CBG MEB

Public Assessment Report

Scientific discussion

Twicor 10 mg/10 mg, film-coated tablets

(rosuvastatin calcium/ezetimibe)

NL/H/3647/001/DC

Date: 1 March 2018

This module reflects the scientific discussion for the approval of Twicor 10 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
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 Twicor 10 mg/10 mg, film-coated tablets from BGP Products B.V.

Twicor 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 (10 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 10 mg film-coated tablets (rosuvastatin, as rosuvastatin calcium) was first registered in the Netherlands by AstraZeneca BV (NL Licence RVG 26872) through a national procedure on 6 November 2002. Crestor is currently registered through mutual recognition procedure NL/H/0343/001/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 were the Czech Republic, Spain, Poland, Portugal, Sweden and Slovenia.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

Indication
The originally proposed indication was: "*Treatment of hypercholesterolemia in second line therapy as adjunctive therapy to diet for use in adult patients not appropriately controlled with a statin or ezetimibe alone or already treated with a statin and ezetimibe.*"

The MAH provided published clinical literature about improved efficacy of the concomitant use of rosuvastatin and ezetimibe compared to rosuvastatin monotherapy or up-titration of rosuvastatin, in support of the indications. Following comments of the involved member states, a revised indication was proposed and accepted. The assessment of the indication is discussed in section IV.

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

Twicor is a pink coloured round shaped bilayer film-coated tablet embossed with "AL" on one side.

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

Twicor 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 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 more than five stages with isolated intermediates. The proposed starting materials are acceptable. The carry over of potential impurities and residual solvents has been adequately discussed. The manufacturing process has been sufficiently described.

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

Stability of drug substance
Stability data on rosuvastatin calcium have been provided for 13 batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (up to six months). No trends or changes were seen under any of the conditions. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

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 described in the ASMF procedure that is used.

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. Development studies have investigated the compression of single layer and bilayer combination tablets, and included optimization of formulation and process variables. Overall, sufficient information has been provided on formulation and manufacturing process development.

One bioequivalence study has been submitted. The test and reference products contain the same amounts of the same active moieties and concern the same pharmaceutical form. The product batches used in the bioequivalence study are acceptable. *In vitro* comparative dissolution studies with the test and reference products have been presented (pH 1.2, 4.5, 6.6). Clear differences were observed for ezetimibe in pH 6.6 citrate buffer. In response, the MAH addressed these differences with possible reasons. Hence, ezetimibe is practically insoluble at various pH conditions. Further in the QC release media (pH 4.5 with surfactant), bio-relevant media, and other media (such as pH 2.1) the MAH has clearly demonstrated that the drug product is equivalent to reference drug of ezetimibe.

Appropriate formulation development has been undertaken as well as use of micronized active substance, to ensure strong immediate release pattern *in vivo* and *in vitro*. It is anticipated that such formulation development enables better solubility of the drug product. Also as bioequivalence has been demonstrated in *in vivo* studies, the difference in *in vitro* dissolution was accepted.

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 industrial scale batches in accordance with relevant European guidelines.

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. Release and shelf-life limits are identical, except for the content of butylated hydroxyanisole. 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 three 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 24 months data for three batches. On the basis of the data submitted, a shelf life was granted of 30 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 encephalopathies
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 Twicor 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, pharmacokinetics and toxicology 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 Ecotoxicity/environmental risk assessment (ERA)

Since Twicor 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.3 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

Rosuvastatin and ezetimibe are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Additional data are provided from clinical

literature aimed to demonstrate that the concomitant treatment of rosuvastatin and ezetimibe has improved efficacy compared to rosuvastatin monotherapy or up-titration of rosuvastatin.

For this application, the MAH has submitted one bioequivalence study, which is discussed below.

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 Twicor 10 mg/10 mg film-coated tablets (BGP Products B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference products Crestor 10 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 randomised, open label, two treatment, three period, three sequence, single dose, partial replicate pivotal bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 19-42 years. As per pilot study data and literature review, the intra subject CV of ezetimibe was found more than 30%, and hence the partial replicate study design was chosen. The reference treatment was administered twice to assess variability. Treatment 1 was a single dose of one fixed dose combination of rosuvastatin 10 mg and ezetimibe 10 mg tablet. Treatment 2 consisted of a rosuvastatin 10 mg film-coated tablet and an ezetimibe 10 mg film-coated tablet taken concomitantly. A single dose of the assigned formulations were orally administered with 200 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. Three dosing periods were conducted which were separated by a respective washout period of 14 days.

For rosuvastatin analysis, 16 blood samples were collected in each study period. One pre-dose blood sample was collected within one hour prior to dosing and 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 7.50, 12.00, 16.00, 24.00, 48.00 and 72.00 hours post dose.
For ezetimibe analysis, 19 blood samples were collected in each study period. One pre-dose blood sample was collected within one hour prior to dosing and 0.33, 0.67, 1.33, 1.67, 2.00, 2.50, 3.00, 4.00, 5.00, 6.50, 8.00, 10.00, 12.00, 16.00, 24.00, 48.00 and 72.00 hours post dose.

The design of the study is acceptable. A partial replicate design is justified to evaluate variability of ezetimibe. The design is acceptable, wash-out long enough, sampling period long enough, sampling scheme adequate to estimate pharmacokinetic parameters. Both drugs can be taken with and without food. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Results
Two subjects were withdrawn from study evaluation as they did not show up in the second period. One subject did not show up for the third period. Thirty-nine subjects completed the clinical phase of the study. Forty 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=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	91.08 ± 34.51	95.49 ± 34.80	9.68 ± 3.82	5.50 (1.00 - 5.52)	14.75 ± 11.45
Reference	96.68 ± 33.51	100.26 ± 33.72	10.37 ± 3.99	4.50 (1.00 - 5.52)	14.06 ± 3.68
***Ratio (90% CI)**	0.93 (0.88 – 0.99)	--	0.92 (0.87 – 0.99)	--	--
CV (%)	17.16	--	20.59	--	--

$AUC_{0-\infty}$ 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	100986.67 ± 45906.45	111127.53 ± 53983.14	5221.33 ± 2841.26	6.50 (0.33 -16.00)	16.83 ± 10.92
Reference	93685.89 ± 34066.03	100878.89 ± 37060.01	5415.86 ± 2908.01	6.50 (0.33 - 12.00)	15.81 ± 6.97
***Ratio (90% CI)**	1.04 (0.98 – 1.10)	--	0.96 (0.88 – 1.04)	--	--
CV (%)	18.39	--	26.12	--	--

$AUC_{0-\infty}$ 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 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe under fasted conditions.

Treatment N=40	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	886.33 ± 311.09	940.00 ± 324.89	105.64 ± 46.01	0.67 (0.33 - 3.00)	16.00 ± 9.01
Reference	930.22 ± 304.51	973.74 ± 305.17	124.34 ± 59.08	1.00 (0.67 - 4.00)	14.98 ± 5.35
***Ratio (90% CI)**	0.95 (0.91 – 1.00)	--	0.86 (0.81 – 0.92)	--	--
CV (%)	15.09	--	21.12	--	--

$AUC_{0-\infty}$ 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 Twicor 10 mg/10 mg film-coated tablets is considered bioequivalent with Crestor 10 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 4: 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

Fixed combination product may improve adherence to medication

A number of studies have shown that a substantial proportion of patients do not reach recommended lipid targets with regard to Low Density Lipoproteins (LDL-C), High Density Lipoprotein (HDL-C), or Apolipoprotein (ApoB) as recommended by the National Cholesterol Education Program (NCEP), The European joint Task force of European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD), thereby keeping these patients at a high risk for premature cardiovascular disease and death (Daskalopoulou et al., 2010; Stone et al., 2005; Waters et al., 2009).

There is some evidence that fixed dose combination products improve adherence to medication and patient compliance due to reduced pill burden and improved ease of administration as expressed by the World Health Organisation (WHO) in WHO: Gaining Health: The European Strategy for the Prevention and Control of Non-Communicable Disease, 2006 WHO, 2006). It has been demonstrated that the adherence to medication in cardiovascular disease and in particular hyperlipidaemia is less than desirable, which often results in an inability to meet treatment goals as recommended by European Society of Cardiology (ESC) and National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (NCEP, 2002; Reiner et al., 2011).

Adherence to medication is a recognised problem in patients due to polypharmacy, and hence, any approach that can reduce the pill burden and ease adherence to medication could be beneficial. The development of the proposed drug product needs to be looked at within this context. Patient adherence to medication has been shown to be significantly greater with a single-pill regimen compared with a two-pill regimen, or a two-pill regimen compared to a three- or four-pill regimen. Concerns about increasing patient's pill burden often result in reluctance from physicians in adding further medications to a patient's existing regimen despite potential therapeutic benefits (Daskalopoulou et al., 2010; Ho et al., 2006; Lamb et al., 2009).

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 5: 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 from 10 to 20 mg.	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 was % of subjects reaching the NCEP ATP III LDL-C targets.	• 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 <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 6: 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 in patients undergoing elective vascular surgery.	Patients were randomly assigned to rosuvastatin 10 mg/d or rosuvastatin 10 mg/d plus ezetimibe 10 mg/d, starting prior to scheduled surgical procedure. Primary end point was the first major cardiovascular event, including death from cardiac causes, nonfatal myocardial infarction, ischemic stroke, and unstable angina.	• 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 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

Reference	Description	Study Design	Efficacy results
			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 study: Six months 8 high-risk patient study to evaluate efficacy and safety of ezetimibe plus rosuvastatin.	Male patients, mean age 56 ±10 years, 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.	Co-administration of ezetimibe 10 mg plus 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	• 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

Reference	Description	Study Design	Efficacy results
		months after the treatment. Patients with LDL >190 mg/dl and triglycerides <400 mg/dl were enrolled in the study.	rosuvastatin/ezetimibe group (83% vs 60%).
Farnier et al., 2016	24 weeks, 305 patient, multicentre, double-blind, double-dummy, randomised, 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)	Patients entered a 2 to 6-week screening period and were then randomised according to their baseline rosuvastatin regimen (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	• 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). • 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 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.	• 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 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.

Indication
The MAH initially applied for the indication: '"*Treatment of hypercholesterolemia in second line therapy as adjunctive therapy to diet for use in adult patients not appropriately controlled with a statin or ezetimibe alone or already treated with a statin and ezetimibe.*"

The MAH provided the results of three studies on the combination of rosuvastatin and ezetimibe to support the proposed indication (Bays et al., 2011; Ballantyne et al., 2014; Ballantyne et al., 2007).
The EXPLORER study in patients with high CV risk was considered most relevant as it specifically addresses the beneficial effects of the combination of ezetimibe and rosuvastatin (40 mg) in comparison to rosuvastatin alone. However, the study design was open-label and missing a maximum dose run-in phase, and therefore not considered robustly designed for a non-responder add-on evaluation. The ACTE and GRAVITY study were considered supportive as these compare the combination (rosuvastatin and ezetimibe) to up-titration of rosuvastatin or to combination of simvastatin and ezetimibe, respectively.
Other studies have also been tabulated and described to further support the pivotal data (Kosoglou et al., 2004; Kouvelos et al., 2013; Foody et al., 2013; Styliadis et al., 2007; Boufidou et al., 2007). These studies were considered to be supportive because of limited patient numbers, limitations on design, or evaluation of a specific type of patient group.

However, concerns were raised with the substitution indication:

- First, a substitution indication of any statin and ezetimibe was requested, while current fixed dose combination deals with the rosuvastatin-ezetimibe combination. This should be addressed accordingly in the indication to have a suitable substitution indication.
- Second, the indication implicated that the MAH requested an add-on indication. To fulfil this requirement the "*Guideline on clinical development of fixed combination medicinal products*" (EMA/CHMP/281825/2015) states that a randomised controlled trial (RCT) to prove superiority in inadequate/non-responders to single (or multiple) active components of the fixed dose combination is required to demonstrate that the fixed dose combination has greater efficacy in comparison with the respective mono-components. Superiority – or 'add on efficacy' can only be claimed to (mono)components to which patients have been demonstrated to be non-responsive and where the fixed dose combination has been shown to be more effective than treatment continuation of that (mono)component.
  This requirement was not fulfilled as no such non-responders study has been submitted. The ACTE and EXPLORER study, which were provided, are not specifically designed to address the additional effect of ezetimibe in optimal treated rosuvastatin non-responders on the current 10 mg dose. Also, the EXPLORER study had an open-label design and missing a maximum dose (optimal treated) rosuvastatin run-in phase. Therefore, it is not considered appropriate to robustly evaluate the add-on effect of ezetimibe. Moreover, the MAH proposed an 'add-on' indication to patients not controlled with any statin. Considering the differences in potency between statins, it was not clear if the combination of rosuvastatin 10 mg and ezetimibe 10 mg is the logical next step to any previous dose of statin used. Even though, rosuvastatin is the most potent statin marketed.
  Further, an add-on indication should not read 'not appropriately controlled with a statin or ezetimibe'. Ezetimibe is indicated as add-on to statin, or as monotherapy when statins cannot be tolerated or are contra-indicated. There are also no clinical (literature) data in support of this particular add-on step submitted. Therefore, an add-on to ezetimibe was not accepted.

Following these comments the indication was changed to: "*Twicor is indicated as adjunctive therapy to diet and exercise in high to very high cardiovascular risk adult patients with primary hypercholesterolaemia:*
- not appropriately controlled with a maximal tolerated statin dose, or
- already treated with the corresponding dose of rosuvastatin and ezetimibe"

It was agreed that life-style modifications are expected to be implemented and motivational support provided by health care professionals as the cornerstone of treatment of these high risk patients. The 'as adjunctive to diet and exercise' in the indication was therefore also agreed.
The part of the indication referring to 'substitution' or switch indication was also found acceptable as it is now narrowed to patients who were previously 'treated with the corresponding dose of rosuvastatin and ezetimibe' not any statin. This is in line with the data from the submitted pharmacokinetics study that showed bioequivalence of the individual components given concomitantly with the fixed combination medicinal product.
Also the add-on indication to non-responders of ezetimibe is no longer claimed by the MAH.

New concerns were raised though:

- The first sentence of the proposed indication delineates the general population that stand to benefit from lipid-modifying treatment; adult patients with high to very high cardiovascular risk and primary hypercholesterolemia. This population is narrower than the indications of both rosuvastatin and ezetimibe. LDL-C treatment targets are set based on an assessment of cardiovascular risk. Combination therapy would be indicated when these targets have not been achieved with a maximal tolerated statin dose. The specification of a high to very high cardiovascular risk population could suggest the combination would be considered a more appropriate strategy while still a first line therapy with statin would be recommended. The addition of 'in high to very high cardiovascular risk' should be removed from the indication statement.
- The clinical rationale in ezetimibe non-responders and the evidence supporting an add-on indication to any statin: The MAH provided an overview of the evidence supporting the use of the combination of rosuvastatine 10 mg and ezetimibe 10 mg in patients who do not respond adequately to (any) statin therapy. To this end the MAH indicated that a combination of statin and ezetimibe can be considered a valid therapeutic second line option in patients not receiving LDL-C targets. The results from the IMPROVE-IT study that showed cardiovascular benefit in a large trial with long follow-up (seven years) now lend further support to ezetimibe as add-on lipid-modifying agent. That benefit was demonstrated in patients who were on 40 mg of simvastatin. Addition of ezetimibe has also been shown to be effective in further lowering LDL when added to other statins, e.g. atorvastatin.
  Therefore, the European Society of Cardiology (ESC) guidelines suggest combination therapy in patients in whom treatment goals have not been achieved after a suitable dose of an appropriate statin. In this guideline a statin at a dose should be chosen that are known to achieve a suitable reduction in LDL-C levels to achieve targets. In clinical practice (Dutch cardiovascular risk management guideline: "Multidisciplinaire richtlijn cardiovasculaire risicomanagement, herziening 2011" https://www.nvvc.nl/media/richtlijn/106/2011_MDR_CVRM.pdf) a switch to a more potent statin is recommended if targets are not achieved before combination therapy would be considered. The ESC guideline acknowledges that response to statins may be variable and may thus require optimising – including switching – the statin. Equally, if a statin would not be tolerated, guidelines recommend a switch to another statin (https://www.nice.org.uk/advice/ktt3/chapter/evidence-context#intolerance-to-statins). True statin intolerance (statin-associated myopathy) is rare (Stroes et al., 2015). Ezetimibe is therefore second-line therapy (ESC guideline 2016) after a maximal tolerated statin dose, but optimal statin therapy remains standard of care.
  Therefore an add-on indication to any statin is not a viable indication statement. The clinical literature data presented are acknowledged showing differences in potency between statins and the added efficacy of ezetimibe when combined with most statins. This has been established also in patients who initially did not respond adequately, i.e. reached treatment goals, on rosuvastatin therapy alone. Nevertheless, these data were not sufficient to support that this combination of rosuvastatin 10 mg and ezetimibe 10 mg would be the next treatment step in patients insufficiently responding to any statin at maximal tolerated dose or rosuvastatin 10 mg. Although, superior LDL-C lowering may be expected in most scenarios evidence of cardiovascular benefit remains most robustly established for statins. Specifically, where ezetimibe add-on may result in more LDL-C lowering than increasing the rosuvastatin 10 mg dose to 20 mg, the strongest support for cardiovascular benefit of rosuvastatin comes from the JUPITER trial where a 20 mg dose has been used. Thus the fixed medicinal dose combination may not be recommended in patients currently on 10 mg or 20 mg rosuvastatin doses if well tolerated.

The substitution indication appropriately refers to switching only like-with-like, patients 'already controlled with the corresponding dose of rosuvastatin and ezetimibe'. The add-on indication in patients 'not appropriately controlled with a maximal tolerated statin dose' is not supported. Although, sufficient argumentation has been provided that the 10 mg rosuvastatin dose in the combination is more potent or at least equipotent as other statin at any dose currently marketed this only refers to LDL-C lowering. Cardiovascular benefit has been established most robustly with fixed statin doses. In case of rosuvastatin that is with 20 mg, therefore a dose increment from 10 mg rosuvastatin to 20 mg in patients tolerating such dose step is preferred over adding ezetimibe 10 mg to patients whose LDL-C targets have not been reached with rosuvastatin 10 mg. Therefore, an add-on indication to rosuvastatin at 10 mg specifically could not be granted either. Finally, the indication should be revised further to bring it in line with the monocomponents with respect to the target population.

Subsequently, the add-on indication to non-responders of rosuvastatin was no longer claimed by the MAH. Further, the MAH has adjusted the wording of the substitution indication. The indication: "*Twicor 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."* is acceptable. It is in line with that of ezetimibe and rosuvastatin.

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. Total duration of the study was 32 days from period one check-in till the last blood sample collection of period three including a wash out period of 14 days between each dosing. 42 healthy volunteers were included.

During the entire study, three adverse events were recorded in three subjects. One adverse event of body ache in a subject was recorded in period one, one adverse event of fever in a subject was recorded in period two and one adverse event of elevated creatine kinase in a subject was recorded during post-study. The reported adverse events resolved completely.

The reported adverse events were mild to moderate in intensity.

Post-study examination done at the end of period three, all the subjects were found to be healthy during clinical examination. One subject had elevated creatine kinase which was clinically significant and was reported as adverse event. This event was 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.

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 7: Key clinical studies with reported safety of rosuvastatin/ezetimibe

Reference	Description	Study Design	Safety results
Bays et al., 2011	Multicentre, 6-week, randomised, double-	Subjects were centrally randomised into equal-	• Analysis of the pooled rosuvastatin (5 mg and 10

	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.	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.	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 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. The secondary objectives included a safety assessment	• All treatments were well-tolerated. One case of myopathy occurred during simvastatin 80 mg monotherapy. The adverse events were 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	• 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

		tolerability.	(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 Twicor.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Skeletal muscle effects: myalgia, myopathy, myositis, increased CK-levels, rhabdomyolysis (with or without acute renal failure), immune-mediated necrotising myopathy, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy) • Hypersensitivity reactions including angioedema • Abnormal liver function: increased transaminases, hepatitis, jaundice • Urinary effects (proteinuria) • Pancreatitis • Diabetes mellitus • Stevens-Johnson syndrome and toxic epidermal necrolysis • Drug-drug interactions (including: cyclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and ezetimibe) • Tendon rupture and rotator cuff syndrome • Thrombocytopenia/decreased platelet count • Memory loss • Depression • Sleep disorders (including insomnia and nightmares)
Important potential risks	• Hepatic failure: including hepatic necrosis and fulminant hepatitis • Interstitial lung disease • Renal failure (including acute and chronic renal failure) and renal impairment • Peripheral neuropathy • Amyotrophic lateral sclerosis • Cholecystitis/cholelithiasis • Drug-drug interaction with fibrates (other than gemfibrozil) • Off-label use (including paediatric off-label use)
Missing information	• Product use in children • Product use in elderly • Pregnancy and lactation • Product use in patients with severe hepatic impairment • Product use in patients with severe renal impairment

	• Product use in Asian population: increased plasma exposure • Product use in patients with very low low-density lipoprotein cholesterol (LDL-C) levels • Product use in patients with genetic polymorphisms: increased plasma exposure

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 Twicor. Bioequivalence is shown between Twicor and the concomitant use of Crestor and Ezetrol. The safety profile of Twicor 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

Twicor 10 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.

Twicor 10 mg/10 mg film-coated tablets were shown to be bioequivalent to the concomitant use of Crestor 10 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 Twicor 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 Twicor 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

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