks and is maintained after that.

Ezetimibe

Ezetimibe is in a class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. 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). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. The molecular mechanism of action is not fully understood. In a two week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of (14C)-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

A beneficial effect of ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated.

IV.4 Clinical efficacy

Efficacy data from clinical studies on concomitant use of rosuvastatin and ezetimibe

The individual components (rosuvastatin and ezetimibe) comprising the proposed drug product have well-established clinical use and well-characterised safety and efficacy profiles. Clinical efficacy of rosuvastatin and ezetimibe has been studied in well-controlled randomised clinical studies across different ethnicities, ages and geographies (Crestor SmPC; Ezetrol SmPC). Efficacy of concomitant therapy with rosuvastatin 10 mg and ezetimibe 10 mg has been investigated in several clinical studies. Among them, there are three primary prospective clinical trials with high significance published in reputed journals: The ACTE study (Bays et al., 2011), the EXPLORER study (Ballantyne et al., 2007), and the GRAVITY study (Ballantyne et al., 2014). These studies have been conducted according to GCP guidelines and are summarised in the SmPC of the approved combination medicinal products comprising rosuvastatin and ezetimibe (Rosuzet product information; Rosuvastatine/Ezetimibe EGIS SmPC). Therefore, these studies have been selected as key studies supporting the safety and efficacy of concomitant use of rosuvastatin and ezetimibe.

It has been shown that the clinical efficacy of rosuvastatin/ezetimibe combination (10 mg each) has superior clinical performance compared to 10 mg rosuvastatin alone. Moreover, some of the clinical studies demonstrate that the LDL-C reduction is more efficient in patients that receive an add-on of 10 mg ezetimibe compared to up-titration of rosuvastatin (Bays et al., 2011).

The overview of the studies and key findings on efficacy as well as the respective references are detailed in the tables below.

Table 4: Key clinical studies reporting efficacy of rosuvastatin/ezetimibe

Reference	Description	Study Design	Efficacy results
Bays et al., 2011	Multicentre, 6-week, randomised, double-blind, parallel-group, 440 patient clinical trial to evaluate the safety and efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or	Subjects were centrally randomised into equalise double-blind treatment groups of ezetimibe 10 mg added to the run-in dose of rosuvastatin or up-titration of the run-in dose of rosuvastatin for 6 weeks. The primary efficacy end point was the % change from LDL-C baseline evaluated in the overall population and secondary point	• Compared to rosuvastatin up-titration, ezetimibe add-on achieved significantly greater LDL-C levels of <70 or <100 mg/dl (59.4% vs 30.9%, p <0.001), and <70 mg/dl in all subjects (43.8% vs 17.5%, p<0.001). • Ezetimibe added to stable rosuvastatin 5 mg or 10 mg reduced LDL cholesterol by 21%. In contrast, doubling rosuvastatin to 10 mg or 20 mg reduced LDL cholesterol by 5.7% (p

	from 10 to 20 mg.	was % of subjects reaching the NCEP ATP III LDL-C targets.	<0.001) • Combination cohort demonstrated significantly greater reductions in TC, non-HDLC and Apo B
Ballantyne et al., 2014	An open-label, 833 patient, randomised study, examined the efficacy and safety of 10 mg of rosuvastatin or 20 mg of rosuvastatin along with 10 mg of ezetimibe and compared it with significantly higher dosages of simvastatin 40 mg or simvastatin 80 mg along with 10 mg of ezetimibe	After a 6-week dietary lead-in and washout of lipid-lowering drugs, patients received rosuvastatin 10 mg, rosuvastatin 20 mg, simvastatin 40 mg, or simvastatin 80 mg monotherapy for 6 weeks. Ezetimibe 10 mg was then added to each regimen for a further 6 weeks. Primary outcome studied was % change from baseline LDL-C at week 12 of the study.	• 93.3% of patients reached the NCEP ATP III goal of LDL-C <100 mg/dl with the treatment with rosuvastatin 10 mg and ezetimibe 10 mg, and 67.1% reached goal of LDL-C <70 mg/dl; 95.6% of patients reached NCEP ATP III goal of LDL-C <100 mg/dl, and 77% reached goal of LDL-C <70 mg/dl. • Rosuvastatin 10 mg and ezetimibe 10 mg combined treatment significantly reduced LDL-C, TG, non-HDL-C, and Apo-B compared with simvastatin 40 mg and ezetimibe 10 mg.
Ballantyne et al., 2007	Multicentre, 6-week, randomised, double-blind, study of 469 patients was designed to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease.	Patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks. The primary end point was the % of patients achieving ATPIII LDL-C goal (<100 mg/dl) at week 6.	• Significantly more patients receiving rosuvastatin/ezetimibe than rosuvastatin alone achieved ATP III LDL-C goal (<100 mg/dl, 94.0% vs 79.1%, p <0.001) and the optional LDL-C goal (<70 mg/dl) for high-risk patients (79.6% vs 35.0%, p <0.001). • The combination of rosuvastatin/ezetimibe reduced LDL-C significantly more than rosuvastatin (69.8% vs. 57.1%, p <0.001). • Other components of the lipid profile were also

			significantly (p <0.001) improved with rosuvastatin/ezetimibe.

Additionally, further clinical trials evaluating the safety and efficacy of concomitant use of rosuvastatin and ezetimibe have been included in the present clinical overview (Kosoglou et al., 2004; Boufidou et al., 2007; Kouvelos et al., 2013; Styliadis et al., 2007). However, only a limited number of patients have been enrolled in most of these studies and no information on GCP compliance has been provided by the authors. In addition to the clinical trials, a large retrospective ezetimibe add-on study has been described by Foody et al. (2013) demonstrating improved efficacy of ezetimibe add-on therapy compared to up-titration of statins.
Additional data provided are the ODYSSEY OPTIONS II study (Farnier et al., 2015) that recently reported its results.

Table 5: Further clinical studies reporting efficacy of rosuvastatin/ezetimibe

Reference	Description	Study Design	Efficacy results
Kosoglou et al., 2004	Randomised, evaluator (single)-blind, placebo controlled, parallel-group study in 40 healthy hyper-cholesterolaemic subjects (untreated LDL-C ≥130 mg/dl [3.37 mmol/l]) evaluating the effects of ezetimibe 10 mg and rosuvastatin 10 mg either alone or in combination	Subjects were randomised to one of the four treatments: rosuvastatin 10 mg plus ezetimibe 10 mg (n=12); rosuvastatin 10 mg plus placebo (matching ezetimibe 10 mg) (n=12); ezetimibe 10 mg plus placebo (matching ezetimibe 10 mg) (n=8); or placebo (two tablets, matching ezetimibe 10 mg) (n=8) Dosing: once daily in the morning for 14 days as part of a 16-day inpatient confinement period.	• The co-administration of ezetimibe and rosuvastatin achieved a significantly (p <0.01) greater percentage reduction in mean LDL-C (-61.4%) than rosuvastatin alone (-44.9%), with a mean incremental reduction of -16.4% (95% CI, -26.3 to -6.53). • In this two-week inpatient study with restricted physical activity there was no apparent effect of any treatment on HDL-C or triglycerides.
Kouvelos et al., 2013	One-year, 262 patient study to evaluate rosuvastatin (RVZ) with or without ezetimibe (EZT) on clinical outcomes	Patients were randomly assigned to rosuvastatin 10 mg/d or rosuvastatin 10 mg/d plus ezetimibe 10 mg/d, starting prior to scheduled surgical	• 6.6% of patients in the RSV group experience a major cardiovascular event within 30 days after surgery versus 5.6% in the RSV/EZT group (p=0.72). • From month 1 to 12 of the

Reference	Description	Study Design	Efficacy results
	in patients undergoing elective vascular surgery.	procedure. Primary end point was the first major cardiovascular event, including death from cardiac causes, nonfatal myocardial infarction, ischemic stroke, and unstable angina.	follow-up period, primary end-point was observed (9 taking RSV vs 2 in the RSV/EZT group (p = 0.04)). • Intensified lipid-lowering therapy with RSV/EZT was associated with a greater decrease in LDL-C levels compared with RSV (75.87 +31.64 vs 87.19 +31.7, p=0.004). • No differential effect on triglyceride, HDL-C or high-sensitivity C-reactive protein levels was noted between groups.
Foody et al., 2013	Retrospective, observational ezetimibe add on study: Managed care data based 17,830 patient retrospective analysis to evaluate adding ezetimibe to simvastatin, atorvastatin, or rosuvastatin therapy versus titrating these statins on LDL-C changes and goal attainment in CHD or CHD risk-equivalent patients.	Eligible patients, identified between 1 November 2002 and 30 September 2009, included those >18 years of age who had a prescription for statin monotherapy with baseline and follow-up LDL-C values. No overlap with other lipid-lowering therapy. No discontinuations of lipid-lowering therapy at baseline or follow-up during the study period.	• LDL-C reductions from baseline and goal attainment improved substantially in patients treated with ezetimibe added onto simvastatin, atorvastatin, or rosuvastatin therapy (n = 2,312) versus those (n = 13,053) who titrated these statins. • In multi-variable models, % change from baseline in LDL-C was −13.1% to −14.8% greater for those who added ezetimibe onto simvastatin, atorvastatin, or rosuvastatin versus those who titrated. • LDL-C reduced in rosuvastatin + ezetimibe group by 32.3% versus 19.3% in the rosuvastatin titration group.
Styliadis et al., 2007	Six months co-administration	Male patients, mean age 56 ±10 years,	Co-administration of ezetimibe 10 mg plus

Reference	Description	Study Design	Efficacy results
	study: Six months 8 high-risk patient study to evaluate efficacy and safety of ezetimibe plus rosuvastatin.	serum concentration of lipoproteins, liver enzymes (ALT, AST) and creatine kinase (CK) were measured after 12h fasting, before and 6 months after the treatment Patients with LDL>190mg/dl and triglycerides<400mg/dl were enrolled in the study.	rosuvastatin 10 mg in patients with mixed dyslipidaemia (LDL >190 mg/dl, triglycerides <400 mg/dl) led to: • Statistically significant reduction of LDL-C (-60%) • Borderline statistically significant reduction of triglycerides (-9%) • Borderline statistically significant increase of HDL (+8%) • 75% of patients achieved LDL-C target
Boufidou et al., 2007	Six months comparison of combinations: 6-months, 22 patient study to compare efficacy and safety of rosuvastatin/ ezetimibe versus atorvastatin ezetimibe.	Ten patients received atorvastatin 10-20 mg/ezetimibe 10 mg (Group A) and 12 patients received rosuvastatin 10-20 mg/ezetimibe 10 mg (Group B). The two groups were comparable concerning age, gender, BMI, and the baseline levels of cholesterol. Serum lipoproteins, liver enzymes and CK were measured after 12h fasting, before and 6 months after the treatment. Patients with LDL >190 mg/dl and triglycerides <400 mg/dl were enrolled in the study.	• LDL-C was significantly reduced in both treatment groups. • LDL-C reduction was greater in rosuvastatin/ezetimibe group (-63% vs -59.4%). • Ezetimibe/atorvastatin (10-20 mg) was more effective in triglycerides reduction (-47.3% vs -31%). • Ezetimibe/rosuvastatin (10-20 mg) led to greater increase in HDL-C levels (19% vs 8%). • LDL-C target was achieved in higher percentage in the rosuvastatin/ezetimibe group (83% vs 60%).
Farnier et al., 2016	24 weeks, 305 patient, multicentre, double-blind, double-dummy, randomised,	Patients entered a 2 to 6-week screening period and were then randomised according to their baseline rosuvastatin regimen	• From baseline, add-on ezetimibe reduced LDL-C by 14.4%, and double-dose (20 mg) rosuvastatin reduced LDL-C by 16.3% (n=47).

Reference	Description	Study Design	Efficacy results
	phase III study to compare lipid-lowering efficacy of adding alirocumab to rosuvastatin versus other treatment strategies (ezetimibe add-on to rosuvastatin, doubling of rosuvastatin dose)	(10 mg or 20 mg/day). Treatment with either add-on therapy with alirocumab 75 mg every two weeks, add-on therapy with ezetimibe 10 mg/day, or doubling of the rosuvastatin dose Primary endpoint was percent change in calculated LDL-C from baseline to 24 weeks	• In the baseline rosuvastatin 10 mg regimen group, the proportion of patients at very-high and high CV risk who reached a LDL-C level <70 mg/dl (1.8 mmol/l) or <100 mg/dl (2.6 mmol/l) was higher with the ezetimibe add-on group (n=47) compared to the rosuvastatin 20 mg group (n=48) (57.2% vs. 45.0%).
Kim et al., 2016	Multicentre, 407 patients, 8-week, randomised, double-blind phase III study: Comparison of rosuvastatin-ezetimibe fixed dose combinations with rosuvastatin monotherapy	407 patients with primary hypercholesterolemia were randomised to one of the following 6 treatments for 8 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). Primary efficacy endpoint was the percentage change from baseline in LDL-C in the overall study population. Secondary efficacy endpoints included the percent changes from baseline in other lipids, including total cholesterol, HDL-C, TG, non-HDL-C, Apo A1, and Apo B. Another secondary efficacy	• In the pooled-data analysis, LDL-C reduction was greater in the rosuvastatin/ezetimibe group compared to rosuvastatin monotherapy (-59.1% vs -49.4%, P<0.001) at week 8. • Combination therapy revealed significant greater percent reductions in total cholesterol, TG, non-HDL-C and ApoB compared to monotherapy. • HDL-C levels increased in both treatment groups with no difference between the groups. • Target LDL achievement rate was higher in patients treated with the combination than with monotherapy • Patients with CHD/CHD risk equivalents or a 10-year risk >20% treated with combination therapy

Reference	Description	Study Design	Efficacy results
		endpoint was the percentage of patients reaching pre-specified goals of LDL-C levels depending on CHD risk factors according to the ATP III guideline.	showed higher achievement rate of the LDL-C target than those treated with monotherapy (94.4% versus 84.7%, p=0.003).

Efficacy of combination therapy has also been investigated in the Asian population (Masuda et al., 2015; Okada et al., 2011; Torimoto et al., 2013; Yamazaki et al., 2013). However, a lower dosage of rosuvastatin (2.5 mg up to 5 mg) has been administered with respect to the higher exposure (higher C_{max}, AUC) in Asian subjects compared to Caucasians.

Monocomponents
Efficacy of the monocomponents has been described based on information provided in the SmPC of Crestor (rosuvastatin) and Ezetrol (ezetimibe), respectively.

IV.5 Clinical safety

Safety in bioequivalence study
Beside pharmacokinetic analysis, safety parameters comprising physical and systemic examination, vital signs measurement, clinical laboratory tests and adverse event monitoring including a subject well-being questionnaire were performed during the bioequivalence study. Clinical laboratory safety assessment was done at the end of the study.

Adverse events
Adverse event monitoring in the form of clinical examination, vital checks and subject well-being questionnaire were done during the study. Clinical laboratory safety assessment was done at the end of the study.

During the entire study, two adverse events were recorded in two subjects. Both adverse events were recorded during post-study. One adverse event of Increased Liver Enzymes and one adverse event of increased creatine kinase which were resolved completely.

The reported adverse events were mild to moderate in intensity.

Post-study examination done at the end of period two, all the subjects were found to be healthy during clinical examination. One subject had increased liver enzymes and one subject had elevated creatine kinase which was clinically significant and was reported as adverse event. These events were followed up till resolution. Vital signs of all subjects showed no marked changes throughout the study. Post study laboratory investigations done at the end of the study were either normal or abnormal but clinically insignificant.

Five subjects who dropped out from the study during period two did not visit the facility upon repeated contacts to undergo Post study Evaluation.

From the results of the safety evaluation, it can be concluded that both the treatments were well tolerated.

Safety data from clinical studies on concomitant use of rosuvastatin and ezetimibe

Clinical literature reports three main studies in which the concomitant use of rosuvastatin and ezetimibe has been studied at various dosages. Further studies reporting safety data are also provided. The overview of the studies and key findings on safety as well as the respective references are detailed in the tables below.

Table 6: Key clinical studies with reported safety of rosuvastatin/ezetimibe

Reference	Description	Study Design	Safety results
Bays et al., 2011	Multicentre, 6-week, randomised, double-blind, parallel-group, 440 patient clinical trial to evaluate the safety and efficacy 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.	Subjects were centrally randomised into equal-size double-blind treatment groups of ezetimibe 10 mg added to the run-in dose of rosuvastatin or up-titration of the run-in dose of rosuvastatin for 6 weeks. The secondary objectives included a safety assessment.	• 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 >1 AEs, drug-related AEs, and serious AEs. • No serious drug-related AEs were observed during the present study. • Drug-related discontinuations during rosuvastatin plus ezetimibe add-on therapy included mild or moderate arthralgia, constipation, myalgia, dermatitis allergic, or eczema. • The incidence of pre-specified AEs of special interest was low, with no significant differences seen between the pooled groups
Ballantyne et al., 2014	An open-label, 833 patient, randomised study, examined the efficacy and safety of 10 mg of	After a 6-week dietary lead-in and washout of lipid-lowering drugs, patients received rosuvastatin 10 mg,	• All treatments were well-tolerated. One case of myopathy occurred during simvastatin 80 mg monotherapy. The adverse events were

	rosuvastatin or 20 mg of rosuvastatin along with 10 mg of ezetimibe and compared it with significantly higher dosages of simvastatin 40 mg or Simvastatin 80 mg along with 10 mg of ezetimibe	rosuvastatin 20 mg, simvastatin 40 mg, or simvastatin 80 mg monotherapy for 6 weeks. Ezetimibe 10 mg was then added to each regimen for a further 6 weeks. The secondary objectives included a safety assessment	generally comparable across the groups. • The serious adverse events were few, with rosuvastatin 10 mg monotherapy group showing 3 serious adverse events (1.4%), rosuvastatin 20 mg group showing 5 (2.4%), rosuvastatin 10 mg + ezetimibe 10 mg group showing 4 (2.0%), rosuvastatin 20 mg + ezetimibe 10mg group showing 1 (0.5%).
Ballantyne et al., 2007	Multicentre, 6-week, randomised, double-blind, study of 469 patients was designed to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease.	Patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks. The primary end point was the percentage of patients achieving the Adult Treatment Panel III (ATP III) LDL cholesterol goal (<100 mg/dl) at week 6. Secondary end-points included safety and tolerability.	• Both treatments were well tolerated, and the overall frequency and type of adverse events were similar between treatment groups. • Treatment-related adverse events were reason for discontinuation in 2 patients in the combination therapy group and in 3 patients in the monotherapy group. • Most adverse events were mild to moderate. • The frequency of serious adverse events was low (combination therapy group 2.1%, monotherapy group 1.7%), and no treatment-related serious adverse events were reported in either treatment group.

Safety of individual components

Safety for the individual components has been presented based on the information in the SmPC, respectively, including contraindications, special warnings and precautions for use, fertility, pregnancy, lactation, and undesirable effects.

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 Rosuvastatine/Ezetimibe Althera.

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	• Use in patients with moderate or severe liver problems • Use in children less than 18 years of age

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

IV.7 Discussion on the clinical aspects

The literature data submitted by the MAH support the use of the active substance combination in Rosuvastatine/Ezetimibe Althera. Bioequivalence is shown between Rosuvastatine/Ezetimibe Althera and the concomitant use of Crestor and Ezetrol. The safety profile of Rosuvastatine/Ezetimibe Althera is acceptable. Risk management is adequately addressed. This fixed dose medicinal product can be used 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.

V. USER CONSULTATION

The package leaflet has (PL) been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 5 participants, followed by two rounds with 10 participants each aged between 22 and 74 years. The 15 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatine/Ezetimibe Althera 20 mg/10 mg film-coated tablets has a proven chemical-pharmaceutical quality and is considered an approvable fixed-dose combination. Both active substances are well known, and are used in combination in clinical practice.

Rosuvastatine/Ezetimibe Althera 20 mg/10 mg film-coated tablets were shown to be bioequivalent to the concomitant use of Crestor 20 mg 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 Rosuvastatine/Ezetimibe Althera 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 fixed dose combination, 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 Rosuvastatine/Ezetimibe Althera with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 May 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3679/002/IB/008/G	To combine the SmPCs and Pls of the German texts of both strengths of Rosuzet (10 mg/10 mg and 20 mg/20 mg) into one SmPC and PL according to the authorized common texts. To implement the outcome of new product information - recommendation of the PSUSA/0002664/201711-outcome.	--	15-5-2019	Approval	--
NL/H/3679/002/IB/010	To change the name of the medicinal product from Rosuvastatine/Ezetimibe Klinge to Rosuvastatine/Ezetimibe Althera in the Netherlands.	--	18-4-2019	Approval	--
NL/H/3679/002/IA/011	A new manufacturer for Rosuvastatin Calcium has been introduced.	--	3-6-2019	Approval	--
NL/H/3679/002/IA/012	To add an alternative site responsible for importation and batch release (not including batch control/testing) of the finished product.	--	25-6-2019	Approval	--
NL/H/3679/002/IB/013	PI update in line with outcome of PSUFU/00002664/201711	--	19-10-2019	Approval	--

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