COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rosuvastatin/Ezetimibe Mylan Healthcare 10 mg/10 mg and 20 mg/10 mg, film-coated tablets

(rosuvastatine calcium/ezetimibe)

NL/H/4175/001-002/DC

Date: 5 September 2019

This module reflects the scientific discussion for the approval of Rosuvastatin/Ezetimibe Mylan Healthcare 10 mg/10 mg and 20 mg/10 mg, film-coated tablets. The procedure was finalised at 11 October 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CK	Creatine Kinase
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 Rosuvastatin/Ezetimibe Mylan Healthcare 10 mg/10 mg and 20 mg/10 mg, film-coated tablets from Mylan Healthcare B.V.

Rosuvastatin/Ezetimibe Mylan Healthcare 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 or 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 10 mg and 20 mg film-coated tablets (rosuvastatin, as rosuvastatin calcium) was first registered in the Netherlands by AstraZeneca BV (NL Licence RVG 26872-3) through a national procedure on 6 November 2002. Crestor is currently registered through mutual recognition procedure NL/H/0343/001-002/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:

- Addition of another lipid-lowering agent to statin monotherapy at maximally tolerated dose may help patients achieve target lipid goals and reduce cardiovascular risk.
- Existing clinical literature demonstrate superior clinical performance of concomitant therapy of rosuvastatin and ezetimibe compared to rosuvastatin alone or up-titration.
- 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 Spain, France, Croatia, Italy and Portugal.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC. The application is based on a full dossier, comprising mixed data from the literature as well as clinical studies for the demonstration of bioequivalence of the proposed drug product with Crestor (rosuvastatin) and Ezetrol (ezetimibe) as reference products.

Indication

The originally proposed indication was:

Hypercholesterolaemia
Rosuvastatin/Ezetimibe Mylan Healthcare is indicated as adjunctive therapy to diet and exercise in adult patients with primary hypercholesterolaemia

- *not appropriately controlled with the maximal tolerated dose of any statin,*
- *already treated with the corresponding dose of rosuvastatin and ezetimibe.*

Prevention of Cardiovascular Events
Rosuvastatin/Ezetimibe Mylan Healthcare is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

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

Rosuvastatin/Ezetimibe Mylan Healthcare is a pink coloured round shaped film-coated tablet embossed with "AL" on one side (10 mg/10 mg strength) or plain on both sides (20 mg/10 mg).

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

Rosuvastatin/Ezetimibe Mylan Healthcare 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 Substance

II.2.1 Rosuvastatine calcium

The active substance is rosuvastatine calcium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Rosuvastatine calcium is a white or almost white powder. It is slightly soluble in water and practically insoluble in anhydrous ethanol. 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. The specification includes additional requirements for particle size, polymorphic form an additional solvents. 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.

II.2.2 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.

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 and meets the requirements of the monograph in the Ph.Eur. The specification 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

Primary 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.

Bioequivalence studies have been performed for each strength. The proposed products and the reference products contain the same amounts of the same active moiety and concern the same pharmaceutical form. The product batches used in the bioequivalence study are acceptable. *In vitro* comparative dissolution studies with the reference products have been presented. Overall, *in vitro* dissolution similarity could not be demonstrated, but bioequivalence has been demonstrated in *in vivo* studies. This is 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 has been performed on three industrial scale batches of rosuvastatin granules, ezetimibe granules and film-coated tablets 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. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The MAH committed to re-evaluate the specification on a specified impurity at the end of shelf-life for the 20 mg/10 mg tablets and to submit results post-approval.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength 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 of each strength in the primary packaging material. The batches are the same as used in process validation. The currently provided data at long-term conditions consist of 24 months data for three batches for the 10 mg/10 mg tablets and 12 months data for the 20 mg/10 mg data. The proposed shelf-life of 36 months for the 10 mg/10 mg tablets can be granted. For the 20 mg/10 mg tablets the one year long-term stability results support the claimed shelf-life of two years when stored in the original package in order to protect from light and moisture.

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 Rosuvastatin/Ezetimibe Mylan Healthcare has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH has committed to provide the 36 months long term stability results after these are available and to re-evaluate a specification limit, based on these results. If necessary, a variation for the change in the specification for the limit of this degradation product will be filed.
- The MAH committed to submit a Type IA variation B.III.1.a.2. Submission of an updated Ph.Eur. Certificate of suitability for the revision of R0-CEP 2015-188-Rev 01 to Rev 02 accordingly, after approval of this procedure. All relevant dossier sections will be updated and documentation will be provided to all Member States.

III. NON-CLINICAL ASPECTS

III.1 Introduction

A non-clinical overview of published literature has been submitted, supplemented by the results from three studies to qualify a degradation product of ezetimibe.

III.2 Pharmacology

The pharmacology of rosuvastatin and ezetimibe is well characterized in many studies. Rosuvastatin, like other members of the statins, functions as a competitive blocker of the enzyme HMG-CoA reductase, the first committed enzyme of the mevalonate pathway. Statins compete with HMG-CoA with for binding with the enzyme's active site, resulting in a reduced production of mevalonate, an essential molecule in the cascade that eventually produces cholesterol. This reduced synthesis of mevalonate and consequently of cholesterol is the underlying mechanism of diverse pharmacological effects of statins, and this activity results also in a reduction of the circulating cholesterol level in blood. Since mevalonate is also involved in a number of other reactions, in addition to the specific effect on cholesterol synthesis, other (pleiotropic) activities of statins including anti-inflammatory, anti-proliferative and antithrombotic effects, to name only a few, are also reported, which are independent on the cholesterol level. The multiplicity of these effects contributes to the overall pharmacological activity and its clinical utility, reaching beyond treatment of hypercholesterolemia into primary and secondary prevention of cardiovascular disease. Pharmacological studies demonstrate its utility in reduction of arteriosclerosis manifestation, including stabilization of atherosclerotic plaques, improvement of endothelial dysfunction, reduction of thrombus formation, and control of inflammatory responses. In addition, rosuvastatin as a member of the statin family has been shown to be effective for purposes

other than treatment of hypercholesterolemia. It was active in models of atherosclerosis, in a model of neointima formation, it ameliorated remodelling in left ventricular hypertrophy in models of myocardial diseases, it reduced myocardial fibrosis in a model of diabetes, it improved pulmonary artery hypertension, and it was active in peripheral hypoperfusion. Rosuvastatin was found to be also active in a model of asphyxia induced cardiopulmonary arrest with cardiopulmonary resuscitation in rats, resulting not only in increased survival, but also in neurological outcome. Secondary pharmacological effects were seen in models of glomerulonephritis, in a model of high-fat diet induced nephropathy, and in models of malignant diseases. Rosuvastatin treatment improved the insulin resistance in an animal model of diabetes. Treatment with rosuvastatin decreased the high compensatory insulin secretion and increased glucose uptake in diabetic animals, while in non-diabetic animals the blood glucose level was lowered and the insulin sensitivity was increased.

Like rosuvastatin, ezetimibe also results in reduced circulating cholesterol levels, but the mode of action and primary target is different. Ezetimibe inhibits the absorption of cholesterol from the small intestine and decreases the amount of cholesterol normally available to liver cells, leading them to absorb more from circulation and thus lowering levels of circulating cholesterol. It appears that ezetimibe blocks the critical mediator of cholesterol absorption, the NPC1L1 protein on the gastrointestinal tract epithelial cells, and this was found to be the main mode of action. As a result, ezetimibe is especially active in conditions with high dietary intake of cholesterol. The effect is selective for cholesterol, and other nutrients and vitamins with high lipophilicity, such as triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D are not affected. Ezetimibe was also found to promote the brush border membrane-to-lumen cholesterol efflux in the small intestine, resulting in increased intestinal excretion of cholesterol. Most likely, the glucuronide of ezetimibe is the active principle, but due to the rapid glucuronidation, ezetimibe is as active as is its glucuronide *in vivo*. Due to its strong effect on diet induced hypercholesterolemia, ezetimibe was shown to be active in a series of models of diverse disease symptoms including hepatic steatosis, atherosclerosis, and arteriosclerosis. Using the transgenic ApoE-/-mouse as model system of atherosclerosis, the protective effect of ezetimibe was found to be comparable to the activity of atorvastatin. Ezetimibe was found to be addition, glucotoxicity was reduced in pancreatic β-cells through a decrease in fatty acid influx. Ezetimibe also prevented the formation of gallstones if animals were fed a lithogenic diet. Finally, the compound was even found to be active in a model of dementia associated with high fat diet, and in a model of glomerulosclerosis.

Due to the complementary mode of action of both drugs, combining synthesis inhibition with uptake inhibition, a synergistic pharmacodynamic effect can be expected from a combination of ezetimibe with rosuvastatin. However limited animal data are available to support this hypothesis. A detailed analysis in one model, utilizing also gene expression analysis, is in support of a combination. In fact, combinations of ezetimibe with other statins are marketed, and preclinical studies support the utility of the combination of a statin in general with ezetimibe.

The safety pharmacology of rosuvastatin and ezetimibe was evaluated in a number of preclinical studies, and further evidence on safety pharmacology can be derived from pharmacology studies and long standing clinical use. Noteworthy, rosuvastatin was found to block the cardiac hERG channel. Dosed at 10 mg/kg i.p. rosuvastatin prolonged the corrected QT interval in guinea pigs. However, the clinical dose in man is much lower, and from clinical use, a clinically relevant effect on QT interval or on repolarization is not known. Safety pharmacology evaluation of ezetimibe did not reveal any target organ. No data are available to evaluate the safety pharmacology of the combination, but based on the complementary mode of action and the excellent tolerability of both individual agents, no critical effects are to be expected.

Pharmacodynamic interaction has been reported for the combination of rosuvastatin and other statins with ezetimibe, and this positive interaction is one of the main reasons for development of the fixed combination. Based on the mode of action, positive pharmacodynamic interaction may be also expected to occur with fibrates, but no preclinical data are available supporting this interaction. One study supports the use of rosuvastatin add on to candesartan for the treatment glomerulonephritis. Rosuvastain was recently shown to interact with a novel AT2-inhibitor on neointima formation in a model of vascular injury. While rosuvastatin inhibited neointima formation and oxidative stress, a combination with the undisclosed selective AT2 receptor antagonist synergistically potentiated the effect of rosuvastatin.

III.3 Pharmacokinetics

The pharmacokinetics of rosuvastatin was evaluated in rats and dogs. The absorption of rosuvastatin after oral intake was found to be incomplete, and the administration with a high fat diet in dogs reduced the bioavailability to about 30% compared to fasting condition. The absolute bioavailability in rats was found to be only 19-27%, with a high fat diet causing reduced exposure. After oral uptake, rosuvastatin is selectively distributed into the liver, and based on total radioactivity, an 8 to 25 fold enrichment in the liver could be demonstrated. This is due to selective uptake in liver cells by active transport. At the same time, the excretion in bile is also mediated by active transport. In fact, due to the high hydrophilicity of the molecule, the passive diffusion is limited. While the plasma and tissue levels are low compared to hepatic levels, active transport was found to be also responsible for intracellular muscle concentration, which is important to consider with regard to one adverse class effect of statins, the muscle toxicity, which is HMG-CoA inhibition related. While rosuvastatin enriches in the liver as main site of pharmacodynamic action, any interference with the balance between uptake and clearance from muscle cells by transporter inhibition can therefore influence the safety margin of this statin. The metabolism of rosuvastatin is limited, and unchanged compound accounted for 88.3% of biliary excretion and 87.5% of faecal excretion. The primary route of excretion of rosuvastatin and its metabolites is via biliary excretion.
The pharmacokinetics of ezetimibe was evaluated in mice and rats. Ezetimibe is very well and rapidly absorbed, but it is in the enteral mucosa already metabolized by glucuronidation. At least three different enzymes are capable of this reaction. The glucuronide is rapidly

excreted in bile, utilizing active transport mechanisms, reaching the gut lumen again, where ezetimibe glucuronide is taken up in the gut mucosa, utilizing again active transporters. Ezetimibe glucuronide enriches in enteral mucosa, and at this site of action, it inhibits the uptake of cholesterol by selective interaction with the cholesterol transporter. At any time after oral dosing, the majority of compound (ezetimibe and its glucuronide, evaluated together) can be found in gut lumen and gut mucosa, and in bile. The metabolism of ezetimibe is restricted to glucuronidation, and the nearly exclusive route of excretion is the faecal route.

The fact that both, rosuvastatin and ezetimibe utilize transporters for uptake, distribution and excretion, makes this process sensitive for pharmacokinetic drug interaction. While in theory all potent inhibitors of the transporters involved can result in modulation of the uptake, distribution and excretion of rosuvastatin, and also of ezetimibe, and while such interaction is well known from long-standing clinical use, limited preclinical data are available to support this type of interaction. Cyclosporine, being a potent inhibitor of organic anion-transporting polypeptides, was shown to cause a 7-fold increase in rosuvastatin exposure in plasma. Clatrinomycin and erythromycin being also known inhibitors of this transporter, as shown in *in vitro* studies, are also at risk to cause such interaction. In addition, blockers of efflux transporters of the ABC transporter family may cause an accumulation of rosuvastatin in muscle and liver cells, potentially leading to increased myotoxicity. Piperine, cinnamic acid and gallic acid, three naturally occurring such blocker, caused some interaction with the pharmacokinetics of rosuvastatin. For another blocker of efflux transporters, probenecid, a pharmacokinetic interaction could be demonstrated, resulting in increased myotoxicity.

While pharmacokinetic interaction with ezetimibe may result from interaction with efflux transporters, responsible for biliary excretion and enteral uptake of the glucuronide, no preclinical data are available to support this interaction. However, the NPC1L1 transporter, which is the target for ezetimibe, is also responsible for the uptake of vitamin K. As vitamin K antagonists are used to modulate blood coagulation, a pharmacodynamic interaction with warfarin is to be expected, since ezetimibe causes reduced vitamin K absorption. In addition, gamma-tocotrienol is a member of the vitamin E family that displays potent anticancer activity, was found to also utilize the NPC1L1 transporter, making interference with vitamin E uptake possible.

III.4 Toxicology

Rosuvastatin

The single dose toxicity of rosuvastatin is not well described, but based on chronic oral studies in rats, using 80 mg/kg, and in mice, using 200 mg/kg, representing about 20 fold the human therapeutic dose, the acute toxicity is at least low, if not very low. The repeat dose toxicity of rosuvastatin is also low. Only incomplete data are available, and information on chronic toxicity may be supplemented also with long standing clinical experience. Any toxicity symptoms reported for rosuvastatin were only seen at doses producing high multiples of the human exposure. In one study in rats, the liver and the kidney were identified as potential target organs, with hepatic enzymes being significantly increased and proteinuria being found. Hepatic enzyme increase is known to be an asymptomatic finding

associated with statin treatment, and proteinuria is a target mediated effect due to inhibition of a kidney reuptake mechanism, and not due to kidney toxicity. One class effect toxicity of statins is its myotoxicity, and rosuvastatin also can induce myotoxicity. This toxicity is target mediated. Due to liver enrichment of rosuvastatin, this agent was found to have a better safety margin as some other statins. As efflux transporters are responsible for rosuvastatin clearance from intracellular space, inhibition of these transporters with probenecid could aggravate the toxicity of rosuvastatin. The reduced potential to induce myotoxicity was also demonstrated in a recent study comparing the high dose of 80 mg/kg rosuvastatin with an equivalent dose of atorvastatin.
Rosuvastatin was found to be not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test. While these data, derived from FDA approved labelling information of rosuvastatin, hint to a lack of genotoxicity, the compound was found to have a genotoxic potential in another non-Good Laboratory Practice (non-GLP) conform set of studies, and in again other studies, the compound was found to protect from DNA damage. Based on the overall evidence, it is most likely that rosuvastatin has no or only a limited genotoxic potential.

In two carcinogenicity studies, increased incidences of uterine stromal polyps and increased incidence of hepatocellular adenoma/carcinoma were observed, but only in the high dose group, representing at least a 20 fold exposure as compared to a human dose of 40 mg/kg, while at lower doses these incidences were not increased. At the same time, statins and also rosuvastatin are reported to inhibit growth of several different tumour cell lines and experimental tumours in various animal models.
In reproduction toxicity studies, at very high doses, some minor effects on male fertility were observed. At the same time, rosuvastatin, at therapeutic doses, could reverse the negative effects on male fertility induced in a diabetes model. Rosuvastatin was not teratogenic in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (systemic exposures equivalent to the human exposure at 40 mg/day based on AUC or body surface area, respectively). In pre- and postnatal toxicity studies in rats and rabbits, decreased pub survival occurred in the high dose group. In a non-GLP study administering a dose which is above the therapeutic range in man, juvenile exposure resulted in a retarded puberty and a trend towards reduced testosterone levels were found, in combination with impaired testicular and epididymal morphology.
No local tolerance data and no data on sensitizing potential can be derived from preclinical studies, but based on long-standing clinical use there is no reason for concern. Rosuvastatin can undergo photo degradation, and based on a non-GLP study in daphnia and an in silico evaluation, some of the degradation products may even have an increased toxicological potential. Based on long-standing clinical use, phototoxicity of rosuvastatin is not a concern. These findings may be only of limited relevance for human use. However the fact that rosuvastatin can undergo photo degradation indicates, that the molecule, which is mainly excreted as parent compound, can undergo metabolic degradation in the environment, preventing environmental enrichment.

Ezetimibe

The single dose toxicity of ezetimibe is very low, an LD50 could not be determined. The low repeat dose toxicity of ezetimibe is remarkable, as following oral dosing, no specific toxicity and no target organ of toxicity could be identified.

In a fully GLP-compliant study, comparing oral administration of ezetimibe for 90 days in rats with comparable doses of ezetimibe containing 3% of a degradation product, ezetimibe was found to be very safe. Even at the highest dose of 500 mg/kg per day no systemic or local toxicity could be observed and no target organ of toxicity was identified.

Ezetimibe was not genotoxic or mutagen, and it was negative in dedicated carcinogenicity studies. In addition to a lack of effect on neoplastic findings, no non-neoplastic toxicity was observed in these two year studies in mice and rats, although the drug was dosed at the highest possible dose which the highest exposure; higher oral doses did not result in higher exposure.

Ezetimibe was also negative for reproduction toxicity at all stages of reproduction, including fertility, embryo foetal development, and pre- and postnatal development including maternal function.

There is no evidence for local irritation, sensitization, or phototoxicity for ezetimibe from preclinical studies, and this is supported by long-standing clinical use.

In two fully GLP-compliant studies, the ezetimibe cyclic ether impurity was found to be non-genotoxic in the bacterial reverse mutation test and non-clastogenic in the *in vitro* mammalian chromosome aberration test. These data in combination with the 90 day comparative toxicity study in rats are in support of a drug product specification extension for the cyclic ether impurity of NMT 0.80%.

III.4.1 Three studies on ezetimibe cyclic ether impurity

Ezetimibe cyclic ether impurity is a known degradation product of ezetimibe. Three fully GLP-compliant studies were conducted to evaluate the toxicological profile of a known degradation product of ezetimibe. The genotoxicity and mutagenicity were evaluated in a bacterial reverse mutation test and in an *in vitro* chromosome aberration test, evaluating the pure impurity. The overall toxicological profile was evaluated in a 90 days comparative toxicity study, evaluating pure ezetimibe with ezetimibe blended with 3% of the impurity.

The results of the Ames test and micronucleus test show that the impurity has no genotoxic potential. In the 90 days comparative toxicity study no toxic effects were observed apart from a marginal increase in alanine aminotransferase (ALT) levels in all male dose groups, which is consistent with previously conducted studies showing the low toxic potential of ezetimibe. The addition of the impurity at 3% did not induce any toxicity either.

III.5 Ecotoxicity/environmental risk assessment (ERA)

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

III.6 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. Three studies have been submitted to sufficiently evaluate the qualification level of a known degradation product of ezetimibe. 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. Additional data are provided from clinical literature 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 two bioequivalence studies, which are 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 studies
The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Rosuvastatin/Ezetimibe Mylan Healthcare film-coated tablets (BGP Products B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference products Crestor 10 mg or 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 in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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.

Pharmacokinetic study BR-R-C13225
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 coefficient of variation 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.

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} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/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*

Pharmacokinetic study RP15.1112

Design

A randomised, open label, two treatment, two period, two sequence, single dose bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 20-44 years. Treatment 1 was a single dose of one fixed dose combination of rosuvastatin 20 mg and ezetimibe 10 mg tablet. Treatment 2 consisted of a rosuvastatin 20 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. The wash-out period and sampling period are long enough. The sampling scheme is considered adequate to estimate pharmacokinetic parameters of rosuvastatin and ezetimibe. As free ezetimibe is the parent compound it is considered the most relevant analyte, therefore it is acceptable that the total ezetimibe

concentrations have not been determined in this study. Both drugs can be taken with and without food, hence a bioequivalence study under fasting conditions is considered acceptable.

Results

Six subjects did not visit facility for period two check in. Hence these subjects were not dosed. One subject dropped out form the study during period two due to non-health related personal emergency. Therefore 65 subjects completed both periods of the study. Sixty-six subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rosuvastatine under fasted conditions.

Treatment N=66	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	250.139 ± 97.9551	254.384 ± 99.1268	27.539 ±12.9299	3.02 (1.00, 5.50)	12.351 ± 2.7424
Reference	253.090 ± 102.5506	256.981 ± 102.9060	27.864 ± 12.6965	3.25 (1.00, 5.50)	12.013 ± 2.5160
***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 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of unconjugated ezetimibe 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	92872.693 ± 30010.6765	101513.201 ± 37384.5595	4530.791 ± 1725.6468	6.50 (0.33, 16.00)	16.893 ± 7.4661
Reference	87337.025 ± 27367.2808	93206.338 ± 30485.5076	4659.401 ± 1948.3054	6.50 (0.33, 16.00)	14.996 ± 6.8633
***Ratio (90% CI)**	1.07 (1.02 - 1.12)	--	1.00 (0.93 - 1.06)	--	--
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*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rosuvastatin/Ezetimibe Mylan Healthcare is considered bioequivalent with Crestor 10 mg or 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 low-density lipoprotein (LDL) receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of very low-density lipoprotein (VLDL), thereby reducing the total number of VLDL and LDL particles.

Rosuvastatin reduces elevated LDL-cholesterol (LDL-C), total cholesterol and triglycerides and increases high-density lipoprotein-cholesterol (HDL-C). It also lowers Apolipoprotein B (ApoB), non-HDL-C, VLDL-C, VLDL-triglycerides (VLDL-TG) and increases ApoA-1. Rosuvastatin also lowers the LDL-C/HDL-C, total cholesterol (total-C)/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 6. 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 (%)	Non-HDL-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.

Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

IV.4 Clinical efficacy

Addition of another lipid-lowering agent to statin monotherapy at maximally tolerated dose may help patients achieve target lipid goals and reduce cardiovascular risk

The most effective class of drugs for the reduction of LDL-C levels is 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors or statins. Statins are recognised as first-line treatment for lowering LDL-C. However, despite the beneficial effect of statin therapy on the risk of cardiovascular events, there is a significant patient population not achieving target lipid goals and therefore being at high to very high cardiovascular risk as outlined in the recently published guidelines on the management of dyslipidaemias by the European Society

of Cardiology and European Atherosclerosis Society (ESC/EAS) (Catapano et al., 2016). High efforts have been made to improve the treatment of this group of patients. There is evidence from clinical studies that these patients may require statin therapy in combination with another lipid lowering agent to reach target lipid goals (Catapano et al., 2016). It has been demonstrated that addition of the cholesterol-absorption inhibitor ezetimibe to statin monotherapy revealed significant greater reductions in LDL-C and other atherogenic lipids compared to a statin alone (see section below). Statins inhibit cholesterol synthesis but can upregulate cholesterol absorption, with higher doses producing larger effects. In a community-based, randomized trial of ezetimibe added to statins, patients were first grouped according to statin potency related to LDL-C lowering effects. One hundred and fifty nine patients were in the high statin potency group defined by a LDL-C-lowering effects of ~46-55%. Patients on high-potency statins had the lowest levels of cholesterol synthesis markers and the highest levels of cholesterol absorption markers at baseline. The addition of ezetimibe treatment in the high-potency group produced significantly greater reductions from baseline in LDL-C than medium-/low-potency groups. This was paralleled with the greatest reduction in absorption markers and the smallest increases in synthesis markers with ezetimibe addition in this group compared with low or moderate intensity statin (Thongtang et al., 2012). Therefore, such patients are good candidates for ezetimibe therapy if additional LDL-C lowering is needed.

Existing clinical literature demonstrate superior clinical performance of concomitant therapy of rosuvastatin and ezetimibe compared to rosuvastatin alone or up-titration

Based on the pharmacological synergistic mechanism of action, the use of rosuvastatin and ezetimibe monotherapy as well as concomitant use of ezetimibe and a statin is supported by the guideline of the European Society of Cardiology (ESC) (Catapano et al., 2016). Rosuvastatin and ezetimibe taken concomitantly in patients with primary hypercholesterolemia or mixed hyperlipidaemia leads to significantly greater reduction in TC, LDL-C, VLDL-C, ApoB and triglycerides (TG) as well as in an increase of the anti-atherogenic high-density lipoprotein cholesterol (HDL-C) compared to rosuvastatin alone (Ballantyne et al., 2014; Ballantyne et al., 2007; Kosoglou et al., 2004). It has also been demonstrated that addition of ezetimibe to rosuvastatin is superior to up-titration to a higher dose of rosuvastatin monotherapy in terms of reduction in TC, LDL-C, ApoB, and TG (Bays et al., 2011). In 4132 Spanish patients with heterozygous familial hypercholesterolemia, attainment of LDL-C was improved after an average 5 years of follow-up by increasing statin regimen to maximally tolerated dose or addition of ezetimibe (Perez de Isla et al., 2016).

These studies also demonstrate that the combination of rosuvastatin and ezetimibe is well tolerated and does not result in synergistic toxicity. Hence, the safety and tolerability profile of the combination is consistent with administration of each of the compounds alone.

Fixed dose combination products may improve adherence to medication

Fixed dose combination products may 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) (Catapano et al., 2016; Stone et al., 2005; NCEP, 2002).

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 of 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).

In a recent survey in Italy using a claim database (IMS Health Longitudinal Patient Database), in 18423 very high cardiovascular (CV) risk patients, the fixed combination of simvastatin and ezetimibe had the largest ratio (4.15 fold) to reach LDL-C <70 mg/dL goal when comparing adherent (≥80% percent of days covered) with non-adherent patients (Guglielmi et al., 2017).

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

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 7. 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. In 2016, a GCP-compliant RCT investigating the efficacy and safety of alirocumab add-on treatment to rosuvastatin baseline therapy compared to rosuvastatin-ezetimibe combination and up-titration of rosuvastatin monotherapy has been published by Farnier et al. However, statistical analyses results have only been shown for alirocumab treatment compared to ezetimibe add-on and rosuvastatin up-titration.
In addition to the clinical trials, a large retrospective ezetimibe add-on study has been described by Foody et al. demonstrating improved efficacy of ezetimibe add-on therapy compared to up-titration of statins. The effect of adding ezetimibe to simvastatin, atorvastatin, or rosuvastatin monotherapy versus titrating these statins on LDL-C changes and goal attainment in CHD or CHD risk-equivalent patients was assessed in a large, retrospective, observational, managed-care database in the USA. Eligible patients (n=17.830) were initially on statin monotherapy for >42 days with available baseline and follow-up LDL-C values, and no concomitant use of other lipid-lowering therapy. The percent change from baseline in LDL-C levels and the odds ratios for attainment of LDL-C <2.6 mmol/L and <1.8 (100 and 70 mg/dL) were estimated using an analysis of covariance and logistic regression, respectively, adjusted for various baseline factors (Foody et al., 2013).
While this study is not an RCT, this large-scale study supports the results demonstrated in the RCTs described above given the increasing relevance of real-world evidence. The patients in this study included CHD or CHD risk-equivalent for previous 12 months and only 3-15% of the patients were on goal of <1.8 mmol/L (<70 mg/dL) after treatment with statin monotherapy. Hence, this patient population is representative of inadequate/non-responder subjects at CVD risk. The study demonstrated that in this population at risk to CVD, the addition of ezetimibe to a statin permitted to achieve greater reduction in LDL-C and goal attainment than up-titration with statin monotherapy. In patients who received rosuvastatin-ezetimibe combination, LDL-C reduction was 27.0% compared to 8.8% with up-titration of rosuvastatin monotherapy. In addition, 36.2% of patients reached the goal of <1.8 mmol/L (<70 mg/dL) when treated with rosuvastatin-ezetimibe combination being significantly higher as compared to the 25.7 % of patients on rosuvastatin up-titration (Foody et al., 2013).

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 largely been administered with respect to the higher exposure (higher C_{max}, AUC) in Asian subjects compared to Caucasians.

In one 12-week study and its one-year extension (Okada et al., 2011), the decrease in LDL-C level in the ezetimibe-plus-statin group was stable and greatest in patients with baseline levels of higher absorption and lower synthesis markers and smallest in patients with baseline levels of lower absorption and higher synthesis markers. These studies are not described in further detail in the present clinical overview.
Recently, two clinical trials investigating the efficacy and safety of concomitant use of rosuvastatin and ezetimibe in Korean subjects have been published by Kim et al., 2016 and Okada et al., 2012.
Yang et al., 2017, used rosuvastatin 20 mg for the first time. Data from these clinical trials have also been included in the present document. These multicentre, 8-week, randomised, double-blind phase III trials compared fixed dose combinations comprising rosuvastatin and ezetimibe with rosuvastatin monotherapy in patients with primary hypercholesterolaemia and high cardiovascular risk.
Another randomized study compared rosuvastatin/ezetimibe with rosuvastatin monotherapy in Chinese patients with acute coronary syndrome (Ran et al., 2017). These three RCTs have been added to tabulation of efficacy and safety. However, there are some limitations, in particular the authors did not give any statement regarding GCP compliance. Furthermore, since there is a 2-fold higher exposure of rosuvastatin in Korean or Chinese subjects compared to Caucasians, comparability of the dose regimens between these clinical trials and above-mentioned studies conducted in Caucasians is limited (Kim et al., 2016).

Table 8. Key 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	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.	• 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-

Reference	Description	Study Design	Efficacy results
	surgery.	Primary end point was the first major cardiovascular event, including death from cardiac causes, nonfatal myocardial infarction, ischemic stroke, and unstable angina.	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 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	Ten patients received atorvastatin 10-20	• LDL-C was significantly reduced in both treatment groups.

Reference	Description	Study Design	Efficacy results
	combinations: 6-months, 22 patient study to compare efficacy and safety of rosuvastatin/ ezetimibe versus atorvastatin ezetimibe.	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 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, 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.	• 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

Reference	Description	Study Design	Efficacy results
		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.	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).
Ran et al., 2017	Single centre, 125 patients, 12-week, randomised, open label: Comparison of rosuvastatin-ezetimibe combination with rosuvastatin monotherapy	125 patients with acute coronary syndrome primary hypercholesterolemia were randomised to one of the following three treatments for 12 weeks combination with ezetimibe 10 mg daily plus rosuvastatin alone, 10 mg, or 20 mg daily. Primary efficacy endpoint was the percentage of patients reaching specified goal of LDL-C <70 mg/dL	• Target LDL-C <70 mg/dL achievement was higher in patients treated with the combination (81.0%) compared to 10 mg (33.3%) and 20 mg (68.3%) rosuvastatin monotherapy. • Combination therapy reduced LDL-C at week 12 to a significantly larger extent 67.3% compared to 10 mg (43.9%) and 20 mg (52.8%) monotherapy.

Monocomponents

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

IV.4.1 Indication

The MAH initially applied for the following indication:

Hypercholesterolaemia

Rosuvastatin/Ezetimibe Mylan Healthcare is indicated as adjunctive therapy to diet and exercise in adult patients with primary hypercholesterolaemia

- *not appropriately controlled with the maximal tolerated dose of any statin,*
- *already treated with the corresponding dose of rosuvastatin and ezetimibe.*

Prevention of Cardiovascular Events

Rosuvastatin/Ezetimibe Mylan Healthcare is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

No add-on to rosuvastatin indication

For an add-on indication as mentioned in the proposed indication ("not appropriately controlled with the maximal tolerated dose of any statin") a dedicated study demonstrating

the additional effect of ezetimibe in patients not sufficient responding to a maximum rosuvastatin therapy is required. Of note, although the initial ezetimibe monotherapy indication includes above mentioned indication, this indication has only been supported with data of other statins than rosuvastatin in the original dossier and based on other referred studies in the ezetimibe SmPC. For the main studies presented in current dossier, the EXPLORER study design was open-label and missing a maximum dose run-in phase, and is therefore not considered robustly designed to evaluate additive efficacy in a non-responder population. The ACTE compared the up-titration of 5 mg or 10 mg rosuvastatin to adding ezetimibe after a 4 week run-in period. The GRAVITY study compared the combination of rosuvastatin and ezetimibe to combination of simvastatin and ezetimibe. In both studies treatment with ezetimibe was more effective in reaching treatment goals in comparison to up-titration. However, both studies are not specifically designed as rosuvastatin non-responder studies. Another relevant study is the recently published ODYSSEY OPTIONS II study where patients not on LDL-C target, who were treated with baseline doses of rosuvastatin of 10 mg or 20 mg received ezetimibe (or alirocumab) add-on, which resulted in greater LDL-C lowering compared to doubling the statin doses, though this was not the primary analysis of this study. Moreover, this study is subject to data protection and cannot be used to support the current application.
Overall, these studies are not sufficient to demonstrate the add-on effect of ezetimibe on rosuvastatin non-responders. While, the MAH has not performed and submitted any dedicated study demonstrating an additional effect of ezetimibe in patients not sufficiently responding to maximum relevant rosuvastatin dose. The MAH dropped this indication, which is supported.

No cardiovascular prevention indication
The MAH proposed to include a cardiovascular prevention indication:

Prevention of Cardiovascular Events
Rosuvastatin/Ezetimibe Mylan Healthcare is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

This indication is supported by the MAH based on a discussion of the JUPITER and the IMPROVE-IT studies. However, both studies lack sufficient support for CV prevention for this specific combination. Therefore, these studies cannot be used to support the proposed CV prevention indication. Moreover, CV prevention statements have not been included in any other available fixed dose combination (FDC) substitution indication of a statin with ezetimibe combination. Consequently, the proposed CV prevention indication cannot be supported. The MAH has dropped this indication, which is supported.

Substitution indication
The MAH provided a tabulated description of three main studies on the combination of rosuvastatin and ezetimibe, ACTE, GRAVITY and EXPLORER based on published data. The EXPLORER study in patients with high CV risk is considered relevant as it specifically addresses the beneficial effects of the combination of ezetimibe and rosuvastatin (40 mg) in

comparison to rosuvastatin alone. The ACTE and GRAVITY studies compare the combination (rosuvastatine and ezetimibe) to up-titration of rosuvastatin or to combination of simvastatin and ezetimibe, respectively. In both studies treatment with ezetimibe was more effective in reaching treatment goals in comparison to up-titration to higher statin doses. Other studies have also been tabulated and described in support of the pivotal data. Though, these studies have some limitations as acknowledged by the MAH including open-label design, retrospective observational data, Asian population (with a different dose response curve), lack of statistical data for comparison of ezetimibe add-on to rosuvastatin, or lack of any GCP statement.
Overall, the factorial designed studies as mentioned above are of sufficient evidence for a substitution indication by demonstration that additional effect can be seen with addition of ezetimibe to ongoing rosuvastatin therapy.
The MAH has not specifically discussed the use of the combination in clinical practice. Data presented is a survey in the Netherlands (Heintjes et al., 2017) and the retrospective observational study in the US (Foody et al., 2013) may be the best available clinical practice data provided in this dossier and is considered sufficient. Moreover, clinical practice guidelines acknowledge the combined use.

Approved indication
The “add-on indication” and “prevention of cardiovascular events” have been deleted by the MAH. The following indication is approved:

Rosuvastatin/Ezetimibe Mylan Healthcare 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.

IV.5 Clinical safety

Safety data of a substantial number of patients treated with the combination have been provided based on literature data. The MAH provided data on the dedicated literature studies in rosuvastatin and ezetimibe as being used in combination as also presented in the efficacy section.
Further, a meta-analysis study on the safety of the different statins is also presented. These data do not appear to raise any concern and can be considered in line with the known safety profile of the monocomponents and that of the combination of ezetimibe with other statins.
No interference on the safety profile of the components is expected, therefore, the safety profile of the individual components are also considered of importance. In this respect, the MAH has provided sufficient information based on the SmPC information, although the safety profile of the monocomponents is well known.
In addition, the MAH provided data on the adverse events observed in the bioequivalence study. Although this is appreciated, the data in the bioequivalence study is only of limited value for evaluation of the combined safety profile of the FDC especially due to the limited study size.

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

Safety data from literature

The individual components (rosuvastatin and ezetimibe) comprising the proposed drug product have well-established clinical use and well-characterised safety and efficacy profiles. Clinical safety and efficacy of rosuvastatin and ezetimibe have been studied in well controlled randomised clinical studies across different ethnicities, ages and geographies (SmPC Crestor; SmPC Ezetrol). Safety 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 (Kosoglou et al., 2004) and the GRAVITY study (Ballantyne et al., 2014). These studies have been conducted according to GCP guidelines and are summarised in the SmPCs of approved combination medicinal products comprising rosuvastatin and ezetimibe (Merck Sharp & Dohme Australia Pty Ldt, 2014; Egis Pharmaceuticals Plc., 2014). Therefore, these studies have been selected as key studies supporting the safety and efficacy of concomitant use of rosuvastatin and 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; Styliadis et al., 2007; Farnier et al., 2016; Okada et al., 2012; Kim et al., 2016). However, only a limited number of patients have been enrolled in most of these studies and information regarding GCP compliance has only been provided by Farnier et al., 2016. As part of the development programme of alirocumab, 444 patients received ezetimibe plus a statin in control groups, including 264 with high dose statins and 179 with not high dose statins plus ezetimibe 10 mg. The proportion of patients reporting any adverse events was 71.2% in those with high dose statins and ezetimibe; the most frequent adverse events in about 5% of patients were upper respiratory tract infection, hypertension, dizziness and nasopharyngitis (Catapano et al., 2017).

Safety data from bioequivalence studies no. C13225 and RP15.1112

For determination of bioequivalence, two randomised, open label, pivotal studies in a total of 114 healthy male volunteers under fasting condition have been conducted using Crestor (rosuvastatin) and Ezetrol (ezetimibe) as reference products. Beside pharmacokinetic analysis, safety parameters comprising physical and systemic examination, vital signs measurement, clinical laboratory tests and adverse event monitoring including a subject wellbeing questionnaire were performed during the study. Clinical laboratory safety assessment was done at the end of the study.

A total of five adverse events were recorded in five subjects during the entire period of the study including body ache, fever, increased transaminases and elevated creatine kinase (n=2). The reported adverse events resolved completely. Vital signs showed no marked changes throughout the study. No abnormal findings were observed during the post-study physical examination.

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

Additional data are provided from clinical literature based on existing clinical studies demonstrating that the concomitant treatment of rosuvastatin and ezetimibe is, in general, well tolerated and has similar tolerability compared to rosuvastatin monotherapy or up-titration of rosuvastatin.

Safety data from the monocomponents SmPC

The MAH presented safety data for rosuvastatin and ezetimibe as stated in the SmPC of the respective monocomponents (Crestor and Ezetrol) including information from section 4.3, 4.4, 4.5, 4.8, 4.9 and 5.1, if applicable.

Additional safety data

When considering the most potent statins available, the highest doses are 40 mg for rosuvastatin, 80 mg for atorvastatin and simvastatin and 4 mg for pitavastatin. However, the highest dose of simvastatin presents some safety concerns due to a higher rate of myopathy observed in patients titrated to the 80 mg dose (Zocor SmPC) and pitavastatin is marketed in very few countries in Europe.

The most concerning adverse event experienced with statin therapy are muscle symptoms. While in principle benign and reversible, statin-induced muscle symptoms may compromise physical activity – an important component of cardiovascular prevention. Importantly, these side effects have substantial impact on drug adherence and consequently on cardiovascular risk reduction, as they frequently result in discontinuation or suboptimal dosing of statins. Notably, low adherence to statin therapy is associated with a higher mortality in elderly secondary prevention patients with low vs. high adherence to statin therapy (24% vs. 16%, respectively; adjusted hazard ratio, 1.25; p= 0.001) and a 15% increase in cardiovascular risk among secondary prevention patients (Koskinas et al., 2016).

In contrast to randomised clinical trials, patient registries, together with clinical experience, indicate that 7-29% of patients complain of statin associated muscle symptoms (SAMS). These are usually associated with normal or slightly elevated CK concentrations. SAMS likely contribute significantly to the very high discontinuation rates of statin therapy (up to 75%) within two years of initiation. Indeed, in 65% of previous statin users, the main reason for statin non-adherence or discontinuation was the onset of side effects, predominantly muscle-related effects (Stroes et al., 2014).

However, individual patient differences are likely more important than statin differences in affecting statin uptake by skeletal muscle tissue (Koskinas et al., 2016).

When considering the overall statin adverse events and across the totality of the evidence base from a study-level network meta-analysis of 246.955 participants from 135 randomised clinical trials, higher doses of some statins result in higher odds of experiencing transaminase elevations, CK elevations, and discontinuations because of adverse events. When compared head-to-head in network meta-analyses, there are differences among individual statins, with simvastatin and pravastatin likely to be ranked superior to their alternatives in terms of their safety profile.

When the individual statins were ranked in terms of the magnitude of the estimated treatment effect, as well as the uncertainty around it, pravastatin (0.71) and simvastatin (0.70) had the highest combined score out of a total of 1.00, suggesting that these statins had the most favorable tolerability and harm profile on the basis of discontinuations

because of adverse events, myalgia, transaminase elevations, and CK elevations (see Figure 1) (Naci et al., 2013). Inversely, rosuvastatin, atorvastatin and pitavastatin had the lowest combined score suggesting the most potent statins have the less favourable tolerability and safety profile.

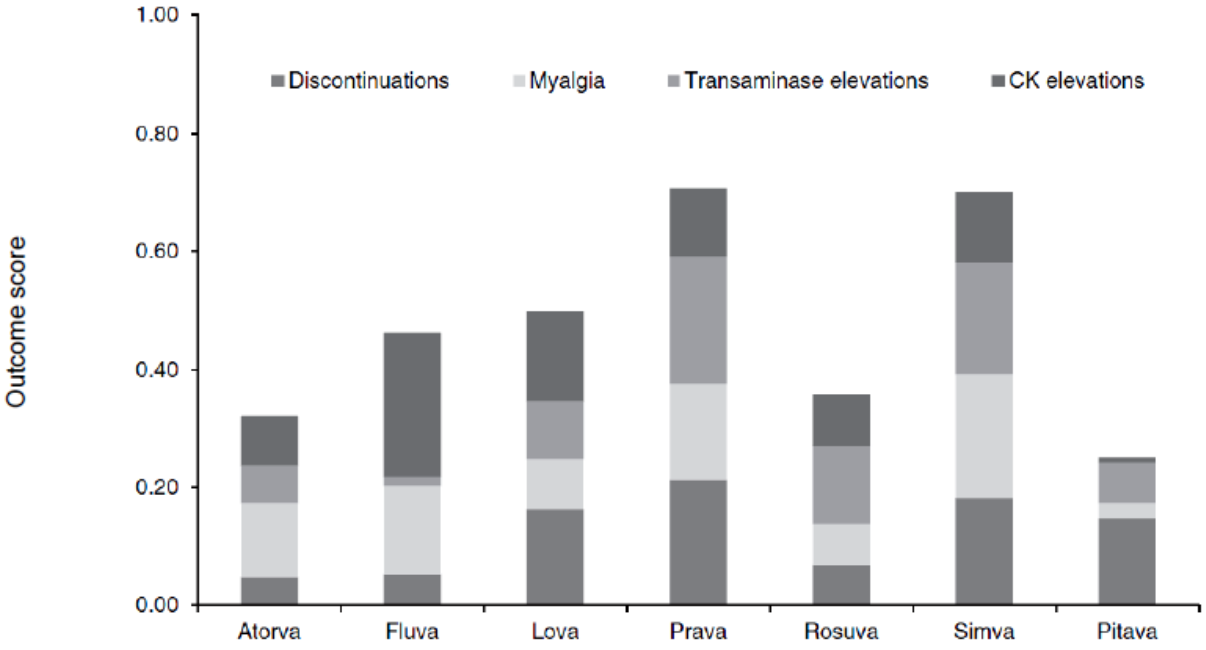

Figure 1. Overall ranking of individual statins in placebo-controlled and active comparator trials of participants by their overall probability to be the best treatment in terms of discontinuations because of adverse events, myalgia, hepatic transaminase elevation, and CK elevation.

In addition to the overall score for each statin, the relative contribution of each of the four outcomes to the overall score is also shown. Each statin was scored with points up to a maximum of 0.25 for each outcome (overall maximum score: 1.00). Higher scores indicate a better tolerability and safety profile. CK indicates creatine kinase (Naci et al., 2013).
In summary, the tolerance of statins varies from statin to statin and tolerance issues increase with increasing statin dose. Moreover, individual patient differences come in addition to the intrinsic variability within the statin class. Furthermore, it may be difficult to define what maximal tolerated statin dose means to physicians. However, it appeared important to give recommendation to prescribers to increase the statin dose to reach LDL-C target – according to patient's level of CVD risk – before adding another lipid-lowering agent. Ultimately, it is the responsibility of the physician to judge on a case-by-case basis what should be the maximal tolerated dose of a statin and it may not correspond to the highest statin dose available in a significant number of patients.
Therefore, the proposed indication has been restricted to patients not appropriately controlled with a maximal tolerated statin dose, recommending treating physicians to use their best medical judgement to determine the appropriate dose according to their patients.

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 Rosuvastatin/Ezetimibe Mylan Healthcare.

Table 11. 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 Rosuvastatin/Ezetimibe Mylan Healthcare. Bioequivalence is shown between Rosuvastatin/Ezetimibe Mylan Healthcare and the concomitant use of Crestor and Ezetrol. The safety profile of Rosuvastatin/Ezetimibe Mylan Healthcare is acceptable. Risk management is adequately addressed. This fixed dose combination 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Twicor (NL/H/3647/001/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rosuvastatin/Ezetimibe Mylan Healthcare 10 mg/10 mg and 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.

Rosuvastatin/Ezetimibe Mylan Healthcare film-coated tablets were shown to be bioequivalent to the concomitant use of Crestor 10 mg or 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 Rosuvastatin/Ezetimibe Mylan Healthcare 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 Rosuvastatin/Ezetimibe Mylan Healthcare 10 mg/10 mg and 20 mg/10 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 October 2018.

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/4175/001-002/IA/002/G	An additional batch release site is added for batch release	--	1-3-2019	Approval	--
NL/H/4175/001-002/IA/001/G	New certificate from a new manufacturer (replacement or addition) Deletion of certificate (in case multiple certificates exist per material)	--	10-3-2019	Approval	--
NL/H/4175/001/E/001	Repeat use procedure to register the product in Austria	--	26-6-2019	Approval	--

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