COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezevast 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg tablets

(atorvastatin calcium trihydrate/ezetimibe)

NL/H/4864/001-004/DC

Date: 12 August 2020

This module reflects the scientific discussion for the approval of Ezevast. The procedure was finalised at 23 June 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

ADR	Adverse Drug Reaction
AE	Adverse Event
ASMF	Active Substance Master File
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
ICH	International Conference of Harmonisation
LDL-C	Low-Density Lipoprotein Cholesterol
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MI	Myocardial Infarction
NPC1L1	Niemann Pick C1-Like 1
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TC	Total Cholesterol
TG	Triglycerides
TSE	Transmissible Spongiform Encephalopathy
ULN	Upper Limit of Normal
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 Ezevast 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg tablets from Fidia Farmaceutici S.p.A.

Ezevast as an adjunct to diet is indicated as substitution therapy for treatment of adults with primary (heterozygous and homozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia already controlled with atorvastatin and ezetimibe given concurrently at the same dose level.

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 Ezevast, 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. The Lipitor 80 mg strength (NL License RVG 27148) has been registered in the Netherlands (MAH: Pfizer B.V.) since 4 June 2002 through MRP DE/H/0109/004.
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.

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

Scientific advice

Scientific advice was requested at the Medicines Evaluation Board (MEB), and received on 17 March 2015, regarding the possibility to apply for a marketing authorisation in accordance

with Article 10b of Directive 2001/83/EC despite the approval of Atozet. The MEB agreed that another application based on article 10b is possible but that no reference can be made to the own (pre) clinical data included in the dossier of Atozet (still under data exclusivity). The proposed data package and more specifically proposed proof of bioequivalence is considered adequate clinical data in respect to the legal basis of Article 10b of Directive 2001/83/EC as proposed and in line with the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017).

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

Ezevast is a white to off white, capsule shaped tablet:

- The 10 mg/10 mg tablet is debossed with "1" on one side
- The 10 mg/20 mg tablet is debossed with "2" on one side
- The 10 mg/40 mg tablet is debossed with "3" on one side
- The 10 mg/80 mg tablet is debossed with "4" on one side

Each tablet contains as active substance 10 mg ezetimibe and contains as active substance 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin, as 10.85 mg, 21.70 mg, 43.40 mg or 86.80 mg of atorvastatin calcium trihydrate.

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

The excipients are lactose monohydrate, calcium carbonate, microcrystalline cellulose, sodium lauryl sulfate (E487), croscarmelose sodium, povidone K30, hydroxypropylcellulose, magnesium stearate, and polysorbate 80.

II.2 Drug Substances

Ezetimibe

The active substance is ezetimibe, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to almost white crystalline powder. Ezetimibe is freely soluble in ethanol and methanol, soluble in acetonitrile, practically insoluble in water and aqueous solutions with pH value range from 1.0 to 11.0. Ezetimibe is crystal or amorphous. The crystals show polymorphism. The product obtained in the synthesis is crystal. The substance is hygroscopic.

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.

<u>Manufacturing process</u>

The manufacturing process consists of five stages: four synthetic steps and one crystallization step. Crude ezetimibe is recrystallized. Starting materials are sufficiently characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The proposed specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the drug substance is provided for three commercial scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). No significant changes were observed. Based on the provided stability data, the claimed re-test period of two years and storage conditions "Preserve in tight container, protected from light" are justified.

Atorvastatin calcium trihydrate
The active substance is atorvastatin calcium trihydrate, 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. Atorvastatin is supplied as atorvastatin calcium trihydrate "Form I" by the drug substance manufacturer.

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 an additional test for residual solvents. Furthermore, the MAH included an additional test and limit for particle size distribution. The proposed specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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. A quality target product profile (QTPP) and critical quality attributes (CQA) have been defined. The development was based on risk assessments performed in accordance with ICH Q8 (R2) guidance. An extensive and satisfactory description of the risk assessment performed at various development stages has been provided.

A pivotal bioequivalence study with uncoated tablets has been performed in which the 80 mg/10 mg strength was compared with Sortis 80 mg and Ezetrol 10 mg. With respect to *in vitro* dissolution tests complementary to bioequivalence studies satisfactory data and discussion have been provided. The development of the dissolution method was sufficiently addressed. The initial dissolution test procedure is based on the Food and Drug Administration (FDA) recommended method for atorvastatin calcium/ezetimibe tablets. Since the proposed test method was not able to discriminate between the proven non-bioequivalent (with respect to atorvastatin) batch and the bioequivalent batches, the MAH developed a supplementary dissolution method for atorvastatin. This supplementary method is discriminatory towards the biobatch. Both dissolution methods are applied for the drug product (at release and at shelf life).
The MAH also performed dissolution studies to support a biowaiver for the additional strengths: 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg. Based on the provided data the biowaiver of strengths is accepted.

Manufacturing process

The manufacturing process has been classified as a standard process. The wet granulation method for both active substances separately is applied. At the end tabletting of bilayer tablets is performed. The manufacturing process has been described in sufficient detail. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per product strength in accordance with the relevant European guidelines.

Control of excipients

All excipients are of the Ph.Eur. quality. 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, identification, assay, uniformity of dosage units, dissolution (tested with two methods), related substances, average weight, disintegration time, resistance to crushing, friability and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

An elemental impurity risk assessment in accordance with the Guideline ICH Q3D has been performed. It is concluded, that the total elemental impurity levels from all sources in the drug product are expected to be consistently less than 30% of the permitted daily exposure (PDE). Hence, no additional controls are required.

Stability of drug product

Stability studies were conducted on three batches of the 10 mg/10 mg and 80 mg/10 mg strength of the proposed product. The explained bracketing approach is considered acceptable. The conditions used in the stability studies are according to the ICH stability guideline. The control tests for the drug product are adequately drawn up. Submitted long term (25°C/60% RH) and accelerated stability data (40°C/75% RH) remain within the proposed specification. Based on the available stability a shelf life was granted of 24 months.

Based on the provided photostability study data and information on sensitivity of the drug product to moisture, protection from light is necessary while protection from moisture is not. The storage conditions with respect to those aspects are “Store in the original package to protect from light”.

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 Ezevast has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitment was made:

- The MAH is kindly asked to update the SmPC when information for the specific combination of atorvastatin and ezetimibe becomes available, since this is considered more relevant than the combination with statins in general as currently included in the SmPC.

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

The combination atorvastatin/ezetimibe inhibits both the absorption of dietary cholesterol (ezetimibe) and the synthesis of cholesterol in the liver (atorvastatin). Animal studies indicate therapeutic effects including lowering of cholesterol and (cardio)vascular protection.
In addition, a beneficial effect of atorvastatin/ezetimibe combination therapy has been observed in non-alcoholic steatohepatitis. Atorvastatin has a beneficial effect on oxidative stress in rats fed with high-cholesterol diet. A combination of ezetimibe with atorvastatin diminishes the beneficial effects of atorvastatin on oxidative stress.
Brain haemorrhage and optic nerve vacuolation were seen in some dogs at doses >120 mg/kg/day atorvastatin. Platelet deposition rate was reduced in atherosclerotic rabbits given atorvastatin.

III.3 Pharmacokinetics

Atorvastatin
For atorvastatin, the highest percentage of dose absorbed in rats after injection of a radiolabelled compound (1 mg/kg) into ligated loops of the gastrointestinal tract was obtained 2h post-injection into the duodenum followed by the jejunum, stomach, ileum, cecum and colon. Atorvastatin is mainly metabolized by oxidation in rats and dogs. Statin metabolism depends on the animal species studied, particularly the β-oxidation of the dihydroxy heptanoic side chain that occurs *in vivo* either exclusively or primarily in rodents. When atorvastatin was orally administered to rats and mice most of the radioactivity was excreted in the faeces, compared with urine (98.5% vs. 2.0% in rats and 98.4% vs. 1.5% in mice). All data taken together suggest that statins undergo enterohepatic circulation, which is probably the reason for their maintained presence in the target organ. The contribution of enterohepatic circulation to high biliary recovery of statins has been investigated mainly in rats after intraduodenal administration of bile collected from donor rats receiving the statin. For atorvastatin, the percentage of radioactivity reabsorbed was 42%. For atorvastatin, peak radioactivity levels in milk were close to or lower than those in plasma.

Ezetimibe
Following oral administration, ezetimibe was rapidly absorbed, extensively conjugated to its glucuronide, and exhibited multiple plasma peaks suggestive of enterohepatic recycling. The glucuronide is a more potent inhibitor of cholesterol absorption than the parent compound.

Ezetimibe metabolism was similar across different species (rat, dog, and human). Ezetimibe was excreted primarily in the faeces.

III.4 Toxicology

The safety profile of the individual active ingredients ezetimibe and atorvastatin is well understood. Pre-clinical data indicate acceptable risk for humans based on conventional studies of acute-dose toxicity, repeat-dose toxicity, genotoxicity and carcinogenic potential. However, there is evidence from animal experimental studies that HMG-CoA reductase inhibitors like atorvastatin may affect the development of embryos or foetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic. However, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer.
Co-administration studies with ezetimibe and statins resulted in toxic effects typically associated with statins, although some of the toxic effects were more pronounced than observed during treatment with statins alone (probably due to pharmacokinetic and pharmacodynamic interactions in co-administration therapy).
Furthermore a combination product currently marketed contains ezetimibe and a statin (simvastatin). Based on the safety profile of the individual active ingredients and the similarities between atorvastatin and simvastatin a waiver for conducting non-clinical combination studies is applied for.
From the information available of both atorvastatin and simvastatin it can be assumed that when replacing simvastatin with atorvastatin and taking into consideration different dosing regimens for these compounds this will not result in large differences in safety and efficacy between these combination therapies.
Based on the available data of the individual compounds and data from a comparable combination product there are no causes for significant toxicological concern for Ezevast.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Ezevast 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

For Ezevast, 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 one pivotal bioequivalence study with the 10 mg/80 mg tablets. For the three other strengths (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 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

The objective of the pivotal bioequivalence study was to demonstrate the bioequivalence of atorvastatin and ezetimibe administered as single dose concomitantly (Sortis 80 mg (Pfizer Pharma GmbH, Germany); Ezetrol 10 mg tablets (Merck Sharp & Dohme Limited, United Kingdom)) with the atorvastatin/ezetimibe FDC.

The MAH sufficiently described the potential for (absence of) interaction of the active substances using available information from literature.

In total three bioavailability studies were conducted during the pharmaceutical development. The first study was an open, randomized, three-way, three period, three sequences pilot study (EZAT-MOL-T0216/1231) which was conducted to evaluate if one of the two proposed two-layer tablet formulations was suitable for further development. After upscaling of the elected formulation to a commercial batch size, samples of one of the validation batches were tested against the two reference products in a pivotal, open, randomized, three period, two sequences, full replicative design bioequivalence study (EZAT-MIDA-T1116/1299). Although the same reference batches as in the pilot study were used this pivotal study failed to demonstrate bioequivalence due to lower peak plasma levels of atorvastatin. A root cause analysis demonstrated that the process of filming the tablets in a commercial scale had a negative impact on the *in vivo* dissolution of the atorvastatin layer. Since filming of the new FDC tablet formulation of atorvastatin and ezetimibe is not essential it was decided to resign from this process. Consequently another pivotal bioequivalence study was needed in order to demonstrate that the un-filmed tablet formulation is equivalent to the reference products. This study is considered pivotal and is described in the following.

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

The biowaiver of strengths can be granted. The proposed product is a bilayer tablet consisting of an atorvastatin and ezetimibe layer. All tablets are dose proportional with regard to the atorvastatin layer and have an identical ezetimibe layer. The tablets are manufactured by the same manufacturer and process. Atorvastatin exposure increases dose proportional and the highest atorvastatin dose is used in the bioequivalence study.
The provided dissolution data support the claimed biowaiver of strengths as similarity has been demonstrated. Initially similarity was not demonstrated at pH 6.8, as f2 could not be calculated due to high RSD values. As a possible solution it was noted that the RSD values were too high for all the strengths (at pH 6.8). The MAH repeated the dissolution experiment with additional 12 tablets per batch and provided results of the similarity analysis of the pooled data. Due to high RSD values, the f2 confidence interval was calculated using a bootstrap method. The lower 90% percentile is 61.87 and above 50. Similarity of dissolution profiles can be concluded and a biowaiver of strengths accepted. Of note, the re-analysis dissolution profiles would have resulted in the same conclusion without pooling.

Bioequivalence study

Design

A monocentric, open, randomized, single-dose, two treatments, two periods, two sequences crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-49 years. Each subject received a single dose (80 mg atorvastatin and 10 mg ezetimibe) of one of the two formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 16, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The sampling time duration of 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. For atorvastatin the data from the parent compound have been used to evaluate the bioequivalence between the test and reference product which is acceptable.

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 three subjects withdrew for personal reasons after study drug administration in study period I, but before study drug administration in study period II. Therefore 57 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=57	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	58.0 ± 24.4	5.4 ± 2.9	1.0 (0.5 - 5.0)
Reference	59.5 ± 22.8	5.9 ± 3.1	1.0 (0.5 - 6.0)
***Ratio (90% CI)**	0.96 (0.91 - 1.02)	0.90 (0.82 – 0.98)	--
CV (%)	18.28	28.7	--

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

**ln-transformed values*

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

Treatment N=57	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	441.1 ± 198.5	49.9 ± 16.6	0.8 (0.5-5.0)
Reference	449.2 ± 179.2	55.7 ± 21.3	0.8 (0.5-5.0)
***Ratio (90% CI)**	0.98 (0.92 – 1.04)	0.91 (0.86 – 0.96)	--
CV (%)	20.22	17.55	--

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

**ln-transformed values*

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

Treatment N=57	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	217 ± 117	49 ± 26	0.8 (0.5 - 12)	15.1 ± 3.3

Reference	220 ± 131	48 ± 30	0.8 (0.5 - 3.5)	15.8 ± 3.1
***Ratio (90% CI)**	1.00 (0.96 - 1.05)	1.07 (0.95 – 1.20)	--	--
CV (%)	15.4	37.2	--	--

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ezevast 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).

Interaction

The MAH showed sufficiently that there is no significant interaction for ezetimibe and atorvastatin. According to the guideline on clinical development of fixed combination medicinal products (EMA/CHMP/58268/2017) a new FDC is therapeutically equivalent with the respective single drug products in free combination if it contains the same active substances or therapeutic moieties and, clinically, shows the same efficacy and safety as that products, whose efficacy and safety have been established. In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence. Since equivalence in biopharmaceutics quality between the FDC applied for and Sortis and Ezetrol was demonstrated in a respective bioequivalence study bridging of non-clinical and clinical trials associated with the respective reference medicinal products is allowed.

No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin. In this respect it needs to be pointed out that ezetimibe is indicated to be co-administered with a statin (Ezetrol SmPC).

Furthermore the MAH provided a respective reference to a randomized, three-period, six-sequences cross over study conducted by Patiño-Rodríguez et al. who investigated the influence of ezetimibe on atorvastatin and conversely. Area under the concentration-time curve (AUC) and maximum plasma drug concentration (C_{max}) were measured for each drug alone or together and tested for bioequivalence-based hypothesis. The estimation computed (90% confidence intervals) for AUC and C_{max}, were 96.04% (85.88–107.42%) and 97.04% (82.36–114.35%), respectively for atorvastatin – ezetimibe combination versus atorvastatin alone, while 84.42% (77.19–92.32%) and 95.60% (82.43–110.88%), respectively, for

atorvastatin – ezetimibe combination versus ezetimibe alone were estimated. These results also show that atorvastatin and ezetimibe have no relevant pharmacokinetic drug–drug interaction.

IV.3 Pharmacodynamics

Ezetimibe

Ezetimibe is a potent and selective inhibitor of intestinal cholesterol and phytosterol absorption that does not require exocrine pancreatic function for its activity and does not alter the absorption of fat-soluble vitamins and nutrients [Kosoglou et al., 2005]. Ezetimibe binds to the Niemann Pick C1-Like 1 (NPC1L1) protein in the brush border of the intestine, which is thought to be involved in cholesterol absorption. Ezetimibe has been shown to inhibit >50-55% of cholesterol absorption in patients with mild to moderate hypercholesterolaemia [Backes et al., 2005].

Atorvastatin

Atorvastatin as other statins such as simvastatin is a lipid regulating drug. It is a competitive inhibitor of HMG-CoA reductase, the rate-determining enzyme for cholesterol synthesis. Inhibition of HMG-CoA reductase leads to reduced cholesterol synthesis in the liver and lower intracellular cholesterol concentrations. This stimulates an increase in LDL-C receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Atorvastatin reduces TC, LDL-C and very-low-density lipoprotein cholesterol (VLDL-C) concentrations in plasma. As other statins it tends to reduce triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) [Martindale, 2014].

IV.4 Clinical efficacy

In various clinical trials add-on ezetimibe was significantly more effective in reducing LDL-C levels than atorvastatin monotherapy, enabling more patients to achieve LDL-C goals. This is illustrated in the following table.

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

Reference	Design	Patients	Treatment	Results
Gagné et al 2002 [29]	randomized, double-blind, parallel-group study	50 patients ≥12 years old with a diagnosis of HoFH on the National Cholesterol Education Program Step 1 or stricter diet and taking open-label atorvastatin 40 mg/d or simvastatin 40 mg/d (statin-40) with (n=25) or without (n=25) concomitant LDL apheresis	Atorvastatin or simvastatin 80 mg/d (statin-80, n=17); ezetimibe 10 mg/d plus atorvastatin or simvastatin 40 mg/d (n=16); or ezetimibe 10 mg/d plus atorvastatin or simvastatin 80 mg/d (n=17) for 12 weeks	• Ezetimibe plus statin-40/80 significantly reduced LDL-C levels compared with statin-80 (-20.7% versus -6.7%, P=0.007). • In the high-dose statin cohorts, ezetimibe plus statin-80 reduced LDL-C by an additional 20.5% (P=0.0001) versus statin-80. • Similar significant reductions in LDL-C concentrations were observed for patients with genotype-confirmed HoFH (n=35).
Ballantyne et al 2003 [30]	Randomized, double-blind, placebo-controlled, balanced–parallel group	628 patients with baseline LDL-C 145 to 250 mg/dL and triglycerides ≤350 mg/dL	Ezetimibe (10 mg/d); atorvastatin (10, 20, 40, or 80 mg/d); ezetimibe (10 mg) plus atorvastatin (10, 20, 40, or 80 mg/d); or placebo	• Ezetimibe plus atorvastatin significantly improved LDL-C, HDL-C, TG, TC:HDL-C, and hs-CRP compared with atorvastatin alone (P<0.01). • Coadministration of ezetimibe provided a significant additional 12% LDL-C reduction, 3% HDL-C increase, 8% TG reduction, and 10% hs-CRP reduction versus atorvastatin alone. • Ezetimibe plus atorvastatin provided LDL-C reductions of 50% to 60%, triglyceride reductions of 30% to 40%, and HDL-C increases of 5% to 9%, depending on atorvastatin dose. LDL-C reductions with ezetimibe plus 10 mg atorvastatin (50%) and 80 mg atorvastatin alone (51%) were similar
Stein et al 2004 [31]	Multicenter, randomized, double-blind	621 adults HeFH, coronary heart disease, or multiple ≥2) cardiovascular risk factors, and a LDL-C level ≥130 mg/dL after a 6- to 10-week dietary stabilization and atorvastatin (10 mg/day) open-label run-in period	Atorvastatin 10 mg + ezetimibe 10 mg or atorvastatin 20 mg; atorvastatin dose in both groups was doubled after 4 weeks, 9 weeks, or both when the LDL-C level was not at its goal ≤100 mg/dL) to a maximum of 40 mg in the combination group and 80 mg in the monotherapy group	• The proportion of subjects reaching their target LDL-C level goal of < or =100 mg/dL was significantly higher in the combination group than in the atorvastatin monotherapy group (22% vs 7%; P<0.01). • At 4 weeks, levels of LDL-C, triglycerides, and non-high-density lipoprotein cholesterol were reduced significantly more by combination therapy than by doubling the dose of atorvastatin (LDL-C -22.8% versus -8.6%; P<0.01).
Cruz-Fernández et al 2005 [32]	Randomised, double-blind, placebo-controlled	450 hypercholesterolaemic patients with coronary heart disease who had not achieved their LDL-C goal ≤2.60 mmol/L while on a stable dose of atorvastatin 10 or 20 mg/day for ≥6 weeks	Atorvastatin + ezetimibe or atorvastatin + placebo	• Significantly more patients achieved an LDL-C goal ≤2.6 mmol/L with ezetimibe than placebo (81.3 vs. 21.8%; p < or = 0.001). • Compared to placebo, co-administration of ezetimibe with ongoing atorvastatin led to significantly (P≤0.001) greater reductions in LDL-C, TC, TG, non-HDL-C, and apolipoprotein B; HDL-C was significantly (P≤0.05) increased.
Blagden & Chipperfield 2007 [33]	Multicentre, double-blind, placebo-controlled	148 patients with primary hypercholesterolaemia and coronary heart disease	Atorvastatin 10 mg + ezetimibe 10 mg or atorvastatin 10 mg + placebo for 6 weeks	• At 6 weeks, atorvastatin + ezetimibe provided a significantly greater adjusted mean change from baseline in LDL-C compared with atorvastatin monotherapy (-50.5% vs. -36.5%; p < 0.0001), equating to an additional 14.1% reduction (95% CI -17.90, -10.19) in LDL-C. • Patients receiving the combiantion were 12 times more likely to reach LDL-C targets (odds ratio 12.1; 95% CI 5.8, 25.1; P<0.0001) compared with patients receiving atorvastatin monotherapy.
Matsue et al 2013 [34]	Monocenter, randomized	250 patients with coronary artery disease and LDL-C≥70 mg/dL after treatment with atorvastatin 10 mg	Atorvastatin 10 mg+ezetimibe 10 mg (A10E10; n=117) or atorvastatin 20 mg (A20; n=133) for 12 weeks	• After treatment, high-sensitivity C-reactive protein (hs-CRP) and all lipids except triglyceride and high-density lipoprotein cholesterol were significantly reduced in both groups. • The mean percent changes in LDL-C for the A10E10 and A20 groups were -25.8% and -9.1%, respectively (P<0.001). • Absolute change in endothelial function measured by logarithmic-scale reactive hyperemia index (L_RHI) was significantly higher in the A20 than A10E10 group (0.02±0.29 vs. 0.16±0.27, P<0.001).
Foody et al 2013 [35]	Retrospective, observational study	17,830 adult patients, identified between Nov-2002 and Sep-2009 in a large US managed-care database	Initially on statin monotherapy (≥42 days), no concomitant use of other lipid-lowering therapy	• 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 multivariable models, percent 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. • The odds of attaining LDL-C<1.8 and <2.6 mmol/L (70 and 100 mg/dL) increased by 2.6-3.2-fold and 2.5-3.1-fold, respectively, in patients who added ezetimibe onto simvastatin, atorvastatin, or rosuvastatin versus titrating statins.
Luo et al 2014 [36]	Monocenter, randomized, open-label	84 elderly hypercholesterolemic patients with carotid atherosclerosis	Atorvastatin 20 mg or with atorvastatin 20 mg plus ezetimibe 10 mg for 12 month	12 months after treatment, LDL-C (3.31±0.46 to 2.75±0.58 mM vs.3.27±0.36 to 2.31±0.54 mM), high-sensitivity C-reactive protein (hs-CRP) and carotid intima-media thickness (CIMT) were more reduced in the group treated with atorvastatin+ezetimibe than in the group treated with atorvastatin alone.
Japaridze et al 2016 [37]	Monocenter, randomized, open-label	323 patients hospitalized for acute coronary syndrome	Atorvastatin 20 mg for 4 weeks, then either atorvastatin 20 mg+ezetimibe 10 mg or atorvastatin 40 mg for 8 weeks and then another 8 weeks maintenance or doubling statin dose in both treatment groups	• Atorvastatin+ezetimibe (n=146): LDL-C (mmol) reduced from 2.83±0.55 (wk 4) to 1.60±0.39 (wk 16); atorvastatin (n=146): LDL-C reduced from 2.74±0.64 (wk 4) to 1.91±0.40 (wk 16); P<0.0001 (btween group) • Kaplan-Meier survival rate (wk 16) 88.1% in atorvastatin+ezetimibe group and 77.0% in atorvastatin group; hazard ratio 2.099, 95% CI 1.165-3.781; P=0.014

Results of meta-analyses that included more than 2,000 patients for the comparison of atorvastatin/ezetimibe versus atorvastatin indicate that add-on ezetimibe is significantly more effective in reducing LDL-C levels than doubling the statin dose, enabling more patients to achieve LDL-C goals.

In the prospective, randomized, controlled, multicentre PRECISE-IVUS clinical trials (Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound [Tsujita et al., 2015]; 202 Japanese patients), the combination of atorvastatin plus ezetimibe (10 mg) showed greater coronary plaque regression compared with atorvastatin monotherapy.

Simvastatin and ezetimibe

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMRPOVE-IT) was a double-blind, randomized trial involving patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL-C levels of 50 to 100 mg/dl (1.3 to 2.6 mmol/l) if they were receiving lipid-lowering therapy or 50 to 125 mg/dl (1.3 to 3.2 mmol/l) if they were not receiving lipid-lowering therapy [Blazing et al., 2014, Cannon et al., 2015]. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin-ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary endpoint was a composite of cardiovascular death, nonfatal MI, unstable angina requiring rehospitalisation, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years. 18,144 patients were enrolled with either ST-segment elevation MI (STEMI, n=5,192) or UA/non-ST-segment elevation MI (UA/NSTEMI, n=12,952) from October 2005 to July 2010. Western Europe (40%) and North America (38%) were the leading enrolling regions. The STEMI cohort was younger and had a higher percentage of patients naive to lipid-lowering treatment compared with the UA/NSTEMI cohort. The UA/NSTEMI group had a higher prevalence of diabetes, hypertension, and prior MI. Median LDL-C at entry was 100 mg/dl for STEMI and 93 mg/dl for UA/NSTEMI patients. The median time-weighted average LDL-C level during the study was 53.7 mg/dl (1.4 mmol/l) in the simvastatin-ezetimibe group, as compared with 69.5 mg/dl(1.8 mmol/l) in the simvastatin-monotherapy group (P<0.001). The Kaplan-Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; P=0.016). Rates of pre-specified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups. When added to statin therapy, ezetimibe resulted in incremental lowering of LDL-C levels and improved cardiovascular outcomes. Moreover, lowering LDL-C to levels below previous targets provided additional benefit.

IV.5 Clinical safety

Introduction

Adverse events

Atorvastatin showed an excellent safety profile in randomized controlled clinical trials and in post-marketing surveillance in a wide variety of patient groups, including those with Type 2

diabetes mellitus, chronic kidney disease, coronary heart disease, the elderly and combinations of the above. Liver toxicity of atorvastatin is rare, rhabdomyolysis extremely rare and both do not show any consistent dose-dependency [Athyros et al., 2010].

In the SmPC of Sortis/Lipitor the following adverse drug reactions (ADRs) to atorvastatin are listed:

Table 7: Adverse drug reactions to atorvastatin

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)

In the SmPC of Ezetrol the following ADRs to ezetimibe (without and with concomitant statin) are listed:

Table 8: Adverse drug reactions to ezetimibe monotherapy

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)

Atorvastatin/ezetimibe combination

The addition of ezetimibe to statin therapy allows the use of a lower statin dosage and therefore reduces the risk of dose-dependent statin adverse effects [Backes et al., 2005].

Long-term safety and tolerability of ezetimibe plus atorvastatin co-administration therapy were compared to those of atorvastatin monotherapy in patients with primary hypercholesterolaemia [Ballantyne et al., 2004]. Upon completion of a 12-week randomised, double-blind, placebo-controlled study comparing ezetimibe 10 mg; atorvastatin 10 mg, 20

mg, 40 mg or 80 mg; ezetimibe 10 mg/atorvastatin 10 mg, 20 mg, 40 mg or 80 mg or placebo, 246 patients were enrolled in a 12-month extension, with reassignment to double-blind ezetimibe 10 mg (n=201) or matching placebo (n=45) co-administered daily with open-label atorvastatin 10 mg. At intervals of six weeks, patients not at National Cholesterol Education Program Adult Treatment Panel II LDL-C goals were titrated to the next higher atorvastatin dose. Safety evaluations included adverse event (AE) reports and laboratory test results. Ezetimibe/atorvastatin and atorvastatin monotherapy groups were similar with regard to incidence of all AEs (71% vs. 67%), treatment-related AEs (22% vs. 27%) and discontinuations due to AEs (9% vs. 7%) or treatment-related AEs (6% vs. 7%), respectively. Neither clinically significant elevations in hepatic transaminases or creatine kinase nor any cases of myopathy or rhabdomyolysis were observed in either group during the extension study. After 6 weeks, ezetimibe/atorvastatin 10 mg produced greater reductions in LDL-C (-5% vs. -37%), TC (-38.8% vs. -26.0%) and TG (-28 vs. -12%) and similar increases in HDL-C (4.6% vs. 4.5%) compared to atorvastatin 10 mg, respectively, and these changes were maintained and significant at one year (P<0.01 for LDL-C, TC and TG). More ezetimibe/atorvastatin patients achieved LDL-C goal than atorvastatin patients at study endpoint (91% vs. 78%, respectively; P=0.02). Thus, the co-administration of ezetimibe and atorvastatin for 12 months was well tolerated and more efficacious than atorvastatin monotherapy.
Therapy with the new FDC atorvastatin/ezetimibe is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures and in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding three times the upper limit of normal (ULN).
Special warnings and precautions for use must be considered regarding myopathy/rhabdomyolysis. In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. The new FDC atorvastatin/ezetimibe should be prescribed with caution to patients with pre-disposing factors for rhabdomyolysis.

If creatine phosphokinase (CPK) levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started. Further precautions for use must be considered regarding simultaneous treatment with other products, liver enzymes, hepatic insufficiency, fibrates, anticoagulants and stroke prevention by aggressive reduction in cholesterol levels (SPARCL). These situations are well described in the respective SmPC.

Please find below a tabulated overview of the safety results from seven randomised clinical studies performed the atorvastatin/ezetimibe combination.

Detailed safety evaluation of clinical trials mentioned in the clinical overview

Reference	Design	Safety results
Gagné et al 2002	randomized, double-blind, parallel-group study Treatment: Atorvastatin or simvastatin 80 mg/d (statin-80, n=17); ezetimibe 10 mg/d plus atorvastatin or simvastatin 40 mg/d (n=16); or ezetimibe 10 mg/d plus atorvastatin or simvastatin 80 mg/d (n=17) for 12 weeks	Safety and tolerability were assessed by clinical review of all safety parameters, including adverse events, laboratory test results (including frequent liver function tests and creatine kinase levels), and physical examinations. There were no clinically meaningful differences between treatment groups. Fortyeight patients (96%) completed the double-blind treatment period, with only 2 patients discontinuing treatment early because of adverse events. One patient in the ezetimibe plus statin-40 mg group discontinued the study drug 9 weeks after randomization because of epigastric pain secondary to an intrahepatic echinococcal cyst (with increased liver transaminases) and ischemic chest pain. A second patient in the ezetimibe plus statin-80 group was discontinued from the study 1 week after randomization when it was noted that his baseline prerandomization serum ALT and AST levels were >3 times the upper limit of normal, in violation of the protocol exclusion criteria. Analyses of additional measures of safety (laboratory results, electrocardiograms, and cardiopulmonary examinations) revealed no diff rences between the treatment groups. One patient in the statin-80 group and one patient in the ezetimibe plus statin-40/80 group had asymptomatic single transient increases in serum ALT and/or AST >3 times the upper limit of normal. There were no clinically significant increases in creatine kinase concentrations or episodes of myopathy or rhabdomyolysis.
Ballantyne et al 2003	Randomized, double-blind, placebo-controlled, balanced–parallel group Treatment: Ezetimibe (10 mg/d); atorvastatin (10, 20, 40, or 80 mg/d); ezetimibe (10 mg) plus atorvastatin (10, 20, 40, or 80 mg/d); or placebo	Coadministration of ezetimibe and atorvastatin was well tolerated. Treatment-related adverse events were reported for 17% (42/248) of patients receiving atorvastatin monotherapy and 23% (58/255) of patients receiving combination therapy. Most (≥90%) adverse events were mild or moderate, and 66% were considered unlikely to be related to study treatment. In general, the types of adverse events resulting in treatment discontinuation (34/628, 5% of patients) or interruption (31/628, 5% of patients) were no more common or severe in any treatment group. No patient died during the study. All elevations in hepatic enzymes after random assignment were asymptomatic, and no cases of hepatitis, jaundice, or other clinical signs of liver dysfunction were reported. Consecutive and presumed consecutive elevations in ALT or AST level ≥3xULN occurred in only 5 patients and did not differ significantly between atorvastatin monotherapy (<1%) and combination therapy (2%). Of these patients, 1 receiving atorvastatin (80 mg) monotherapy and 2 receiving ezetimibe plus atorvastatin (40 mg) were discontinued from the study; the other 2, receiving ezetimibe plus atorvastatin (10 mg) and ezetimibe plus atorvastatin (20 mg), completed the study. One patient had CPK elevations ≥10_ULN with associated muscle symptoms. This patient, who received ezetimibe plus atorvastatin (40 mg), reported moderate diffuse myalgias and moderate weakness, coincident with CPK of 403 U/L. Follow-up at a local laboratory indicated values as high as 5379 U/L with ongoing symptoms. After treatment was discontinued, symptoms resolved and CPK level returned to normal (96 U/L). Other measurements of safety (other laboratory tests, vital signs, ECGs, and cardiopulmonary examinations) did not suggest any clinically meaningful differences between the safety profiles of combination therapy and atorvastatin monotherapy in the study overall or in subgroups defined by sex, age, or race. There was no evidence that ezetimibe worsened statin intolerance or statin-related toxicity.
Stein et al 2004	Multicenter, randomized, double-blind Treatment: Atorvastatin 10 mg + ezetimibe 10 mg or atorvastatin 20 mg; atorvastatin dose in both groups was doubled after 4 weeks, 9 weeks, or both when the LDL-C level was not at its goal ≤100 mg/dL) to a maximum of 40 mg in the combination group and 80 mg in the monotherapy group	Safety and tolerability were evaluated by reviewing voluntary subject reports, investigators' observations, physical examinations, and results of specific laboratory tests (including frequent liver function tests and creatine phosphokinase [CPK] levels) at each visit. Clinically significant laboratory abnormalities included elevations in ALT or AST levels to at least 3-times the ULN on 2 consecutive occasions or a transaminase level S:3-tomes the ULN on the final laboratory examination (considered "presumed consecutive"), and an increase in CPK levels > 10-times the ULN. There were no clinically meaningful differences in the treatment groups for the incidence of adverse events or in the number of discontinuations because of adverse events (Table V). Serious adverse events occurred in 12 subjects (4%) in the co-administration group and 9 subjects (3%) in the ATORV group. One subject in the ATORV group died of a myocardial infarction, which was thought to be unrelated to the study drug. Three of the 21 serious adverse events were considered possibly or probably related to study treatment: an episode of pruritus, vasculitis, and macular papular rash (ATORV group); myalgia without a CPK increase (EZE group); and increased ALT reaching a value > 3-times the ULN, initially labeled as "hepatitis," in an iron worker with concurrent hemolytic anemia of unknown etiology (EZE group). The latter subject was also receiving diclofenac, which may elevate liver function tests. Two subjects in the EZE group and 1 subject in the ATORV group had asymptomatic increases in serum ALT, AST, or both S:3-times the ULN. Jaundice did not develop in any subject, and no subject in the EZE group had a significant increase in bilirubin or alkaline phosphatase. Additionally, cholelithiasis and cholestasis were each reported (both in the ATORV group), but no subject required a

		cholecystectomy. One subject in the ATORV group had an increase in CPK S: 10-times the ULN, which was associated with muscle pain but was thought to be caused by weight training. There were no episodes of rhabdomyolysis.
Cruz-Fernández et al 2005	Randomised, double-blind, placebo-controlled Treatment: Free combination of the mono-products atorvastatin + ezetimibe or atorvastatin + placebo	Evaluation of safety was accomplished through patientreported adverse signs and symptoms, investigator observations and assessments and various laboratory tests including blood evaluations. Investigators determined the severity of adverse events (mild, moderate, severe or life threatening) and the potential relationship to study drug (definitely not, probably not, possibly, probably and definitely). Key safety variables were the incidence of any clinical or laboratory adverse event, treatment-related adverse events, serious adverse events and discontinuations due to adverse events. Prespecified safety variables included the incidence of ALT and AST elevations >3 times ULN and CK elevations of 5—10 with muscle symptoms or >10 times ULN with or without muscle symptoms. Myopathy was prospectively defined as CK elevations >10 times ULN associated with muscle symptoms with no other plausible aetiology such as exercise or trauma. The co-administration of EZE with ongoing ATV 10 or 20 mg was generally well tolerated, having an overall safety profile similar to that of PBO plus ATV. There were no significant differences between PBO and EZE groups with regard to the incidence of clinical [31 (14%) vs. 34 (16%), respectively] or laboratory [2 (1%) vs. 2 (1%), respectively] adverse events, discontinuations due to any adverse events [1 (<1%) vs. 2 (1%), respectively] and serious adverse events [4 (1.7%) vs. 3 (1.4%), respectively]. Overall, clinical adverse events classified by the investigator as possibly, probably or definitely drug-related occurred in eight patients [three (1.3%) and five (2.3%) patients in PBO and EZE groups, respectively; between-group p = 0.495]. No subjects in either group discontinued treatment due to drug-related clinical adverse events. One subject in the PBO group died from a myocardial infarction, thought to be probably unrelated to study drug. None of the patients in the PBO group and one patient in the EZE group had consecutive elevations in ALT and AST values >3 times ULN (between-group p = 0.491). There were no cases of hepatitis, jaundice or other clinical signs of hepatic dysfunction reported in this study, including the one patient with high ALT and/or AST values. No patients in either treatment group had elevations in CK levels (>5 to <10 times ULN, or >10 times ULN), and there were no reported cases of myopathy or rhabdomyolysis. Results of other laboratory tests, including routine serum chemistries, and haematologic parameters as well as vital signs and findings on physical examinations revealed no evidence of additional safety concerns with EZE plus ATV co-administration therapy.
Blagden & Chipperfield 2007	Multicentre, double-blind, placebo-controlled Treatment: Atorvastatin 10 mg + ezetimibe 10 mg or atorvastatin 10 mg + placebo for 6 weeks	The safety population comprised all randomised patients who received at least one dose of study medication. In addition to recording of adverse events and laboratory tests, specific safety variables included the incidence of ALT or AST elevations to > 3 x ULN, and CK elevations to 5-10 x ULN with muscle symptoms or CK elevations to £ 10 x ULN without muscle symptoms. Myopathy was prospectively defined as CK elevations > 10 x ULN associated with muscle symptoms with no other plausible aetiology (such as exercise or trauma). Co-administration of EZE 4 ATV 10 mg was well tolerated; rates of all AEs, and AEs judged by the investigator to be related to study treatment were similar in the two groups. The one serious AE that occurred (in a patient in the ATV monotherapy group) was a case of left hip dislocation that was judged as unlikely to be related to study medication. No deaths occurred during the study. The most frequently reported AEs were headache, migraine and dyspepsia. Six patients in the EZE 4 ATV group (including the patient who withdrew at their own request due to diarrhoea, which was coded in reasons for discontinuation as patient request) and one patient in the ATV monotherapy group discontinued treatment due to AEs; the only individual AE associated with more than one discontinuation was headache (one patient in each group). Four patients in each group had AEs related to raised clinical chemistry values; two patients receiving EZE + ATV and two patients on ATV monotherapy showed abnormal liver function tests, but no ALT or AST elevations £ 3 x ULN were observed. Three patients on EZE + ATV reported myalgia during the study; although two of these patients showed slight increases in plasma CK levels, these remained within the normal reference range and were not considered to be clinically significant.
Luo et al 2014	Monocenter, randomized, open-label Treatment: Atorvastatin 20 mg or with atorvastatin 20 mg plus ezetimibe 10 mg for 12 month	There were no events of myocardial infarction and cardiovascular death during a 12-month follow-up. One patient in the control group had a transient elevation in glutamicpyruvic transaminase and glutamic oxalacetic transaminase levels, but they were lower than three times the upper limit of normal, which recovered back to the normal range after application of atorvastatin; creatine kinase was not unusually high; there were no myalgia, rashes or other clinical adverse reactions.
Japaridze et	Monocenter,	There were 9 patients in the atorvastatin group (5 patients had received atorvastatin 40 mg

al 2016	randomized, open-label Treatment: Atorvastatin 20 mg for 4 weeks, then either atorvastatin 20 mg+ezetimibe 10 mg or atorvastatin 40 mg for 8 weeks and then another 8 weeks maintenance or doubling statin dose in both treatment groups	and 4 patients – atorvastatin 80 mg) with ALT, AST, or both >3 x ULN. Discontinuation of study medication owing to the adverse event occurred in 6.2 % of the patients in the atorvastatin-monotherapy group and in 2.7% of those in the atorvastatin-ezetimibe group. The combination of atorvastatin and ezetimibe also resulted in a significantly lower risk of cardiovascular events than that with statin monotherapy, with a 11.1 -percentage-point lower rate of the primary composite end point of cardiovascular death, major coronary events, or nonfatal stroke (hazard ratio, 2.099 ; 95% confidence interval, 1.165 to 3.781; P=0.014). There were some differences between the two study groups in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range (9 patients were in atorvastatin group and 4 patients - in atorvastatin-ezetimibe group). In conclusion, the addition of ezetimibe to statin therapy in stable patients who had had an acute coronary syndrome and who had LDL cholesterol levels within guideline recommendations further lowered the risk of cardiovascular events. The event reduction was consistent with the predicted effects seen with statins, and no offsetting adverse events or toxic effects were observed.

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 Ezevast.

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 liver problems (exposure 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 Ezevast FDC can be used instead of co-administration 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

Ezevast 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg tablets has 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 co-administration of the separate reference products Sortis 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 (heterozygous and homozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia 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 the decentralised procedure by day 210. The RMS and concerned member state 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 23 June 2020.

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

VII. REFERENCES

- Patiño-Rodríguez O, Torres-Roque I, Martínez-Delgado M, Escobedo-Moratilla A, Pérez-Urizar J: Pharmacokinetic non-interaction analysis in a fixed-dose formulation in combination of atorvastatin and ezetimibe. Front Pharmacol. 2014;5:261.
- Martindale, Pharmaceutical Press 2014, 38th edition, p1309-1310 and p1489.
- Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet. 2005;44(5):467-94.
- Backes JM, Gibson CA, Howard PA: Optimal lipid modification: the rationale for combination therapy. Vascular Health and Risk Management 2005:1(4) 317–331.
- Gagné C, Gaudet D, Bruckert E; Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002 May 28;105(21):2469-75.
- Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP; Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003 May 20;107(19):2409-15.
- Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, Lipka L, Suresh R, Maccubbin D, Veltri E; Ezetimibe Study Group. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004 Sep;148(3):447-55.
- Cruz-Fernández JM, Bedarida GV, Adgey J, Allen C, Johnson-Levonas AO, Massaad R. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. Int J Clin Pract. 2005 Jun;59(6):619-27.
- Blagden MD, Chipperfield R. Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. Curr Med Res Opin. 2007 Apr;23(4):767-75.
- Matsue Y, Matsumura A, Suzuki M, Hashimoto Y, Yoshida M. Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function: randomized controlled trial. Circ J. 2013;77(7):1791-8.
- Foody JM, Toth PP, Tomassini JE, Sajjan S, Ramey DR, Neff D, Tershakovec AM, Hu H, Tunceli K. Changes in LDL-C levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or rosuvastatin compared with titrating statin monotherapy. Vasc Health Risk Manag. 2013;9:719-27.
- Luo P, Li L, Wang LX, Zhu HH, Du S, Wu SL, Han YG, Wang GG. Effects of atorvastatin in combination with ezetimibe on carotid atherosclerosis in elderly patients with hypercholesterolemia. Genet Mol Res. 2014 Apr 3;13(2):2377-84.
- Japaridze L, Sadunishvili M, Megreladze I. Combination therapy effectiveness of ezetimibe and atorvastatin in patients with acute coronary syndrome. Georgian Med News. 2016 Mar;(252):15-22.
- Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, Komura N, Sakamoto K, Oka H, Nakao K, Nakamura S, Ishihara M, Matsui K, Sakaino N, Nakamura N,

Yamamoto N, Koide S, Matsumura T, Fujimoto K, Tsunoda R, Morikami Y, Matsuyama K, Oshima S, Kaikita K, Hokimoto S, Ogawa H; PRECISE–IVUS Investigators. 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. J Am Coll Cardiol. 2015 Aug 4;66(5):495-507.

- Blazing MA, Giugliano RP, Cannon CP, Musliner TA, Tershakovec AM, White JA, Reist C, McCagg A, Braunwald E, Califf RM. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. Am Heart J. 2014 Aug;168(2):205-12.e1.
- Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97.
- Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Atorvastatin: safety and tolerability. Expert Opin Drug Saf. 2010 Jul;9(4):667-74.
- Ballantyne CM, Lipka LJ, Sager PT, Strony J, Alizadeh J, Suresh R, Veltri EP. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. Int J Clin Pract. 2004 Jul;58(7):653-8.