COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe/Atorvastatine DOC 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg hard capsules

(ezetimibe/atorvastatin calcium trihydrate)

NL/H/4991/001-003/DC

Date: 17 September 2020

This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatine DOC. The procedure was finalised at 11 March 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ACS	Acute Coronary Syndrome
AE	Adverse Event
ALT	Alanine Aminotransferase
ASMF	Active Substance Master File
CAD	Coronary Artery Disease
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FDC	Fixed Dose Combination
HDL-C	High-Density Lipoprotein Cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
ICH	International Conference of Harmonisation
LDL-C	Low-Density Lipoprotein Cholesterol
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TSE	Transmissible Spongiform Encephalopathy
VLDL-C	Very-Low-Density Lipoprotein Cholesterol

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ezetimibe/Atorvastatine DOC 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg hard capsules from DOC Generici S.r.l.

Ezetimibe/Atorvastatine DOC 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.

Rationale

The efficacy and safety of the concomitant use of atorvastatin and ezetimibe is well established, and their use is supported by the European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias, based on their pharmacological complementary mechanisms of action.
Furthermore, the pharmacokinetic profiles of atorvastatin and ezetimibe are suitable for their combined use. Their half-lives allow once-daily dosing, their major routes of elimination are not suggestive of a relevant pharmacokinetic drug-drug interaction and also there are no data pointing to a clinically relevant inhibition or induction of either enzymes or transporters by any mono-component which could have a relevant impact on the pharmacokinetics of one of the combination partners.

Decentralised procedure

This decentralised procedure concerns a fixed dose combination (FDC) application. FDCs contain active substances from medicinal products already authorised in the EEA. The individual active substances within Ezetimibe/Atorvastatine DOC, atorvastatine and ezetimibe, are established active substances.
Lipitor (atorvastatin) 10 mg, 20 mg, and 40 mg strengths (NL License RVG 21081-21083) have been registered in the Netherlands (MAH: Pfizer B.V.) since 21 April 1997 through Mutual Recognition Procedure (MRP) DE/H/0109/001-003.
Ezetrol (ezetimibe) 10 mg, tablets (NL License RVG 28626) has been registered in the Netherlands (MAH: Merck Sharp & Dohme Ltd.) since 18 April 2003 through MRP DE/H/0396/001.
There is also a registered atorvastatin/ezetimibe FDC of MSD Sharp & Dohme Ltd under the brand names of Atozet, Kexrolt, Orvatez, Ezetimibe/Atorvastatin MSD and Liptruzet 10/10, 10/20, 10/40, and 10/80 mg. It was first authorised on 29 July 2014 in Germany according to Article 10(b) of Directive 2001/83/EC).

The concerned member state (CMS) involved in this procedure was Italy

View of an interested party

In the Netherlands interested parties have the right to give their views during pending applications. These views should be taken into consideration during assessment and decision-making of the respective application procedure.

An interested party took this opportunity and presented its views about pending marketing authorisation applications containing ezetimibe/atorvastatin in January 2019 in a letter, with a request for an oral hearing.

An oral hearing was held in June 2019, in which the interested party raised questions to the MEB with regard to the pending marketing authorisation applications. The interested party provided a list of clinical studies which fall under data exclusivity rights. The interested party considers that pending marketing authorisation applications referring to these studies should not be approved.

The raised concern was carefully assessed and addressed during the evaluation procedure.

Legal base

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC. The clinical dossier (bioequivalence studies versus the mono products) is in line with the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017). The rationale and justification of the FDC is based on bibliographic data. The MAH did not refer to data derived from clinical studies that were conducted to support the marketing authorisation application of Atozet, a different FDC of atorvastatin and ezetimibe.

Paediatric development

A product specific waiver for atorvastatin (calcium)/ezetimibe (EMEA-002047-PIP01-16) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council was requested and approved. The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. Consequently, the proposed FDC product is not indicated for treatment of children.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Atorvastatine DOC is an unmarked, self-closing, hard gelatin capsule filled with atorvastatin pellets and a ezetimibe tablet.

- The 10 mg/10 mg hard capsule has a caramel coloured cap and yellow coloured body and contains 10 mg ezetimibe and 10 mg of atorvastatin (as atorvastatin calcium trihydrate)
- The 10 mg/20 mg hard capsule has a reddish-brown coloured cap and yellow coloured body and contains 10 mg ezetimibe and 20 mg of atorvastatin (as atorvastatin calcium trihydrate)

- The 10 mg/40 mg hard capsule has a dark brown coloured cap and yellow coloured body and contains 10 mg ezetimibe and 40 mg of atorvastatin (as atorvastatin calcium trihydrate)

The tablets are packed in OPA/Aluminium/PVC blisters.

The excipients are:
Core - calcium carbonate (E170), hydroxypropyl cellulose (E463), polysorbate 80 (E433), croscarmellose sodium (E468), sugar spheres, talc (E553B), mannitol (E421), microcrystalline cellulose (E460(i)), low-substituted hydroxypropyl cellulose (E463), povidone (E1201), sodium laurilsulfate (E487) and magnesium stearate (E572)
Capsule shell –

- Ezetimibe/Atorvastatine DOC 10 mg/10 mg hard capsules:
  Cap: titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172) and gelatin (E441)
  Body: titanium dioxide (E171), yellow iron oxide (E172) and gelatin (E441)
- Ezetimibe/Atorvastatine DOC 10 mg/20 mg hard capsules:
  Cap: titanium dioxide (E171), red iron oxide (E172) and gelatin (E441)
  Body: titanium dioxide (E171), yellow iron oxide (E172) and gelatin (E441)
- Ezetimibe/Atorvastatine DOC 10 mg/40 mg hard capsules:
  Cap: titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172) and gelatin (E441)
  Body: titanium dioxide (E171), yellow iron oxide (E172) and gelatin (E441)

II.2 Drug Substances

Ezetimibe
The active substance ezetimibe is an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). It is a white to almost white crystalline powder. Ezetimibe is freely soluble in ethanol and acetone, soluble in ethanol and practically insoluble in water. Ezetimibe contains three asymmetric carbon atoms and therefore exhibits optical isomerism. Ezetimibe exhibits polymorphism and the anhydrous crystalline form is consistently produced. Two manufacturers of ezetimibe are used for the medicinal product.

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

Manufacturing process

Manufacturer one – The synthesis description is in sufficient detail and sufficient chemistry is part of the regulatory synthesis route. The specifications of the starting materials and intermediates are acceptable.

Manufacturer two – four chemical synthesis steps and one final purification step are described in sufficient detail. The specification for the starting material and other raw materials are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and contains tests for description, identification, specific optical rotation, water content, sulphated ash, related substances, diastereomeric impurity, assay and residual solvents. As ezetimibe is dissolved in ethanol during the manufacturing process of the drug product, the polymorphic form and particle size distribution of the drug substance are not relevant. The proposed specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for four industrial scale batches for manufacturer one and for three industrial scale batches for manufacturer two.

Stability of drug substance

Manufacturer one – Stability data on six batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months) have been provided. Based on the provided stability data, the claimed re-test period of 48 months is justified. No special temperature storage conditions are required.

Manufacturer two – Stability data on eight batches stored at 25°C/60% RH (up to 60 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) have been provided. Based on the provided stability data, the claimed re-test period of 5 years and storage conditions "Preserve in well-closed container, protected from light, at controlled room temperature" are justified.

Atorvastatin calcium trihydrate

The active substance atorvastatin calcium trihydrate is an established active substance described in the Ph.Eur. Atorvastatin calcium trihydrate is a white or almost white crystalline powder. It is very slightly soluble in water, slightly soluble in ethanol (96%), practically insoluble in methylene chloride. Atorvastatin calcium trihydrate shows polymorphism and "Form P1" is consistently produced. The MAH included full information of this active substance in the dossier.

Manufacturing process

The manufacturing process has been described in sufficient detail. No class 1 solvents are used in the synthesis. The drug substance and starting materials are adequately characterised. Acceptable specifications have been adopted for starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional tests for tetrahydrofuran content and particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Additional methods have been adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data for atorvastatin hydrochloride trihydrate have been provided for three pilot scale batches stored at 25°C/60% RH (36 months), 30°/65% RH (36 months), 30°/75% RH (36 months), and 40°C/75% RH (6 months). On basis of the data provided a re-test period of 36 months when stored away from moisture and no special temperature storage condition is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. The main development studies were formulation development, dissolution method development, manufacturing process development and the performance of comparative dissolution studies complementary to the bioequivalence study with the 40 mg/10 mg test product and dissolution studies in support of the biowaiver claimed for the additional 20 mg/10 mg and 10 mg/10 mg strengths. The pharmaceutical development of the product has been adequately performed. The provided comparative dissolution data support the requested biowaiver.

Manufacturing process

The manufacturing process consists of manufacturing the atorvastatin pellets (preparation of the layering suspension, layering and sieving) and manufacturing of the ezetimibe tablets (preparation of solutions, preparation of suspension, fluid granulation, drying, regranulation, sieving, blending and tabletting). The manufacturing process has been described in sufficient detail. Process validation data on the product have been presented for three consecutive full production scale batches of atorvastatin immediate release pellets, three pilot scale batches of ezetimibe 10 mg tablets and three full production scale batches of ezetimibe 10 mg tablets. The encapsulation was validated on three pilot scale batches per strength of the final drug product. Given the manufacturing process of the atorvastatin IR pellets and the ezetimibe tablets has been validated at full production scale and the filling into capsules is considered a standard process, the manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
All excipients comply with the Ph. Eur., except for the hard gelatin capsule. The 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 of the capsule, appearance of the capsule filling, colour of the capsule filling, odour of the capsule filling, identification, assay, related substances, dissolution, average mass of the capsule filling, uniformity of mass of the capsule filling, water content, uniformity of dosage units and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability studies were conducted on three commercial scale batches per strength of the proposed product stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The batches were stored in the blisters as proposed for marketing (OPA/Al/PVC-Alu foil blisters). No significant changes have been observed for any of the investigated parameters at long term and accelerated conditions. A photostability study performed on one batch showed that the product is not sensitive to light. On basis of the data provided a shelf life could be granted of 30 months when stored below 30°C in the original packaging in order to protect from moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Both active substances in this FDC product are well known substances. Therefore, no new non-clinical studies have been submitted for this application. The provided non-clinical dossier consists of published literature references.

III.2 Pharmacology

Atorvastatin

Atorvastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Unlike most other statins, however, it is a completely synthetic compound. HMG-CoA reductase catalyses the reduction of HMG-CoA to mevalonate, which is the rate limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases de novo cholesterol synthesis, increasing expression of low-density lipoprotein receptors on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol. Atorvastatin is indicated as an adjunct to diet for the treatment of dyslipidaemia, specifically hypercholesterolemia. It has also been used in the treatment of combined hyperlipidaemia.

Ezetimibe

Ezetimibe is the first member of a new class of selective cholesterol absorption inhibitors. The drug and its active glucuronide metabolite impair the intestinal reabsorption of both dietary and hepatically excreted biliary cholesterol through inhibition of a membrane transporter.

III.3 Pharmacokinetics

Atorvastatin

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning drug administration. However, LDL-C reduction is the same regardless of the time of drug administration.

Distribution
Mean volume of distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

Metabolism
Atorvastatin is extensively metabolised to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion
Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

<u>Ezetimibe</u>
Absorption
Ezetimibe is rapidly absorbed and is extensively metabolised to an active phenolic glucuronide which reaches the systemic circulation after oral administration. Its action is localised at the brush border of the small intestine where it inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This results in a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

Metabolism
The drug is not metabolised by the cytochrome P450 system but extensive glucuronidation takes place in the intestine. Consequently, plasma concentrations of ezetimibe represent approximately 10% of total ezetimibe in plasma. Enterohepatic recirculation observed for ezetimibe and its glucuronamide significantly increases the residence time of these compounds in the intestine, at their site of action. In a rat model, where the glucuronide metabolite of ezetimibe was administered intraduodenally, the metabolite was as potent as the parent compound in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug. Ezetimibe metabolism has been determined in rats, dogs, mice and human plasma and faeces and in biliary excretion studies (in rats and dogs). In all species tested the drug is metabolised almost exclusively via glucuronidation at the 4-hydroxyphenol group to form phenolic glucuronide. *In vivo*, minor

amounts of the oxidative metabolite SCH 57871 (<3.2% of dose) were observed in the faeces of mice, rats, dogs and humans. Human urine also contained SCH 57871 glucuronide (<1% of dose). Trace amounts of benzylic glucuronide (<1%, SCH 488128) were observed in the pooled human urine (0-72 hr following oral administration) and in the pooled dog bile (0.02%, 0-48 hours after oral and iv dosing). Minor amounts of a rearranged isomeric form of the drug (SCH 59566) results from nonenzymatic rearrangement within the drug molecule *in vitro*. However, percentage of SCH 59566 compound was not minor in rats (16.4% of dose in the female rat after iv dosing), or dogs (6.9% of the dose in the female dog after oral dosing). SCH 59566 was not found in males.

Excretion
Following administration of a single oral gavage (mouse, rat, dog), or iv dosing (rat, dog) or dosing (in humans) with 3H or 14C-ezetimibe, the drug was eliminated primarily in faeces (>76%) and small amounts (<1-11%) in urine up to 168-336 hours post-dose. Substantial amount of radioactivity was found in faeces after iv dosing (in rats and dogs) which is consistent with extensive biliary excretion of the drug. No sex differences in excretion of drug were observed in dogs, however higher excretion of radioactivity was observed in urine of female rats than in male rats. This difference in extent of urinary excretion was consistent with sex related differences in plasma levels of glucuronide relative to total drug and excretion of mainly glucuronide drug in urine.

III.4 Toxicology

Atorvastatin
Atorvastatin did not demonstrate mutagenic or clastogenic potential in four *in vitro* tests with and without metabolic activation or in one *in vivo* assay. It was negative in the Ames test with Salmonella typhimurium and Escherichia coli, and in the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test. In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumours were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma, and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. Extrapolation of this evidence of carcinogenesis from rodents to humans is an uncertain process. Longer-term clinical trials and careful post-marketing surveillance during the next several decades are needed to determine whether cholesterol-lowering drugs cause cancer in humans. No adverse effects on fertility or reproduction were observed in male rats given doses of atorvastatin up to 175/mg/kg/day or in female rats given doses up to 225 mg/kg/day. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg basis. Atorvastatin did not cause any adverse effects on sperm or semen parameters, or in reproductive organ histopathology in dogs given doses of 10, 40 or 120 mg/kg for 2

years. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m 2). Atorvastatin is a potent inhibitor of the enzyme HMGCoA reductase, which catalyses the conversion of HMG-CoA to mevalonate and constitutes the rate-limiting step in the biosynthesis of cholesterol. Steroid hormones derived from cholesterol, as well as mevalonate and its isoprenoid derivatives, provide important contributions to the maternal animal during pregnancy and lactation, as well as to the growth and development of the offspring; these contributions may potentially be influenced by inhibition of HMG-CoA reductase. If the woman becomes pregnant while taking atorvastatin, it should be discontinued and the patient advised again as to the potential hazards to the foetus. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin should not breast-feed. In summary, non-clinical data of atorvastatin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. The preclinical data reviewed, and clinical data also suggest that this drug can be considered safe when used in the recommended doses.

Ezetimibe

In acute oral toxicity studies in mice, rats and dogs, the maximum doses (3000-5000 mg/kg/day) were well tolerated with the drug, as no mortality was observed. In repeat-dose toxicity studies, ezetimibe was administered orally to mice for up to 3 months, to rats for up to 6 months, and to dogs for up to 1 year. Ezetimibe was well tolerated in all species examined. The target organs of toxicity in preclinical studies were lymph nodes and heart (in rats/dogs), bone marrow and kidney (in rats). These target organ toxicities were observed at approximately tenfold human doses, suggesting sufficient safety of margin in humans. Ezetimibe is considered non-genotoxic both in *in vitro* and *in vivo* assays. In carcinogenicity studies the survival of male and female mice and rats was comparable in the ezetimibe-dosed and control groups. There were no ezetimibe-related effects on clinical observations, body weight, food consumption, ophthalmology or haematology. The incidence, time of onset, and number of palpable masses were not ezetimibe-related. No ezetimibe related necropsy or histopathologic changes were observed. There were no statistically significant increases in the incidence of tumours in any of the ezetimibe-dosed groups, compared to the vehicle control group. In oral (gavage) embryo-foetal development studies conducted in rats and rabbits during organogenesis, there was no evidence of embryo lethal effects at the doses tested (250, 500, 1000 mg/kg/day). There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the foetus. It is not known whether ezetimibe is

excreted into human breast milk. In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe/Atorvastatine DOC is intended for substitution of the individual mono-products, 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

For Ezetimibe/Atorvastatine DOC, no new data regarding pharmacology, pharmacokinetics or toxicology have been provided. No new studies have been performed and none are considered necessary. This is acceptable, as both active substances are well known and no additional data are needed for the use as fixed dose combination.

IV. CLINICAL ASPECTS

IV.1 Introduction

The two active substances are well-known and have an established efficacy and tolerability.
To support the application, the MAH submitted literature data relevant to each active substance and references to the combinations of statins and ezetimibe published in the scientific literature. In addition, the MAH submitted one pivotal bioequivalence study with the 10 mg/40 mg tablets. For the two other strengths (10 mg/10 mg and 10 mg/20 mg) a biowaiver was claimed. These studies are considered sufficient for this type of application and in line with the requirements of the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017). The pivotal study is summarised below and the biowaiver is also discussed.

IV.2 Pharmacokinetics

<u>Atorvastatin</u>
Atorvastatin is rapidly absorbed after oral administration and maximum plasma concentrations occur within 1 to 2 hours. The extent of absorption increases in proportion to the atorvastatin dose over the range 5-80 mg. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. Food significantly decreases the rate and extent of absorption of atorvastatin: C_{max} and AUC decrease by approximately 25% and 9%, respectively, when the drug is taken after a meal. Furthermore, plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning administration. However, the LDL-C reduction is

similar whether atorvastatin is taken with or without food. Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.
Atorvastatin is extensively metabolised to ortho- and para-hydroxy derivatives, and various beta-oxidation products. Atorvastatin and its metabolites are eliminated primarily in the bile following hepatic and/or extra-hepatic metabolism. The ortho-hydroxy-metabolite is present in similar concentrations in plasma as the parent compound, while the concentrations of the para-hydroxy metabolite are much lower - about 5% of the parent and the ortho-hydroxy metabolite. Approximately 70% of the circulating inhibitory activity of HMG-CoA reductase has been attributed to the active ortho- and para-hydroxy metabolites.
The elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of the inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.
Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations. Concentrations of atorvastatin and its active metabolites in women differ from those in men (women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites. Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease.
Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis. Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

<u>Ezetimibe</u>
Ezetimibe undergoes extensive glucuronidation (ezetimibe glucuronide) after oral administration, presumably while traversing the gut epithelium. Both ezetimibe and ezetimibe-glucuronide are pharmacologically active, with ezetimibe-glucuronide inhibiting cholesterol absorption to at least as great an extent as the unconjugated parent. Thus, total ezetimibe (unconjugated ezetimibe + ezetimibe glucuronide) represents the sum of active ezetimibe-derived substances in plasma following an oral dose.
Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as Ezetimibe 10 mg tablets. Ezetimibe can be administered with or without food. Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours. Following oral administration of 14C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with Ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment, compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment, the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, ezetimibe is not recommended in these patients.
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 ml/min/1.73 m2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renal impaired patients. An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.
Plasma concentrations for total ezetimibe are slightly higher (approximately 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Bioequivalence study
One bioequivalence study of the proposed drug product with the reference products comparing bioavailability of the highest strength of the proposed atorvastatin/ezetimibe FDC with the monocomponents administered concomitantly was submitted, with a waiver for the lower strengths.
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ezetimibe/Atorvastatine DOC 10 mg/40 mg hard capsules (DOC Generici S.r.l., Italy) is compared with the pharmacokinetic profile of the reference products Sortis 40 mg film-coated tablets (Pfizer Manufacturing Deutschland GmbH, Germany) and Ezetrol 10 mg tablets (Schering-Plough Labo N.V., Belgium)

The choice of product used in the bioequivalence study
The choice of the product used in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
For the 10 mg/10 mg and 20 mg/10 mg strengths a biowaiver has been requested. As the following criteria have been met the biowaiver has been accepted:

- Atorvastatin has linear pharmacokinetics concerning the extent of absorption (AUC) in the therapeutic dose range.
- All strengths were manufactured by the same manufacturer and process.
- Qualitative composition of the different strengths is the same.
- The proposed FDC capsules contains separate atorvastatin pellets and ezetimibe tablet in a capsule, therefore the ratio between amounts of active ingredient and excipients was calculated separately for atorvastatin pellets and ezetimibe tablet. The compositions of the different strengths are quantitatively proportional (atorvastatin pellets) or the same (ezetimibe tablets).
- The dissolution profiles for the 10/10 mg and 20/10 mg strengths were similar to the 40/10 mg strengths.

Design
A monocentric, open, randomised, single-dose, two-treatment, four-period, two- sequence crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-65 years. Each subject received a single dose (40 mg atorvastatin and 10 mg ezetimibe) of one of the two formulations for two treatments. The capsule or tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were four dosing periods, separated by a washout period of 14 days.

For atorvastatin blood samples were collected prior to drug administration and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 24, 36, 48, and 72 hours after administration of the products. For ezetimibe blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 20, 24, 48, and 72 hours after administration of the products.

The design of the study is acceptable. The sampling time duration is considered long enough to adequately estimate the pharmacokinetic parameters. The wash-out period of 14 days is long enough to avoid any carry-over effect for unconjugated ezetimibe, total ezetimibe and atorvastatin considering the half life for ezetimibe and atorvastatin.

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

Results

A total of two subjects withdrew for personal reasons after study drug administration. One subject withdrew are study period II and one subject withdrew after study period III. Therefore, 48 subjects received at least one dose of the first two treatments and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atorvastatin 40 mg under fasted conditions.

Treatment N=48	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	89 ± 42	97 ± 42	22 ± 11	1.0 (0.5 - 8.0)
Reference	88 ± 43	95 ± 43	21 ± 11	0.7 (0.5 – 12.0)
***Ratio (90% CI)**	1.02 (0.99 - 1.06)	--	1.07 (0.97 – 1.19)	--
CV (%)	14.6	--	43.7	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of free ezetimibe 10 mg under fasted conditions.

Treatment N=48	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	78009 ± 36307	5506 ± 3241	1.0 (0.5 - 12.0)
Reference	82697 ± 42635	5272 ± 3350	1.0 (0.5 – 10.0)
***Ratio (90% CI)**	0.97 (0.93 - 1.02)	1.08 (1.00 – 1.16)	--
CV (%)	17.7	30.6	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total (unconjugated + conjugated) ezetimibe under fasted conditions.

Treatment N=48	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**
***Ratio (90% CI)**	0.95 (0.92 – 0.98)	1.01 (0.96 – 1.06)
CV (%)	12.5	20.6

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ezetimibe/Atorvastatine DOC is considered bioequivalent with the concomitant use of Sortis and Ezetrol.

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 pharmacodynamics of atorvastatin and ezetimibe are well known and well established by literature. Therefore, no new data have been submitted, which is acceptable.

IV.4 Clinical efficacy

No clinical efficacy studies with the coadministration of the two active substances have been performed by the MAH. Therefore, clinical evaluation of the fixed dose combination of atorvastatin/ezetimibe hard capsules is based on the presented literature data relevant to each active substance and references to the combinations of statins and ezetimibe published in the scientific literature with the aim of proving the clinical benefit provided by the combination.
This assessment report represents an efficacy evaluation of the key elements of the information on the combination of atorvastatin with ezetimibe provided by the company.

Clinical studies performed with atorvastatin and ezetimibe
Thirteen completed studies with published results that investigated the clinical efficacy of coadministered atorvastatin and ezetimibe have been provided by the MAH (table 4).

Table 4 Clinical trials comparing the effects of atorvastatin/ezetimibe versus atorvastatin alone on LDL-C levels in patients with hypercholesterolaemia

Study title	Treatment arm	Enrolled/ completed	LDL-C (mg/dl) baseline	LDL-C (mg/dl) at week 8	LDL-C (mg/dl) at week 12	LDL-C (mg/dl) at week 16	Mean LDL-c change (reduction) from baseline (%)	Statistical test/ P value	Secondary endpoints
Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: The multicenter randomized controlled PRECISE-IVUS Trial (Tsujita_2015)	ato (unknown dose)*+ eze10 mg ato (unknown dose)*	122/100 124/102	109.8 ± 25.4 108.3 ± 26.3	NA	NA	NA	−40 ± 18% −29 ± 24%	p < 0.001	For PAV, a significantly greater percentage of patients who received atorvastatin/ezetimibe showed coronary plaque regression (78% vs. 58%; p I' 0.004).
Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone. (Piorkowski_2007)	ato40 mg ato10 mg+ eze10 mg	28/25 28/26	135 139	NA	NA	NA	-28.9% -37.6%	p< 0.05,	Platelet activation markers (P-selectin) after stimulation (adenosine diphosphate) were reduced by 40 mg/day of atorvastatin, but not by ezetimibe plus low-dose atorvastatin.
Atorvastatin 10 mg plus ezetimibe 10mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. (Uemura_2012)	ato10 mg+eze10 mg** ato20 mg**	20/20 19/19	111.6±16.6 111.6±16.6	NA	82.9±20.5 98.4±22.7	NA	-25.7% -11.82%	p < 0.05	Add-on ezetimibe significantly decreased MDA-LDL (109.0±31.9 mg/dl to 87.7±29.4 mg/dl, p = 0.0009), while up-titration of atorvastatin did not.
Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function: randomized controlled trial. (Matsue_2013)	ato10 mg+eze10 mg ato20 mg	117/115 133/128	94.4±16.8 95.1±18.4	NA	69.6±15.6 85.9±18.2	NA	−25.8% −9.1%,	P<0.001	The percent decreases in TC and MDA-LDL were significantly greater in the A10E10 group than the A20 group
Hypolipidaemic and anti-inflammatory effects of fixed dose combination of atorvastatin plus ezetimibe in Indian patients with dyslipidaemia. (Padhy_2013)	ato10 mg+eze10 mg ato10 mg	15/14 15/14	145.3 ± 11.4 121.6 ± 5.4	NA	NA	NA	-44.2% -24.3%	p = 0.003	The combination treatment significantly reduced total cholesterol (percentage treatment difference −14.4 ± 6.5, 95% confidence interval [CI] −1.0 to −27.7; p=0.041)
Benefit and tolerability of the co-administration of ezetimibe and atorvastatin in acute coronary syndrome patients. (Hamdan_2011)	eze10 mg+ato10 mg ato20 mg+placebo	47/46 46/45	123.7 131.4	NA	69.6 81,2	NA	-43% -38.23%	p=0.6	There was a significant decrease in sCD40L levels in the ezetimibe combination group,
Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: results of the CEZAR study. (Ostad_2009)	ato10 mg+eze10 mg ato80 mg	29/25 29/24	151±31 148±31	67±27 59±21	NA	NA	-55% -60%	p <0.001	NMD of the brachial artery as a secondary endpoint significantly improved in the A80 group (+2.7±4.6%, post vs. pre p < 0.01) but not in the A10E10 group (+0.7±3.5%, post vs. pre p = 0.45) without significant difference between the A80 and A10E10 group.
Effectiveness of ezetimibe alone or in combination with twice a week Atorvastatin (10 mg) for statin intolerant high-risk patients.	ato10 mg+eze10 mg*** eze10 mg***	54/51 56/54	150 ±13	NA	NA 120 ±10	NA	-37% -20%	p<0.05	When patients (n= 34, 25 men) with baseline serum creatinine values in the upper 2 tertiles were analyzed separately, there

Study title	Treatment arm	Enrolled/ completed	LDL-C (mg/dl) baseline	LDL-C (mg/dl) at week 8	LDL-C (mg/dl) at week 12	LDL-C (mg/dl) at week 16	Mean LDL-c change (reduction) from baseline (%)	Statistical test/ P value	Secondary endpoints
(Athyros_2008)									was a significant (p=0.041) decrease in serum creatinine levels after 6 months of treatment.
Combination therapy analysis of ezetimibe and statins in Chinese patients with acute coronary syndrome and type 2 diabetes. (Li_2015)	statin**** statin+eze10 mg	40/40 44/44	104.4 143	NA	NA	NA	-29% -50%	P<0.001.	No significant difference on serum high-sensitivity C-reactive protein (hs-CRP) level between two groups was observed.
Comparison of the effects of combination atorvastatin (40 mg) + ezetimibe (10 mg) versus atorvastatin (40 mg) alone on secretory phospholipase A2 activity in patients with stable coronary artery disease or coronary artery disease equivalent. (Azar_2011)	eze10 mg+ato 40 mg ato40 mg+placebo	50/50 50/50	102 ± 29 99 ±21	77 ±10 86 ±14	NA	NA	-24.5% -13.1%	p <0.001	sPLA2 activity significantly decreased in the ezetimibe/ atorvastatin group from 29 U/ml (interquartile range 23 to 35) to 26 U/ml (23 to 29, p =0.001) but remained similar in the placebo/atorvastatin group (23 U/ml, 19 to 32, vs 22 U/ml, 19 to 28, p = NS)
The short term effect of atorvastatin plus ezetimibe therapy vs. atorvastatin monotherapy on clinical outcome in the acute coronary syndrome patients by gender. (Japaridze_2017)	ato20 mg+eze10 mg ato doubled dose	146/143 146/140	109.43 105.9	NA	NA	61.8 74	-43% -30%	p< 0.0001	There was no statistically significant difference between male and female survival rates in both treatment groups .
Comparative effects of cholesteryl ester transfer protein inhibition, statin or ezetimibe on lipid factors: The ACCENTUATE trial.	ato40 mg+evacetrapib 130 mg ato80 mg	123/86 62/44	(cohort): 83.0	NA	NA	no data	-33.4% -6.2%	p <0.001	While evacetrapib improved traditional atherogenic and putative protective lipid measures compared with ezetimibe

Study title	Treatment arm	Enrolled/ completed	LDL-C (mg/dl) baseline	LDL-C (mg/dl) at week 8	LDL-C (mg/dl) at week 12	LDL-C (mg/dl) at week 16	Mean LDL-c change (reduction) from baseline (%)	Statistical test/ P value	Secondary endpoints
(Nicholls_2017)	ato40 mg+eze10 mg ato40 mg+ placebo	127/91 54/40					-27.,3% +0.04%		and increasing statin dose in patients with ASCVD and/or diabetes, it also adversely affected novel atherogenic risk factors
Therapeutic effects of atorvastatin and ezetimibe compared with double-dose atorvastatin in very elderly patients with acute coronary syndrome (Liu_2017)	ato 10 mg+ eze 10 mg ato 20 mg	114/108 116/111	85 88.9	NA	54.14 58.0	NA	-43.6% -40.1%	p = 0.41	Levels of ALT, CRE, TG, HDL-C, LDL-C, CK, hsCRP.

* Atorvastatin was uptitrated with a treatment goal of low-density lipoprotein cholesterol (LDL-C) <70 mg/dl.
** after12 weeks the twogroups switched their therapy for another 12 weeks
*** eze 10 mg for 3 month, then eze10 mg+ato 10 mg for another 3 month
**** rosuvastain 10 mg/d, or atorvastatin 20 mg/d , or simvastatin 20 mg/d or pravastatin 20 mg/d

ato: ato, eze: ezetimibe, NA: non applicable. PAV percent atheroma volume; MDA_LDL: malondialdehyde-modified LDL; L_RHI: logarithmic-scale reactive hyperemia index, NMD: nitroglycerin-mediated endothelium-independent vasodilation; FMD: Flow-mediated vasodilation; sPLA2: secretory phospholipase A2;
ALT, alanine aminotransferase; CRE, creatinine; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CK, creatine kinase; hsCRP, high sensitive C-reactive protein.

Five out of 13 were randomised controlled trials. Five studies were double-blinded. Eight studies' primary endpoints included the level of LDL-cholesterol. All the studies are summarised below.

Padhy et al. (2013) conducted a double-blind 4-week study to assess the effect of fixed dose combination of ezetimibe 10 mg plus atorvastatin 10 mg compared with atorvastatin 10 mg monotherapy on lipid profile in 30 dyslipidaemia patients with or at high risk of coronary artery disease (CAD). The combination treatment significantly reduced LDL-C (percentage treatment difference −19.9 ± 6.1, 95% CI −7.4 to −32.4; p = 0.003) compared to atorvastatin monotherapy. Thirteen patients on combination treatment achieved the National

Cholesterol Education Program target for LDL-C as compared to 9 patients on atorvastatin monotherapy (p = 0.032).

Piorkowski et al. (2007) investigated the effect of a higher statin dosage compared with combined treatment with ezetimibe plus a low statin dose on LDL-C in 56 patients with CAD. After 4 weeks of treatment, coadministered atorvastatin 10 mg plus ezetimibe 10 mg decreased the baseline LDL-C level by -37,6%, compared to the -28,9% LDL-C level changes achieved by the atorvastatin 40 mg monotherapy (p< 0.05).

In a prospective randomised open-label cross-over 12-week study, the effect of combination therapy with 10 mg/day of atorvastatin plus 10 mg/day ezetimibe versus 20 mg/day of atorvastatin as monotherapy on serum lipids in 39 Japanese patients with CAD and type 2 diabetes or impaired glucose tolerance was evaluated (Uemura et al., 2012). Coadministered atorvastatin 10 mg plus ezetimibe 10 mg decreased mean LDL-C level to 82.9 ± 20.5mg/dl from mean baseline level of 111.6 ± 16.6 mg/dl (-25,7%) (p < 0.05) versus a reduction to 98.4 ± 22.7mg/dl from 111.6 ± 16.6mg/dl (-11,82%) achieved by atorvastatin 20 mg monotherapy (p < 0.05). LDL-C was significantly decreased by both treatments, but the percent reduction with add-on ezetimibe was significantly greater (p<0.05).
Matsue et al. (2013) conducted a prospective randomised controlled 12-week study to compare the effect on endothelial function of increasing statin dose to add-on ezetimibe in 243 patients with CAD and LDL-C > 70 mg/dL even after treatment with atorvastatin 10 mg. The mean percent changes in LDL-C for the 10 mg atorvastatin plus 10 mg ezetimibe group and the 20 mg atorvastatin group were -25.8% and -9.1, respectively (p<0.001).

The CEZAR study (Ostad et al., 2009) evaluated the effect of high versus low dose atorvastatin on endothelial dysfunction in patients with CAD in a setting of comparable cholesterol reduction. Fifty-eight patients with CAD were randomly assigned to double-blind treatment for 8 weeks with atorvastatin 80 mg per day (A80) or atorvastatin 10 mg plus ezetimibe 10 mg per day (A10E10), respectively. LDL-C were significantly reduced with no difference between A80 and A10E10 (-60% vs -55%, respectively).
In the 8-week study of Azar et al. (2011) conducted with 100 patients with stable CAD or CAD equivalent, coadministered atorvastatin 40 mg plus ezetimibe 10 mg decreased mean LDL-C level to 77 ± 10 mg/dl from mean baseline level of 102 ± 29 mg/dl (-24.5%) (p <0.001) versus a reduction to 86 ± 14 mg/dl from 99 ± 21 mg/dl (-13.1%) achieved by atorvastatin 40 mg plus placebo therapy (p <0.001).

The ACCENTUATE study (Nicholls et al., 2017) aimed to compare the effects of adding the cholesteryl ester transfer protein inhibitor evacetrapib, ezetimibe or increasing statin dose in atorvastatin-treated high-vascular risk patients on lipid parameters. 366 patients with atherosclerotic cardiovascular disease and/or diabetes were treated with atorvastatin 40 mg/day for 28 days prior to randomization to atorvastatin 40 mg plus evacetrapib 130 mg, atorvastatin 80 mg, atorvastatin 40 mg plus ezetimibe 10 mg or atorvastatin 40 mg plus placebo, daily for 90 days at 64 centres in the United States. Addition of ezetimibe 10 mg on top of atorvastatin 40 mg resulted in a significant reduction in LDL-C of -27% (p<0.001),

whereas doubling of the statin dose into 80 mg atorvastatin resulted in a -6% reduction in LDL-C (P<0.001).

The PRECISE-IVUS study (Tsujita et al., 2015) was a prospective, randomised, controlled, multicentre study in which the effects of ezetimibe plus atorvastatin versus atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent percutaneous coronary intervention were evaluated. The combination of atorvastatin/ezetimibe resulted in lower levels of LDL-C than atorvastatin monotherapy (63.2 ± 16.3 mg/dl vs. 73.3 ± 20.3 mg/dl; p<0.001). For the absolute change in percent atheroma volume, the mean difference between the 2 groups (–1.538%; 95% confidence interval [CI]:–3.079% to 0.003%) did not exceed the pre-defined non-inferiority margin of 3%, but the absolute change in percent atheroma volume did show superiority for the dual lipid-lowering strategy (–1.4%; 95% CI:–3.4% to–0.1% vs.–0.3%; 95% CI:–1.9% to 0.9% with atorvastatin alone; p=0.001).

The randomised double-blind study conducted by Hamdan et al. (2011) evaluated the effect of ezetimibe 10 mg plus atorvastatin 10 mg versus atorvastatin 20 mg plus placebo for 12 weeks on lipid profile, the CRPhs and the sCD40 ligands and levels in 93 acute coronary syndrome (ACS) patients. Coadministered atorvastatin 10 mg plus ezetimibe 10 mg decreased mean LDL-C level to 81.0 ±7.6 mg/dl from mean baseline level of 123.7 mg/dl (-43%) (p=0.6) versus a reduction to 81.2 mg/dl from 131.4 mg/dl (-24.3%) achieved by atorvastatin 20 mg plus placebo therapy (p=0.06).

In a Chinese study (Li et al., 2015) Chinese patients with ACS and type 2 diabetes mellitus (T2DM) were divided into the statins group (n= 40) and the combination group of ezetimibe and statins (n= 44) (statin group: rosuvastatin 10 mg/d n=28, or atorvastatin 20 mg/d n=8, or simvastatin 20 mg/d n=2, or pravastatin 20 mg/d n=1; combination group: the previous statins+10 mg ezetimibe, rosuvastatin n=25, atorvastatin n=15, simvastatin n=2 and pravastatin n=2). In order to evaluate the clinical effects on lipids-lowering, systemic inflammation response and clinical safety, the follow-up of all patients was carried out at day 7th and 30th after treatment. The level of low-density lipoprotein cholesterol (LDL-C) in combination group and statins group was 1.87 ± 0.42 (72.3 ± 16.2 mg/dl) and 2.18 ± 0.58 mmol/L (82.3 ± 22.4 mg/dl) at day 7th, 1.51 ± 0.29 (58.3 ± 11.2 mg/dl) and 1.94 ± 0.49 mmol/L (75.0 ± 18.9 mg/dl) at day 30th, respectively. The control rates of LDL-C level in the combination group and the statins group were 77% and 45% at day 30th, respectively.

A 16-week, single-centre, prospective, randomised, open-label clinical trial was conducted (Japaridze et al., 2017) to evaluate the effects of atorvastatin and ezetimibe combination in ACS patients on the incidence of composite endpoint in short-term follow-up and to assess differences according their gender. The trial involved 323 patients who had been hospitalised for an ACS within the preceding 14 days. They received atorvastatin 20 mg for 28 days, and after that 292 patients who had LDL-C levels ≥ 1.81 mmol/L (70 mg/dl) were randomised to ezetimibe (EZE) 10 mg/day coadministered with atorvastatin therapy (EZE + statin) or double their current atorvastatin dose. The Kaplan-Meier event-free survival rate at 16 weeks was 88.1% in the EZE + statin group patients and 77.0% in the atorvastatin

monotherapy group (absolute risk reduction: 11.1 percentage points; hazard ratio: 2.099; 95% confidence interval: 1.165-3.781; p = 0.014). The log rank test indicated that there was not a statistically significant difference between male and female survival rates in both treatment groups (p = 0.897). The LDL-C level decreased by 43% in the atorvastatin 20 mg + EZE 10 mg group, while the rate of decline in the statin-group was 30% (p<0.0001). The results of the study demonstrated that when added to statin therapy, EZE resulted in improved cardiovascular outcomes, and the response to atorvastatin and EZE combination was similar for both men and women.

The study of Liu et al. (2017) was a randomised study to compare the effect of atorvastatin 10 mg plus ezetimibe 10 mg with atorvastatin 20 mg on the long-term outcomes in 230 very elderly patients with ACS. At the end of one year, combination of atorvastatin 10 mg plus ezetimibe 10 mg decreased mean LDL-C level to 46.4 mg/dl from mean baseline level of 85 mg/dl (-43.6%) (p=0.15) versus a reduction to 34.76 mg/dl from the mean baseline 88.9 mg/dl (-40.1%) achieved by atorvastatin 20 mg therapy.

A study (Athyros et al., 2008) was undertaken to investigate the effect of ezetimibe (10 mg/day) alone or in combination with atorvastatin (10 mg twice a week) on hypercholesterolemia in 56 high-risk patients who were intolerant to 2 different statins. All patients were not at their LDL-C targets (100 mg/dl for high-risk patients and 70 mg/dl for very high-risk patients) and were treated for 3 months with ezetimibe (10 mg/day) monotherapy. Thereafter, all patients were treated with ezetimibe plus atorvastatin 10 mg twice a week for another 3 months. Ezetimibe monotherapy was well tolerated (2 withdrawals) and induced a mean reduction in LDL-C of 20% (p <0.05) at the third month. However, of the 54 patients still taking ezetimibe, only 5 (9%) were at their LDL cholesterol targets. Atorvastatin 10 mg twice a week was then added to ezetimibe and was well tolerated (3 withdrawals). This combination reduced LDL cholesterol (in a treatment-based analysis) by 37% compared with baseline (p <0.001), with 43 (84%) patients reaching their LDL cholesterol goals. To be noted, this study used an add-on scenario where the statin component was added to the ezetimibe monotherapy and not the usual add-on scenario, where ezetimibe is added-on to statin monotherapy. This scenario supports the FDC scientific requirement on the contribution of all active substances to the desired therapeutic effect from the ezetimibe side.

IV.5 Clinical safety

Safety profile monocomponents

Atorvastatin

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin versus 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo. Based on data from clinical studies and extensive post-marketing experience, Table 5 below presents the adverse reaction profile for atorvastatin from the SmPC of Lipitor.

Table 5 Adverse drug reactions to atorvastatin (SmPC Lipitor)

System Organ Class	ADR	Estimated frequency
Infections and infestations	Nasopharyngitis	Common
Blood and lymphatic disorders	Thrombocytopenia	Rare
Immune system disorder	Allergic reactions	Common

System Organ Class	ADR	Estimated frequency
	Anaphylactic reactions	Very rare
Metabolism and nutrition disorders	hyperglycaemia	Common
	Hypoglycaemia, weight gain, anorexia	Uncommon
Psychiatric disorders	Nightmare, insomnia	Uncommon
Nervous system disorder	Headache	Common
	Dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia	Uncommon
	Peripheral neuropathy	Rare
Eye disorders	Vision blurred	Uncommon
	Visual disturbance	Rare
Ear and labyrinth disorders	Tinnitus	Uncommon
	Hearing loss	Very rare
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, epistaxis	Common
Gastrointestinal disorders	Constipation, flatulence, dyspepsia, nausea, diarrhoea	Common
	Vomiting, abdominal pain upper and lower, eructation, pancreatitis	Uncommon
Hepatobiliary disorders	Hepatitis	Uncommon
	Cholestasis	Rare
	Hepatic failure	Very rare
Skin and subcutaneous tissue disorders	Urticaria, skin rash, pruritus, alopecia	Uncommon
	Angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Rare
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain	Common
	Neck pain, muscle fatigue	Uncommon
	Myopathy, myositis, rhabdomyolysis, tendonopathy (sometimes complicated by rupture)	Rare
	Immune-mediated necrotizing myopathy	Not known
Reproductive system and breast disorders	Gynecomastia	Very rare
General disorders and administration site conditions	Malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia	Uncommon
Investigations	Liver function test abnormal, blood creatine kinase increased	Common
	white blood cells urine positive	Uncommon

common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data)

Ezetimibe

In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2396 patients, with a statin in 11,308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between Ezetrol (reference product ezetimibe) and placebo.

The following adverse reactions were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159) or in patients treated with Ezetrol coadministered with a statin (N=11308) and at a greater incidence than statin administered

alone (N=9361). Post-marketing adverse reactions were derived from reports containing ezetimibe either administered alone or with a statin from the SmPC of Ezetrol (Table 6).

Table 6 Adverse drug reactions to ezetimibe (SmPC Ezetrol)

System Organ Class	ADR	Estimated frequency
EZETIMIBE MONOTHERAPY		
Investigations	ALT and/or AST increased, blood CPK increased, gamma-glutamyltransferase increased, liver function test abnormal	Uncommon
Respiratory, thoracic and mediastinal Disorders	Cough	Uncommon
Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence	Common
	Dyspepsia, gastrooesophageal reflux disease, nausea	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia; muscle spasms; neck pain	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Uncommon
Vascular disorders	Hot flush, hypertension	Uncommon
General disorders and administration site conditions	Fatigue	Common
	Chest pain, pain	Uncommon
ADDITIONAL ADRS WITH EZETIMIBE CO-ADMINISTERED WITH A STATIN		
Investigations	ALT and/or AST increased	Common
Nervous system disorders	Headache	Common
	Paraesthesia	Uncommon
Gastrointestinal disorders	Dry mouth, gastritis	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, rash, urticaria	Uncommon
Musculoskeletaal and connective tissue disorders	Myalgia	Common
	Back pain, muscular weakness, pain in extremity	Uncommon
General disorders and administration site conditions	Asthenia, oedema peripheral	Uncommon
POST-MARKETING EXPERIENCE (WITH OR WITHOUT STATIN)		
Blood and lymphatic system disorders	Thrombocytopaenia	Not known
Nervous system disorders	Dizziness, paraesthesia	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Not known
Gastrointestinal disorders	Pancreatitis, constipation	Not known
Skin and subcutaneous tissue disorders	Erythema multiforme	Not known
Musculoskeletal and connective tissue disorder	Myalgia, myopathy/rhabdomyolysis	Not known
General disorders and administration site conditions	Asthenia	Not known
Immune system disorder	Hypersensitivity, including rash, urticarial, anaphylaxis and angioedema	Not known
Hepatobiliary disorders	Hepatitis, cholelithiasis, cholecystitis	Not known
Psychiatric disorders	Depression	Not known

common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data)

Safety evaluation of the efficacy studies

Ten out of the thirteen efficacy studies, two pharmacokinetic interaction studies published in the literature, as well as the bioequivalence study served for safety evaluation. Available data arise at very different extent from a relatively small number of studies different in

population characteristics, dose and duration of drug administration and safety evaluation methods. Thus, safety data are not pooled, but presented by the individual studies.

Safety evaluation bioequivalence study

A total of 48 subjects entered the study and received at least one of the two treatments:

- Treatment-1: Test product administered alone (Atorvastatin/Ezetimibe 40 mg/10 mg capsule manufactured by DOC)
- Treatment-2: Reference-1 Sortis 40 mg film-coated tablet and Reference-2 Ezetrol 10 mg tablet taken concomitantly

A total of 27 treatment-emergent adverse events (TEAEs) were reported by 14 of the 48 subjects (29%) who participated in this study. Of these TEAEs 11 occurred after administration of Treatment-1 and 16 occurred after administration of Treatment-2. Approximately half of the TEAEs experienced during the study were considered not drug-related (52%) and all were resolved by the end of the study.

The TEAE experienced most commonly in this study was headache, reported by 5 subjects (10%) per treatment group. Oropharyngeal pain was reported by 2 subjects (4%) after administration of only Treatment-2. Other TEAEs experienced less frequently included epistaxis, rhinorrhoea and procedural dizziness, each experienced by 1 subject (2%) per treatment group. Sneezing, diarrhoea, and chills were each experienced by 1 subject (2%) following administration of only Treatment-1, whereas cough, nasal congestion, upper abdominal pain, nausea, procedural complication, and insomnia were each experienced by 1 subject (2%) following administration of only Treatment-2.

The incidence of TEAEs was similar in subjects dosed with Treatment-1 (19%) and Treatment-2 (23%). Drug-related TEAEs were also reported with a similar incidence in subjects dosed with Treatment-1 (10%) and Treatment-2 (15%).

The TEAEs experienced during the study were deemed mild (24/27, 89%), moderate (2/27, 7%), and severe (1/27, 4%) in intensity. One severe adverse event (AE), namely insomnia, was experienced following administration of Treatment-2 in period 1. The AE was considered related to drug administration and was resolved at the end of the study.

Safety evaluation published studies

In the pharmacokinetic non-interaction study of Patiño-Rodríguez (2014) AEs were evaluated based on subject interviews and physical examinations; but the detailed results were not published by the investigators.

In the pharmacokinetic drug interaction study of Park (2017) safety was evaluated by monitoring AEs, vital signs, physical examination, clinical laboratory tests (haematology, blood chemistry, urinalysis), and 12-lead electrocardiogram throughout the study. In the study, 33 AEs were reported in 19 subjects. All cases were mild (30 events) or moderate (three events) and subjects recovered without complications. Commonly reported AEs were nasopharyngitis (four events) and epistaxis (four events). After causality assessment, 13 AE cases (seven subjects), including four in group A, three in group B, and six in group C, were considered as adverse drug reactions. No clinically significant differences were observed

among the treatment groups in terms of vital signs, physical examination, 12-lead electrocardiograms, and clinical laboratory test results.
In the randomised, controlled PRECISE-IVUS Trial safety was monitored throughout the study and evaluated by periodic medical examination and laboratory tests at 3, 6, and 9 to 12 months after enrolment. The most common AEs were cardiovascular adverse events (nonfatal MI, stroke, coronary revascularisation), 24 patients (20%) in both treatment groups. The most common AEs were cardiovascular AEs (nonfatal MI, stroke, coronary revascularisation), 24 patients (20%) in both treatment groups.
In the randomised trial of Uemura (2012) subjects attended the hospital monthly for assessment of their general condition, adherence to treatment, and AEs. The only reported AE was abdominal discomfort without any evidence of liver dysfunction or diarrhoea.
In the randomised controlled trial of Padhy (2013) all the patients were monitored for the development of AEs during the study. The FDC of atorvastatin plus ezetimibe in this study was well-tolerated, with a safety profile comparable to that of atorvastatin monotherapy. Mild dyspepsia was the only AE encountered in this study. There were no clinically significant alterations in aspartate aminotransferase, alanine aminotransferase (ALT), urea and creatinine levels in both patient groups.
In the randomised trial of Hamdan (2011) safety was evaluated through regular monthly phone calls to the patient, the patient's doctor observations, vital signs, physical examinations, and laboratory tests at one and three months. Study treatment was discontinued early in 2 patients (4.3%) in group A (eze 10 mg + ato 10 mg) for side effects, mainly myalgia, versus 10 patients (22.2%) in group B (ato 20 mg + placebo) with a statistically significant difference (p = 0.012). Other side effects including increasing CPK (p = 0.7), ALAT (p = 0.8) and ASAT (p = 0.5) were not significant between the two groups.
In the randomised CEZAR study (2009) the study course consisted of three visits. Blood and urine samples were collected for biochemical analysis. Gastrointestinal complaints were the main AEs in this study. One patient from the A10E10 group died from myocardial infarction 1 day after study enrolment. Two patients of the A10E10 group and five patients of the A80 group discontinued the study due to adverse side effects of the study drug. Of these, six patients discontinued due to gastrointestinal complaints, one patient of the A80 group due to insomnia.
In the study of Athyros (2008) lipid profiles, biochemical parameters, and adverse effects were monitored every month throughout the study. 1 case of myalgia and 2 cases of elevated liver enzymes were reported in the study.
In the study of Li (2015) safety evaluation was based on patient report, investigator observation and laboratory test during the follow-up. AEs were not observed in this study.
In the randomised trial of Japaridze (2017) with ACS patients, at week 16 (visit 4, the end of study), patients underwent a brief exam, review of AEs, liver panel, CPK, and fasting lipid profile. Thirteen patients had no detailed AEs in this study. Six patients had myocardial infarction and seven had unstable angina during the study. Thirteen deaths were reported during this study.
In the ACCENUATE trial (2017) lipoprotein levels and safety laboratory measurements were obtained at all visits. Discontinuation due to AEs was 2.4% in the atorvastatin 40 mg + ezetimibe 10 mg subgroup. AEs have not been detailed in the report of the study.

In the randomised study of Liu (2017) patients' blood samples were collected in hospital to measure creatine kinase myocardial band, troponin-I, creatine, ALT, aspartate aminotransferase, creatinine, low-density lipoprotein cholesterol, high sensitive C-reactive protein levels; further measurements were asked to perform at 3, 6, 12 months after discharge. Patients were followed up with telephone calls at the end of one year. There were 3 patients in combined therapy group and 10 patients in double-dose atorvastatin group whose ALT more than upper normal limit (2.8% vs. 9.0%, p = 0.05), 1 patient in combined therapy group and 3 patients in double-dose atorvastatin group whose ALT more than 3-fold (0.93% vs. 2.7%, p = 0.33). There was no patient whose ALT was more than 5-fold upper normal limit. After descending transaminase treatment, they all recovered and continue previous therapy. There were no confirmed adverse drug reactions to muscle in both groups. There was one new cancer case in each group. The number of patients with new-onset diabetes was 3 in combined therapy group and 5 in double-dose atorvastatin group (2.8% vs. 4.5%, p = 0.50). The primary endpoints of this study were the major adverse coronary events.

Conclusion clinical safety

Ten out of the 13 efficacy studies, two pharmacokinetic interaction studies, as well as the bioequivalence study have been presented separately for safety evaluation. Further, the MAH provided the safety profile of the individual components based on data available from the SmPCs of each monocomponent. This is acceptable as for both single components the safety profile is well known.

The overall safety data on the combination of atorvastatin and ezetimibe do not raise any concern and can be considered in line with the known safety profile of the monocomponents. Moreover, safety data on the combined use of statins, including atorvastatin, with ezetimibe has already been assessed during the registration of Ezetrol which is indicated to be coadministered with a statin.

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 Ezetimibe/Atorvastatine DOC.

Summary table of safety concerns as approved in RMP

Important identified risks	• Muscle injury (rhabdomyolysis/myopathy) • Abnormal liver function
Important potential risks	None
Missing information	• Use in children less than 18 years of age • Use in patients with moderate or severe hepatic insufficiency

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 combined use of atorvastatin and ezetimibe is well established. The literature data submitted by the MAH support the use of the combination. The bioequivalence study shows satisfactory results: a single tablet of the Ezetimibe/Atorvastatine DOC FDC can be used instead of coadministration of the separate products. Risk management is adequately addressed.

V. USER CONSULTATION

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezetimibe/Atorvastatine DOC 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg hard capsules have a proven chemical-pharmaceutical quality and is considered an approvable FDC. Both atorvastatin and ezetimibe are well known, established substances, which are used as a combination in clinical practice.

It is adequately shown that there is no pharmacokinetic interaction between the individual compounds of this FDC product. The proposed combination product was demonstrated to be bioequivalent with coadministration of the separate reference products Lipitor and Ezetrol. The clinical data on concomitant use are considered sufficient to support the FDC for the so-called substitution indication in patients with primary hypercholesterolemia already controlled with atorvastatin and ezetimibe given concurrently at the same dose level.

There was no discussion in the CMDh. Agreement between member states was reached during a written procedure. The RMS and concerned member states considered, on the basis of the data submitted, that the benefit-risk balance for this FDC is positive. The decentralised procedure was finalised with a positive outcome on 11 March 2020.

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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/4991/1-3/II/001	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	No	21-08-2020	Approved	-
NL/H/4991/IA/002/G	Change in test procedure for the finished product; minor changes to an approved test procedure.	No	29-07-2020	Approved	-