COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezeat 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets

(ezetimibe/atorvastatin calcium trihydrate)

NL/H/5238/001-004/DC

Date: 10 November 2022

This module reflects the scientific discussion for the approval of Ezeat 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets. The procedure was finalised at 6 October 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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
CQAs	Critical quality attributes
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
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
ICH	International Conference of Harmonisation
LDL	Low density lipoprotein
MAH	Marketing Authorisation Holder
NPC1	Niemann–Pick type C1
Ph. Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VLDL	Very-low density lipoprotein

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ezeat 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets from Teva B.V.

The product is indicated for hypercholesterolaemia.
Ezeat 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, but as separate products.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns an application for the fixed dose combination (FDC) product of atorvastatin and ezetimibe. Both active substances are approved as monotherapies in the management of (different types of) hypercholesterolemia. The reference products, Lipitor (atorvastatin) and Ezetrol (ezetimibe), were first registered in the EU in 1996 (DE/H/0109/001) and 2002 (DE/H/0396/001), respectively. The use of atorvastatin and ezetimibe monotherapy as well as ezetimibe & statin combination therapy is supported by the guideline of the European Society of Cardiology (ESC), based on the pharmacological synergistic mechanisms of action.

Atorvastatin was initially launched in EU on 7 November 1996 (Sortis, Lipitor, Pfizer Limited). Atorvastatin is authorised in fixed-dose combination with amlodipine, Caduet (Pfizer) (atorvastatin/amlodipine) 5/10 mg, 10/10 mg tablets; Lidorat and Amlator (Richter) (atorvastatin/amlodipine) 10/5 mg, 20/10 mg, 20/10 mg tablets; Atorcombo (Pharma-Regist) (atorvastatin/amlodipine) 5/10 mg, 10/10 mg, and Valongix (Servier) (atorvastatin, amlodipine, perindopril). There is also a registered atorvastatin/ezetimibe fixed-dose combination 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 states (CMS) involved in this procedure were Hungary and Spain.

Legal base
The marketing authorisation has been granted pursuant to Article 8(3) of the Directive 2001/83/EC, as amended, i.e. full dossier application. Since no new active substance is included in the combination products, the submission followed the “mixed application” approach. 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.

PIP waiver
A product-specific waiver for all subsets of the paediatric population and the condition 'Treatment of hypercholesterolaemia' has been granted, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. The waiver has been granted on 6 December 2019, decision number; P/0429/2019.

Scientific advice
Scientific advice was sought by the MAH, in both the Netherlands (22 October 2018) and Germany (26 July 2018). The MAH has followed the advice given.

II. QUALITY ASPECTS

II.1 Introduction

Ezeat are film-coated tablets intended for immediate release containing two active substances, atorvastatin calcium trihydrate and ezetimibe, in separate layers in the same dosage form. The film-coated tablets differ in colour, shape and size according to their strength (ezetimibe/atorvastatin):

- 10 mg/10 mg: white, round and biconvex
- 10 mg/20 mg: white, ovaloid and biconvex
- 10 mg/40 mg: white, capsule shape and biconvex
- 10 mg/80 mg: yellow, oblong and biconvex

Each film-coated tablet contains as active substances 10 mg of ezetimibe and 10, 20, 40 or 80 mg of atorvastatin (as atorvastatin calcium trihydrate).

The film-coated tablets are packed in OPA/Al/PVC//Al blisters and OPA/Al/PVC//Al perforated unit dose blisters.

The excipients are:
Tablet Core (all strengths) – microcrystalline cellulose 101 (E460), mannitol (E 421), calcium carbonate (E170), croscarmellose sodium (E468), hydroxypropylcellulose (E463), polysorbate 80 (E433), iron oxide yellow (E172), magnesium stearate, povidone K29/32 (E1201) and sodium laurilsulfate (E487).

Tablet Coating (10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg) – lactose monohydrate, hypromellose 2910 (E464), titanium dioxide (E171) and macrogol 4000 (E1521)

Tablet Coating (10 mg/80 mg) – hypromellose 2910 (E464), titanium dioxide (E171), talc (E553b), macrogol 400 (E1521), iron oxide yellow (E172).

The excipients and packaging are usual for this type of dosage form.

II.2 Drug Substances

Ezetimibe
One of the active substances is ezetimibe, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.). Ezetimibe is a white to off-white crystalline powder, which is freely soluble in acetone and methanol, soluble in ethanol but practically insoluble in water. The drug substance exhibits polymorphism, the manufacturer consistently produces the anhydrous-crystalline form. Ezetimibe contains three asymmetric carbon atoms and therefore exhibits optical isomerism.

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

Manufacturing process
The manufacturing process consists of seven stages. The synthesis description is in sufficient detail and a clear chemical reaction scheme is provided. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance is adequately characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specification of ezetimibe as applied by the MAH contains tests for appearance, solubility, identification, water content, heavy metals, specific optical rotation, residue on ignition, assay, related substances, other isomer, total impurities, residual solvents, particle size and polymorphic form. Batch analytical data demonstrating compliance with the specifications have been provided for three batches.

Stability of drug substance
Stability data on the active substance has been provided for eleven batches stored at long-term conditions (25°C/60% relative humidity or RH) up to 60 months and accelerated conditions (40 °C/75 %RH) up to six months. The batches were stored adequately in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 48 months. The storage conditions are: "Preserve in well closed containers at controlled room temperature between i.e. 20°C and 25°C (excursions are allowed between 15°C and 30°C)."

Atorvastatin calcium trihydrate
The active substance atorvastatin calcium trihydrate is an established active substance described in the European Pharmacopoeia. Atorvastatin calcium trihydrate has two chiral centres and therefore exhibits optical isomerism. The active substance is a crystalline powder. and is very slightly soluble in water. Atorvastatin calcium trihydrate exhibits polymorphism. Several crystalline forms and amorphous form are known. The approved manufacturers consistently produce the same polymorphic form I.

For both manufacturers, 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 for both manufacturers; 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 for atorvastatin calcium trihydrate in the Ph. Eur. and on additional requirements of the CEP. The following tests are included: appearance, solubility, identification, enantiomeric purity, related substances, sodium, water, assay, residual solvents, particle size distribution and polymorphic form. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches per manufacturer.

Stability of drug substance
Manufacturer I
The active substance is stable for 24 months in suitable polyethylene bags, placed in a polyethylene container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Manufacturer II
The active substance is stable for 36 months if stored in suitable polyethylene bags, placed in either a polyethylene drum or a container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Products

Pharmaceutical development

The development of the drug product has been adequately described, the choice of excipients is justified and their functions explained. The main pharmaceutical development studies were the characterisation of reference products, compatibility studies, formulation development, dissolution methods development, manufacturing process development and the performance of comparative dissolution studies, complementary to bioequivalence studies. These studies were appropriately performed and described. During the manufacturing process development, all the process steps and the corresponding process parameters were investigated. 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.

The MAH performed comparative *in vitro* dissolution studies in three dissolution media without surfactant and in the media intended for drug product release. Based on the submitted analysis data, most dissolution profiles were considered similar. The differences in dissolution behaviour between the test and reference products have been sufficiently justified based on differences in the design of the test product, which is a double layer tablet, compared to the monolayer reference products. The bioequivalence studies were carried out on the highest product strength (10 mg/80 mg), and will be discussed in section IV. A biowaiver was requested for the other product strengths.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The process consists of five steps, namely manufacturing of the atorvastatin blend, manufacturing of the ezetimibe blend, tablet formation, coating and packaging. The manufacturing process has been described in sufficient detail. Mixing/blending times, addition times, granulation times and critical and non-critical relevant process parameters have been provided. Process validation data on the product have been presented for three batches for each strength in accordance with the relevant European guidelines.

Control of excipients

Specifications for all excipients have been provided. Except for coating agents, the specifications for all other excipients are in line with Ph. Eur., with additional testing for some excipients. 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 for appearance, average weight, disintegration time, content uniformity, identification, identification of colourants, water content, dissolution, assay, related substances and microbiological tests. 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 the proposed production site have been provided on twelve batches (two commercial scale and one smaller scale batches per strength), demonstrating compliance with the release specifications.

Stability of drug product

Stability data on the drug product have been provided for three batches per strength in accordance with applicable European guidelines demonstrating the stability of the product up to 24 months (25°C/60%RH), 12 months (30°/65%RH) and 6 months (40°C/75%RH). The batches were stored in OPA/Al/PVC//Al blisters intended for marketing which are placed in carton boxes. No significant changes were observed and all results remained within shelf-life specification. The assay and the dissolution were not significantly altered under any of the storage conditions. Increase of atorvastatin related impurities was observed. No increase in ezetimibe related impurities was observed. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

On basis of the data submitted, a shelf-life was granted of 24 months. The labelled storage conditions are “This medicinal product does not require any special storage conditions”.

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 Ezeat have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished products.

No post-approval commitment were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ezeat is intended for substitution of single component medicinal products containing the same active substances at the same dose, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Pharmacology

Atorvastatin

Atorvastatin belongs to the pharmacotherapeutic group of lipid modifying agents and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) –reductase inhibitors (statins). Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. This results in a reduction of hepatocyte cholesterol levels, which results in up-regulation of low-density lipoprotein (LDL) receptors and, consequently, increase clearance of LDL-cholesterol (LDL-C) from the plasma. Statins also reduce production of apolipoprotein B (ApoB) leading to reduced hepatic output of very low density lipoprotein cholesterol (VLDL-C) and triglycerides. From the available clinical trial data, atorvastatin can be considered one of the most effective statins, not only by taking into account its effects on LDL-C and ability to meet recommended treatment guidelines for this parameter, but also its effect on triglyceride levels and capacity to modify lipoprotein composition in a non-atherogenic manner. Secondary pharmacodynamic effects of atorvastatin include beneficial effects on vessel endothelial tissue, ability to stabilise atheromatous plaques by decreasing inflammation, effects on proliferation of smoot muscle, antithrombotic effect by inhibiting platelet aggregation and stimulation of fibrinolytic mechanisms, improvement of blood viscosity and flow, and decreased LDL oxidation.

Ezetimibe

Ezetimibe belongs to a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. It is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols. Ezetimibe is a potent inhibitor of cholesterol and phytosterol absorption in the small intestine, where both dietary and biliary cholesterol are available for absorption.

However, its action is unique in that it does not affect cholesterol micelle formation (plant sterols) or increase bile acid secretion. It does not alter fat-soluble vitamin and nutrient absorption. Ezetimibe effectively reduces plasma cholesterol in several species including human, monkey, dog, hamster, rat, and mouse, but the potency ranges widely. Secondary pharmacodynamic effects of ezetimibe include vascular protective effects, beneficial effects on coronary heart disease, anti-atherogenic effects, effects on fatty liver disease and hepatic steatosis and effects on dyslipidaemia and insulin resistance.

Atorvastatin + ezetimibe

Atorvastatin and ezetimibe have complementary mechanisms of action. Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary

cholesterol reduction. Ezetimibe, when added to atorvastatin, enhances its LDL-C lowering potential without having any effect on atorvastatin pharmacokinetics. Although statins are effective in reducing cardiovascular risk, combination therapy may be required to meet recommended target LDL-C levels.

III.3 Pharmacokinetics

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide. Total ezetimibe (sum of 'parent' ezetimibe plus ezetimibe-glucuronide) concentrations reach a maximum 1-2 hours post-administration, followed by enterohepatic recycling and slow elimination. The estimated terminal half-life of ezetimibe and ezetimibe-glucuronide is approximately 22 hours. Ezetimibe is excreted primarily in the faeces. The pharmacokinetics of ezetimibe in human is further described in section IV on Clinical aspects.

Atorvastatin

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within one to two hours. Extent of absorption increases in proportion to atorvastatin dose. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. The hepatic first-pass effect of atorvastatin is too small to fully explain the low bioavailability of 14%. It may be a consequence of incomplete intestinal absorption and/or extensive gut wall extraction. Mean volume of distribution of atorvastatin is approximately 381 L. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Atorvastatin is ≥ 98% bound to plasma proteins. Plasma metabolic profiles provided evidence of extensive metabolism. Faeces was the major route of AT-derived radioactivity elimination. Bile was a major route of [^{14}C] drug-derived excretion, accounting for 73 and 33% of the oral dose in the rat and dog, respectively. The pharmacokinetics of atorvastatin in human is further described in section IV on Clinical aspects.

III.4 Toxicology

The safety profile of the individual active substances ezetimibe and atorvastatin is well understood. Pre-clinical studies on acute-dose toxicity, repeat-dose toxicity, genotoxicity and carcinogenic potential indicate acceptable risks for humans. However, animal experimental studies have shown that HMG-CoA reductase inhibitors like atorvastatin may affect the development of embryos or foetuses.

Atorvastatin

The acute toxicity of atorvastatin in rodents and dogs is low. Following repeated dose administration, the liver is the primary target organ. In both the rat and dog studies, the hepatic changes diminished with time suggesting an adaptive response. Atorvastatin was neither mutagenic nor clastogenic in several in vitro and in vivo assays. Atorvastatin was not

found to be carcinogenic in rats, but high doses in mice showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or foetuses. 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. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

Ezetimibe

The acute toxicity of ezetimibe in rodents and dogs is low. No target organs of toxicity were identified in chronic studies at daily doses up to 1500 and 500 mg/kg in male and female rats, respectively, up to 500 mg/kg in mice, or up to 300 mg/kg in dogs. In a series of in vivo and in vitro assays ezetimibe exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative. Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day

Atorvastatin + Ezetimibe

Toxicologic findings were consistent with those seen with statins administered alone. Co-administration of ezetimibe and statins did not result in any new toxicities. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose. In a series of in vivo and in vitro assays ezetimibe co-administered with statins, exhibited no genotoxic potential. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed.

III.5 Discussion on the non-clinical aspects

This product is a FDC product of the mono-therapies Lipitor (atorvastatin) and Ezetrol (ezetimibe) which are available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ezetimibe and atorvastatin are well-known active substances with established efficacy and tolerability. The clinical documentation is based on one pilot and one pivotal bioequivalence study performed with Ezeat 10 mg/80 mg versus atorvastatin mono-product (Lipitor 80 mg) and ezetimibe mono-product (Ezetrol 10 mg), as well as on review of relevant published literature and scientific bibliographic data. The member states agreed that no further clinical studies are required except for the bioequivalence study.

Rationale

Combinations of medicinal products are administered in a number of scenarios to improve clinical outcomes for patients. Potential advantages for combinations of medicinal products compared to treatment with monotherapy could be that:

• the combination improves response in those with inadequate response to monotherapy, has a greater overall effect and/or is more rapidly effective;

• the combination improves safety due to one active substance counteracting the adverse drug reactions of another or by combining doses that are sub-therapeutic when used in monotherapy.

Fixed combination medicinal products offer the possibility to simplify administration where a combination of active substances is already recognized with an existing therapeutic claim (European Medicines Agency, 2017). They have been increasingly used due to the benefit of the combined effects of active substances given together.

The proposed fixed combination contains a dosage in accordance with approved individual dosages for antihyperlipidemic mono-therapy.

Atorvastatin and Ezetimibe are well known antihyperlipidemic drugs. Their combination is indicated for the treatment of primary hypercholesterolemia in adults adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

Current guidelines, such as the ESC/EAS guideline, recommend combinations of statins with other lipid lowering drugs for combination therapy, including the combination of a statin and ezetimibe. This is a treatment option for adults with primary hypercholesterolemia who have been initiated on statin therapy when serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and consideration is being given to changing from initial statin therapy to an alternative statin. Overall, in line with the CHMP/EWP/191583/05 entitled “Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardio-vascular treatment and prevention" the use of the mono-products can be considered widespread, well known, and the rationale of

their combined use is supported by pharmacological principles. Also the arguments of simplifying therapy as justification of a fixed dose combination can be considered valid.

IV.2 Pharmacokinetics

For this application, the MAH has clearly described the pharmacokinetics of both active substances. For both active substances, information was presented on absorption, distribution, metabolism, elimination, linearity and food effect, which is summarised below.

Ezetimibe

Absorption: After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within one to two hours for ezetimibe-glucuronide and four to twelve hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection (Kosoglou et al., 2005; Merck Sharp & Dohme Limited, 2016).

Distribution: Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively (Kosoglou et al., 2005; Merck Sharp & Dohme Limited, 2016).

Metabolism: Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated (Merck Sharp & Dohme Limited, 2016; MHRA, 2017; Sandoz Canada Inc., 2017). 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 (MHRA, 2017). Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling (Patrick et al., 2002). The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours (Kosoglou et al., 2005).

Elimination: 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 (Merck Sharp & Dohme Limited, 2016; MHRA, 2017; Sandoz Canada Inc., 2017).

Linearity: No substantial deviation from dose proportionality in the dose range 5-20 mg (Kosoglou et al., 2005).

Food effect: Concomitant food administration (high-fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered at 10 mg tablets (Merck Sharp & Dohme Limited, 2016; MHRA, 2017; Sandoz Canada Inc., 2017).

Atorvastatin

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within one to two hours. Extent of absorption increases in proportion to the atorvastatin dose. After oral administration, atorvastatin tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG- CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism (FDA, 2009; Pfizer Limited, 2019).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins (FDA, 2009; Pfizer Limited, 2019).

Metabolism: Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. *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 (FDA, 2009; Pfizer Limited, 2019).

Elimination: Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter (Corsini and Bellosta, 2008). Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multidrug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin. Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product does not appear to undergo significant enterohepatic recirculation (FDA, 2009; Pfizer Limited, 2019). Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity of HMG-CoA reductase is approximately 20-30 hours due to the contribution of active metabolites (Lennernäs, 2003).

Linearity: In an SD study (2.5-120 mg) and in MD studies (2.5-80 mg), AUC and C_{max} of atorvastatin equivalents (all compounds capable of inhibiting HMG-CoA reductase), showed nonlinear increases. However, in an MD study, a greater than dose- proportional increase was observed only in C_{max} but not in AUC of either atorvastatin or its active metabolites (Lennernäs, 2003).

Food effect: Administration with food does not affect the rate and extent of absorption (Lennernäs, 2003).

Furthermore, one pilot and one pivotal bioequivalence study were conducted. The results of the pilot study have not been assessed for this authorization procedure. In both bioequivalence studies, the pharmacokinetic profile of the Ezeat 10 mg/80 mg (Teva B.V., The Netherlands) was compared with the pharmacokinetic profile of the combined intake of

reference products Lipitor (Pfizer B.V., The Netherlands) and Ezetrol (N.V. Organon, The Netherlands).

Biowaiver of strengths

A bioequivalence study for the highest strength of ezetimibe/atorvastatin (10/80 mg) was submitted. A biowaiver for the additional strengths 10/40 mg, 10/20 mg and 10/10 mg was applied for. Only the strength of atorvastatin varies between the FDC products, the ezetimibe strength is constant. Both active substances are tableted in separate layers of the tablet. The pharmacokinetics of atorvastatin are linear for the proposed dosing range (10-80 mg). The following criteria for a biowaiver have been met: the products are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the composition of the strengths in each bilayer (atorvastatin and ezetimibe) is quantitatively proportional. Furthermore, the provided *in vitro* dissolution data (see section II) supported the biowaiver. In conclusion, one bioequivalence study using the 10/80 mg strength is acceptable and the results can be extrapolated to the other strengths.

Bioequivalence study

To confirm similarity in bioavailability of atorvastatin, ezetimibe (unconjugated) and total ezetimibe between the FDC products and reference products, a pivotal bioequivalence study was conducted. The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of the reference products. The formula and preparation of the bioequivalence batch in the pivotal study are identical to the formula proposed for marketing.

Design

The study was an open label, single-dose, randomised, two-treatment, two-period, two-sequence, crossover bioequivalence study. The study was carried out under fasted conditions in 80 healthy subjects, aged 20 – 40 years. Each subject received either one 80/10 mg atorvastatin/ezetimibe test product, or one Lipitor 80 mg film-coated tablet and one Ezetrol 10 mg tablet. The tablets were orally administered with 240 ml water after an overnight fast of at least ten hours. Water was not permitted 1 hour before dosing and until 1 hour post-dosing, but it was allowed at all other times. The subjects were served a meal at 4 hours post dose and at appropriate times thereafter. In each period, subjects were housed from 10 hours prior to dosing until 24 hours post dosing. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected within one hour pre-dosing and at 0.17, 0.25, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after oral administration of the tablets.

The safety of the test and reference products was assessed on the basis of clinical and laboratory examinations and registration of adverse events. The design of the study 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. Standard acceptance criteria were used for conclusion of bioequivalence, which is acceptable for atorvastatin, ezetimibe (unconjugated) and total ezetimibe (ezetimibe + ezetimibe (conjugated) obtained from ezetimibe phenoxy glucuronide). The metabolite 4-hydroxy atorvastatin and ezetimibe unconjugated are not used as the pivotal parameters for bioequivalence conclusions.

Results

Out of a total of 80, 75 subjects were eligible for pharmacokinetic analysis. Five subjects withdrew from the study due to positive drug of abuse tests (two subjects), positive alcohol breath tests (two subjects) and an adverse event (vomiting; one subject).

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

Treatment N=75	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	358 ± 198	363 ± 199	96 ± 63	1.00 (0.50 - 4.50)
Reference	346 ± 150	351 ± 151	97±53	0.75 (0.33 - 4.50)
***Ratio (90% CI)**	1.01 (0.95 - 1.06)	--	0.96 (0.87 - 1.05)	--

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

**ln-transformed values*

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

Treatment N=75	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	96 ± 39	101 ± 40	11.3 ± 5.2	1.00 (0.33 - 12.00)
Reference	107 ± 47	112 ± 49	14.3 ± 6.6	0.75 (0.33 - 6.00)
***Ratio (90% CI)**	0.91 (0.87 - 0.96)	--	0.79 (0.73 - 0.85)	--

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

**ln-transformed values*

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

Treatment N=75	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	949 ± 395	983 ± 404	132 ± 41	0.75 (0.50 - 3.67)
Reference	1001 ± 382	1045 ± 403	143 ± 39	0.75 (0.50 - 3.67)
***Ratio (90% CI)**	0.94 (0.90 - 0.98)	--	0.91 (0.87 - 0.96)	--

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

**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 for atorvastatin and total ezetimibe. Based on the submitted bioequivalence study, Ezeat 10 mg/80 mg film-coated tablets is considered bioequivalent to one tablet of Lipitor 80 mg film-coated tablets and one tablet of Ezetrol 10 mg tablets. The results of this bioequivalence study can be extrapolated to the other strengths of Ezeat (10/40 mg, 10/20 mg and 10/10 mg), according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 MAH provided a comprehensive overview of scientific literature on the physiological effects of both active substances. Also, data on their combined pharmacodynamic effect have been submitted. A summary of the submitted data is written below.

Atorvastatin

Atorvastatin is an anti-lipidemic agent, belonging to the drug class of statins which inhibit HMG-CoA reductase. This enzyme converts HMG-CoA to mevalonic acid, which is the rate limiting step in the cholesterol synthesis pathway. Therefore, atorvastatin causes a decrease in hepatocellular cholesterol, to which the hepatocytes respond by increasing their LDL receptor synthesis. This leads eventually to a reduction in serum low density lipoprotein (LDL) cholesterol, very-low density lipoprotein (VLDL) cholesterol and total cholesterol (Istvan and Deisenhofer, 2001; Cheng and Leiter, 2004).

Secondary pharmacodynamic effects of atorvastatin include beneficial effects on vessel endothelial tissue, ability to stabilise atheromatous plaques by decreasing inflammation,

effects on proliferation of smoot muscle, antithrombotic effect by inhibiting platelet aggregation and stimulation of fibrinolytic mechanisms, improvement of blood viscosity and flow, and decreased LDL oxidation (Simons et al., 1998; Malhotra and Goa, 2001; Ali et al., 2007; Rubba, 2007; Kim et al., 2018).

Ezetimibe

Ezetimibe belongs to a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe inhibits the absorption of cholesterol and phytosterols via binding to the Niemann–Pick type C1 (NPC1) protein at the small intestinal epithelial brush border, without affecting the absorption of triglycerides and fat-soluble vitamins. This results in a decreased transport of intestinal cholesterol to the liver (Ge et al., 2008; Merck Sharp & Dohme Limited, 2016; MHRA, 2017; Sandoz Canada Inc., 2017).

Combined effect

The two mono-components have a different mechanism of action which could provide a synergistic effect when combined. Several studies have shown that ezetimibe enhances the potential of atorvastatin to lower LDL cholesterol. The combination of atorvastatin and ezetimibe is well-tolerated, has a similar safety profile to that of the mono-products and shows enhanced efficacy (Athyros et al., 2008; Azar et al., 2011, 2010; Blagden and Chipperfield, 2007; Bulut et al., 2005; Kakara et al., 2014; Tsujita et al., 2015). More information on clinical efficacy is given in section IV.4.

IV.4 Clinical efficacy

According to the *Guideline on clinical development of fixed combination medicinal products* (EMA/CHMP/158268/2017) the following requirements have to be fulfilled:

1. Justification of the pharmacological and medical rationale for the combination.
2. Establishment of the evidence base for the:
    a. relevant contribution of all active substances to the desired therapeutic effect (efficacy and/or safety);
    b. positive benefit-risk for the combination in the targeted indication.
3. Demonstration that the evidence presented - if based on combined administration of separate active substances - is relevant to the fixed combination medicinal product for which the application is made.

Justification of the pharmacological and medical rationale for the combination

Atorvastatin and ezetimibe have different pharmacological mechanisms. These pharmacological effects are considered to be synergistic in treating patient with increased lipid levels. These main pharmacodynamic effects of both components have been discussed. Further, a justification is provided for the use of the combination of atorvastatin and ezetimibe. The use of the combination is supported by Learned Societies' guidelines such as ESC/EAS amongst other references. Further, it can be noticed that combination products of

atorvastatin and ezetimibe with a substitution indication are already approved in the Netherlands and other EU member states.
A reference of Bangalore 2007 is mentioned as reference for improved adherence, which can be acceptable.

Relevant contribution of all active substances to the desired therapeutic effect
The efficacy of the mono-component atorvastatin has mainly been described based on 12 references evaluating comparison to other statins. Further, a placebo controlled study with atorvastatin has been described. Reference is made to 17 articles without further description. For ezetimibe, reference is made to the product information describing three randomised studies, reference to seven other publications and a reference to the use of ezetimibe in phytosterolaemia. Based on these references the efficacy of atorvastatin and ezetimibe have sufficiently been described.

The use of ezetimibe in combination with statins is already included in the approved indication of ezetimibe. Improved LDL cholesterol lowering with the combination of ezetimibe and atorvastatin has been referenced by review publications or meta-analyses (McKenney, 2005; Pirillo et al., 2017; Santee et al., 2012, Ai et al., 2018, Mikhailidis et al., 2007, Bennett et al., 2004, Davidson et al., 2004) or specific (post-hoc) studies (Blagden and Chipperfield, 2007, Athyros et al., 2008, Conard et al., 2010). Addition of ezetimibe to other statins has also been mentioned including references of studies such as Davidson, 2003; Davidson et al., 2013; Davidson and Robinson, 2007, and Pearson et al., 2005. Further references include Sweeney and Johnson, 2007, Bennett et al., 2004, Hamilton-Craig et al., 2010, SmPC reference, Inoue et al., 2010). Studies of combining ezetimibe with statins in Heterozygous familial hypercholesterolemia have also been described (Pitsavos et al., 2008, Oh et al., 2017). Also, a Japanese study (Teramoto et al., 2012), and a study in hyperlipidemia with type 2 diabetes mellitus have been described. Furthermore, data regarding co-prescription of ezetimibe and atorvastatin in France, Greece, Spain, Italy and Germany have been provided. Overall, these data provide sufficient support for the contribution of both components to the desired therapeutic effect.

Demonstration that the evidence is relevant to the fixed combination medicinal product
Bioequivalence of the FDC products is in general required to bridge existing clinical data obtained from the combined use of mono-components with those from the fixed combination formulation. In order to support the clinical equivalence of the FDC products, a bioequivalence study has been performed, which was discussed in section IV.2.

IV.5 Clinical safety

A general description of the safety profile and adverse events of atorvastatin has been described based on data available from the SmPCs of atorvastatin mono-products. Further, several review/meta-analysis publications compared the safety profile of atorvastatin to other statins (Alberton et al., 2011, Bertolini et al., 1997, Black et al., 1998, Dart et al., 1997, Davidson et al., 1997, Hoffman et al., 2012, Wolffenbuttel, 1998). Similarly, for ezetimibe, a general description of the safety profile and adverse events has been described based on

data available from the SmPCs of atorvastatin mono-products. Further, a review article (Sweeney and Johnson, 2007) and specific studies (Almutairi et al., 2009, Bays et al., 2001, Dujovne et al., 2002, Patel et al., 2007) have been referenced to describe safety aspects of ezetimibe in different types of patients.

The adverse events profile as described for the monocomponents is also applicable to the combination. Further reviews/meta-analysis studies (Bennett et al., 2004, Lipka et al., 2004), specific studies (Blagden and Chipperfield, 2007, Enajat et al., 2009, Hamdan et al., 2011, Huang et al., 2019, Kovarnik et al., 2012, Panichi et al., 2006, Teramoto et al., 2012), and case reports (Bergland Ellingsen et al., 2017) have been presented based on references to further inform on the safety profile of the combination in different types of patients.

Overall, the MAH provided the safety profile of the individual components of Ezeat. This is acceptable as for both single components the safety profile is well-known. Further, additional references including review articles, specific studies and a case report have been included to further describe the safety profile of the combination. These data provide sufficient support for description of the overall safety profile of the combination product.

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 Ezeat.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	• 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 Atorvastatine/Ezetimibe Teva 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 language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with two 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezeat 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are FDC products showing similarity with Lipitor (atorvastatin) 10/20/40/80 mg, film-coated tablets and Ezetrol (ezetimibe) 10 mg, tablets. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. Further, sufficient pre-clinical and clinical bibliographic data have been provided that support the clinical efficacy and safety profile of the combination of these active substances in Ezetimibe/Atorvastatin Teva. Therefore, the benefit-risk balance of the FDC products has been positively assessed.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ezeat with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 October 2021.

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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