COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe/Atorvastatine Stada 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/5301/001-004/DC

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This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatine Stada 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 16 March 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ACS	Acute coronary syndrome
ApoB	Apolipoprotein B
ASMF	Active Substance Master File
BCRP	Breast cancer resistance protein
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CoA	Coenzyme A
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
HMG	3-hydroxy-3-methylglutaryl
ICH	International Conference of Harmonisation
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MAH	Marketing Authorisation Holder
MDR1	Multidrug resistance protein 1
NPC1L1	Niemann-Pick C1-Like 1 (molecule)
OATP	Organic anion-transporting polypeptide (1B1 or 1B3)
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
VLDL-C	Very low-density lipoprotein cholesterol

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ezetimibe/Atorvastatine Stada 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets, from Stada Arzneimittel AG.

The product is indicated for:

- Hypercholesterolaemia, 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.
- Prevention of cardiovascular events, as substitution therapy in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), for adults receiving atorvastatin and ezetimibe concurrently at the same dose level.

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

This decentralised procedure concerns a fixed dose combination (FDC) application of ezetimibe and atorvastatin. Fixed dose combinations (pursuant to article 10b of Directive 2001/83/EC) contain active substances from medicinal products already authorised in the EEA individually, but not yet authorised in combination for therapeutic purposes. In these kind of applications, pre-clinical and clinical data relating to the combination are provided and it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The reference products are Ezetrol 10 mg, tablets (ezetimibe) and Lipitor 10, film-coated tablets 10 mg (atorvastatin). Ezetrol was registered first in 2003 (DE/H/0396/001) by N.V. Organon in Europe (including the Netherlands), and Lipitor in 1997 (DE/H/0109/001) by Viatris Netherlands B.V.

The concerned member states (CMS) involved in this current procedure were Czechia, Italy and Spain.

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 and is therefore not authorised as a generic form of Atozet.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Atorvastatine Stada are film-coated tablets of which:

- the 10 mg / 10 mg strength is a white, round, biconvex film-coated tablet,
- the 10 mg / 20 mg strength is a white, ovaloid, biconvex film-coated tablet,
- the 10 mg / 40 mg strength is a white, capsule shape, biconvex film-coated tablet,
- the 10 mg / 80 mg strength is a yellow, oblong, biconvex film-coated tablet.

These tablets contain as active substance 10 mg of ezetimibe and 10 mg, 20 mg, 40 mg, or 80 mg of atorvastatin (as calcium trihydrate), respectively.
The tablets are packed in oriented polyamide (OPA)/Aluminium/PVC/Aluminium blisters and unit-dose blisters packed into carton boxes.

The excipients are:
Tablet core

- For all strengths – microcrystalline cellulose (101), mannitol, calcium carbonate, croscarmellose sodium, hydroxypropyl cellulose, polysorbate (80), yellow iron oxide (E172), magnesium stearate, povidone K-29/32 and sodium lauryl sulphate.

Tablet coating

- For 10 mg/10 mg, 10 mg/ 20 mg and 10 mg/40 mg: Opadry White OY-L-28900 consisting of lactose monohydrate, hypromellose 2910 (E464), titanium dioxide (E171) and macrogol 4000 (E1521),
- For 10 mg/80 mg: DrCoat FCU consisting of hypromellose 2910, titanium dioxide (E171), talc (E553b), macrogol 400 and yellow iron oxide (E172).

The amount of ezetimibe remains the same (10 mg) all over the different strengths; the atorvastatin layer is weight proportional across the four strenghts.

II.2 Drug Substance

II.2.1 Ezetimibe

One of the two active substances is ezetimibe, an established active substance described in the United States Pharmacopoeia (USP) and in a draft monograph of the European Pharmacopoeia (Ph.Eur. 32.3). Ezetimibe is a white to off-white crystalline powder, which is freely soluble in ethanol and methanol, but practically insoluble in water. The drug substance exhibits polymorphism; the anhydrous crystalline form is produced by both ezetimibe manufacturers used by the MAH.

The Active Substance Master File (ASMF) procedure is used for 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

For both manufacturers, the manufacturing process is described in sufficient detail. The synthesis route for ezetimibe consists of four chemical steps and subsequent purification. Adequate specifications have been adopted for starting materials and intermediates. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analysis data of three batches from Manufacturer I comply with the proposed specification. The quantities of impurities, related substances, genotoxic impurities and residual solvents are inside the acceptance criteria of the CHMP guidelines and in-house guidelines of the manufacturer. For Manufacturer II, analysis data of three production scale batches have been provided, which comply with the specification.

Stability of drug substance

Manufacturer I – The re-test period is 48 months, based on stability data of three lower scale batches, seven higher scale batches and one micronised batch, stored at long-term conditions up to 60 months and accelerated conditions up to 6 months.
Manufacturer II – In the ASMF, the provided stability data support a re-test period of 24 months.

II.2.2 Atorvastatin calcium trihydrate

The other active substance is atorvastatin calcium trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Two manufacturers (here named Manufacturer III and IV) are used to produce this active substance.

The CEP procedure is used for atorvastatin calcium trihydrate by both manufacturers. 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 by 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 in the Ph.Eur. The quantities of impurities, related impurities, genotoxic impurities and residual solvents are inside the acceptance criteria as determined according to European Pharmacopoeia, CHMP guidelines, CEP and the

manufacturers. Batch analytical data demonstrating compliance with the specification have been provided for three batches by Manufacturer III and for three batches by Manufacturer IV.

Stability of drug substance

Manufacturer III – The re-test period of the substance is 24 months if stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Manufacturer IV – The re-test period of the substance is 36 months if 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 and their functions explained. The main development studies were the characterisation of the reference product, formulation development, dissolution methods development and manufacturing process development. During the manufacturing process development, all the process steps and the corresponding process parameters were found to be acceptable. All aspects of the drug development were appropriately performed and described.

A bioequivalence study was carried out with the highest strength (10 mg/ 80 mg). In support of a biowaiver for the lower strengths (10 mg/ 10 mg, 10 mg/ 20 mg and 10 mg/ 40 mg), comparative dissolution studies were performed. Given the *in vitro* dissolution data, the biowaiver of strengths is considered acceptable from the chemical pharmaceutical point of view. More information on the biowaiver is discussed in section *IV.2.3 Bioequivalence*.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines and is considered to be a standard process. Process validation data on the product have been presented for two batches in accordance with the relevant European guidelines. The process includes the manufacturing of the ezetimibe blend (dispensing, mixing, binder solution preparation, wet granulation, wet milling, drying, sizing, sieving, mixing, sieving/lubrication), the manufacturing of atorvastatin blend (dispensing, mixing, binder solution preparation, wet granulation, drying, sizing, mixing, lubrication), and tablet formation, coating and packaging. The manufacturing process has been described in sufficient detail.

Control of excipients

Specifications for all excipients have been provided. Except for coating agents, the specifications for all other excipients are in line with the Ph. Eur., with additional testing for cellulose. The coating agents are mixtures for which acceptable in-house specifications are adopted. All specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control t2he relevant parameters for the dosage form. The specification includes tests 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. The release and shelf-life limits are identical except for the limits of water content and related substances, which were acceptable.

Satisfactory validation data for the in-house analytical methods have been provided. Batch analytical data from 12 batches (for each strength two commercial scale batches plus one smaller batch), from the proposed production site have been provided, demonstrating compliance with the release specifications. An adequate risk evaluation on presence of nitrosamine impurities has been provided.

Stability of drug product

Stability data on the product have been provided on two commercial scale and one smaller scale batches for each strength, stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in OPA/Al/PVC//Al blisters, placed in carton boxes. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The proposed shelf-life of 2 years and storage condition “This medicinal product does not require any special storage conditions”, are considered acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For lactose monohydrate, certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

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 of 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

Atorvastatin belongs to the pharmacotherapeutic group of statins: lipid-modifying agents and inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. This results in a reduction of hepatocyte cholesterol levels, which results in an up-regulation of low-density lipoprotein (LDL) receptors and, consequently, increased clearance of LDL-cholesterol (LDL-C) from the plasma. Statins also reduce production of apolipoprotein B (ApoB) leading to a 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 its ability to meet recommended treatment guidelines for this parameter, but also its effect on triglyceride levels and its capacity to modify lipoprotein composition in a non-atherogenic manner (a manner which does not increase atheromatous plaques [plaques in arteries]).

Secondary pharmacodynamic effects of atorvastatin include beneficial effects on vessel endothelial tissue, ability to stabilise atheromatous plaques by decreasing inflammation, effects on proliferation of smooth muscle, antithrombotic effects by inhibiting platelet aggregation and stimulation of fibrinolytic mechanisms, improvement of blood viscosity and flow and decreased LDL oxidation.

Ezetimibe + atorvastatin

Ezetimibe and atorvastatin 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 (such as atorvastatin) 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's pharmacokinetics. Although statins are effective in reducing cardiovascular (CV) risk, combination therapy may be required to meet recommended target LDL-C levels.

III.2 Pharmacokinetics

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide. Total ezetimibe concentrations (sum of 'parent' ezetimibe plus ezetimibe-glucuronide) reach a maximum at 1 to 2 hours post-administration, followed by enterohepatic recycling (reuptake in the gut after bile excretion) and slow elimination. The estimated terminal half-life of ezetimibe and ezetimibe-glucuronide is approximately 22 hours. Ezetimibe is excreted primarily in the feces.

Atorvastatin

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. The extent of absorption increases in proportion to the atorvastatin dose. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. The hepatic first-pass effect (hepatic extraction) of atorvastatin is about 42%, which 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. The mean volume of distribution of atorvastatin is approximately 381 litres. 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 found in the literature provided evidence of an extensive metabolism. Feces was the major route of elimination found in an imaging study using radioactivity. Bile was a major route of excretion when using a [^{14}C]-radiolabelled drug, accounting for 73% and 33% of the oral dose in the rat and dog, respectively.

III.3 Toxicology

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 when given multiple doses of 1000 mg/kg/day.

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 not mutagenic 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. During exposure of the female parent rats to high doses of atorvastatin, the development of the rat offspring was delayed and post-natal survival reduced. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in the milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

Ezetimibe + atorvastatin

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.4 Ecotoxicity/environmental risk assessment (ERA)

It was agreed by the member states that, since Ezetimibe/Atorvastatine Stada is intended to replace the usage of single component medicinal products containing the same active ingredients at the same dose, no increase in use is expected and no increase in environmental exposure is anticipated. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

This product is a combined formulation of Ezetrol (ezetimibe) and Lipitor (atorvastatin) which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 a well-known active substances with established efficacy and tolerability profiles. A clinical overview has been provided, which is based on scientific literature. The overview, summarised in this chapter, justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required, besides the bioequivalence study discussed below.

IV.2 Pharmacokinetics

IV.2.1 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 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high-fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered in 10 mg tablets.

Distribution: Ezetimibe is bound 99.7% to human plasma proteins, and ezetimibe-glucuronide is bound 88 - 92% to human plasma proteins.

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. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination: Following oral administration of [^{14}C]-radiolabelled ezetimibe (20 mg) to human subjects, the 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.

IV.2.2 Atorvastatin

Absorption: Atorvastatin is rapidly absorbed after oral administration; C_{max} occurs within 1 to 2 hours. The extent of absorption increases in proportion to the atorvastatin dose. After oral administration, atorvastatin tablets are 95 - 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 pre-systemic clearance in gastrointestinal mucosa and/or hepatic

first-pass metabolism. Administration with food does not affect the rate and extent of absorption.

Distribution: The mean volume of distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥ 98% bound to plasma proteins.

Metabolism: Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and para-hydroxylated derivatives and various beta-oxidation products. Apart from other pathways, these products are further metabolised via glucuronidation. *In vitro*, inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination: Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. 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. 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 to 30 hours due to the contribution of active metabolites.

IV.2.3 Bioequivalence

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ezetimibe/Atorvastatine Stada 10 mg/80 mg film-coated tablets (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference products Ezetrol 10 mg tablets (Merck Sharp & Dohme, Greece) and Lipitor 80 mg film-coated tablets (Pfizer S.A., Belgium).

The choices of the reference products in the bioequivalence study have been justified by comparison of dissolution results and compositions of reference and test products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Biowaiver</u>

A bioequivalence study was performed on the highest strength (10 mg/80 mg) and a biowaiver for the other strengths was pursued. Because the amount of ezetimibe is constant (10 mg) in all the strengths and because both active ingredients are tableted in separate layers of the tablet, the biowaiver is only applicable for atorvastatin.

The following general requirements must be met where a waiver for additional strength is claimed:

a) the pharmaceutical products are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d) appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The requirements for similar manufacturing, and for the same qualitative and proportional quantitative compositions were met. Dissolution results showed similarity between all the additional strengths and the bioequivalence batch (highest strength) at pH 1.2, 4.5 and 6.8. The initial calculation at pH 6.8 for the highest strength had to be adjusted, because the variation on the sampling time was too great (>10%), and removal of the results of any sampling time was not considered acceptable. To compare the dissolution of the different strengths in a correct way, the confidence intervals were then calculated using the Bootstrap method. Those results were acceptable because no samples' dissolution was >85%, all samples (all time points) were included, and the f_2 similarity factor outcomes were >50, and not close to the 50 limit. An f_2 value between 50 and 100% indicates that the two dissolution profiles are similar. The dissolution was investigated according to the EMA Bioequivalence guideline.

In conclusion, a biowaiver could be granted for the 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg Ezetimibe/Atorvastatine Stada strengths.

Bioequivalence study

Design

A randomised, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study was carried out under fasted conditions in 80 healthy subjects (68 male and 12 female), aged 20 to 44 years. Each subject received a single dose of either one 10 mg/80 mg Ezetimibe/Atorvastatine Stada film-coated tablet, or one Ezetrol 10 mg tablet and one Lipitor 80 mg film-coated tablet together. The tablets were orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected within an hour before dosing and at 0.17, 0.25, 0.33, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The SmPC states that Ezetimibe/Atorvastatine Stada may be taken with or without food. From the literature it is known that food does not interact with the absorption of ezetimibe or atorvastatin. Therefore, a food interaction study was not deemed necessary. The bioequivalence study under fasting conditions was in accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98).

The design of the study was acceptable.

Analytical/statistical methods

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

Results

Five subjects did not complete the study. Four of them were withdrawn due to non-compliance during Period II admission, and one was withdrawn due to vomiting after dosing in Period II. This left 75 subjects eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) and 90% confidence intervals of <u>atorvastatin</u>

Treatment N=75	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} ng/mL**	**t_{max} h**
Test	359 ± 198	364 ± 199	96.6 ± 62.8	1.00 (0.50 - 4.50)
Reference	346 ± 150	351 ± 151	97.2 ± 53.4	0.75 (0.33 - 4.50)
***Ratio (90% CI)**	1.01 0.95 – 1.06	--	0.96 0.87 - 1.06	--

AUC_{0-t}	Area under the plasma concentration curve from administration to last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time
C_{max}	Maximum plasma concentration
t_{max}	Time until C_{max} is reached

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) and 90% confidence intervals of <u>unconjugated ezetimibe</u>

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-t}	Area under the plasma concentration curve from administration to last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time
C_{max}	Maximum plasma concentration
t_{max}	Time until C_{max} is reached

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) and 90% confidence intervals of <u>total ezetimibe</u> (ezetimibe + conjugated ezetimibe obtained from ezetimibe phenoxy glucuronide)

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-t}	Area under the plasma concentration curve from administration to last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time
C_{max}	Maximum plasma concentration
t_{max}	Time until C_{max} is reached

**ln-transformed values*

<u>Conclusion on bioequivalence study</u>

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, 10 mg/80 mg Ezetimibe/Atorvastatine Stada film-coated tablets is considered bioequivalent with Ezetrol 10 mg tablets and Lipitor 80 mg film-coated tablets combined. A biowaiver was granted for the 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg ezetimibe/atorvastatine strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Pharmacodynamics

The pharmacodynamics of atorvastatin and ezetimibe are well-established. Ezetimibe belongs to a class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Atorvastatin is an antilipidemic agent, belonging to the drug class of statins which inhibit HMG-CoA reductase. The two mono-components have a different mechanism of action which could provide a synergistic effect when combined. The combined effect of ezetimibe plus atorvastatin was described by the MAH, based on several studies. Other effects which were described included other markers of the lipid profile and secondary effect on the high-sensitivity C-reactive protein. Plus, a study on plaque regression was described.

IV.4 Clinical efficacy

Hypercholesterolemia

For efficacy of ezetimibe, the MAH has discussed three randomised studies, seven other publications and information on the use of ezetimibe in phytosterolaemia (a lipid metabolic disorder). The efficacy of the component atorvastatin has mainly been described by the MAH based on 12 references evaluating comparison to other statins. Further, a placebo controlled study with atorvastatin has been described and reference is made to 17 articles. Data of the use of the combination in France, Greece, Spain, Italy and Germany has been provided.

The use of ezetimibe in combination with statins is included in the approved indication of ezetimibe. Improved LDL-C lowering with the combination of ezetimibe and atorvastatin has been referenced by the MAH through review publications or meta-analyses. The MAH has described studies regarding addition of ezetimibe to other statins, and studies of combining ezetimibe with statins in patients with heterozygous familial hypercholesterolemia. Also, a Japanese study and a study in hyperlipidaemia with type 2 diabetes mellitus patients have been described. These data provide sufficient support for the contribution of both components to the desired therapeutic effect against hypercholesterolemia.

Prevention of cardiovascular events

The MAH has provided information from 11 studies in support of the indication of prevention of cardiovascular (CV) events, including studies on imaging parameters. A study on the CV benefit with the ezetimibe and simvastatin combination was submitted by the MAH. This study was consistent with meta-analyses on the relationship between LDL-C lowering and CV outcomes of statins. Although any original study demonstrating the CV event prevention of this specific combination in the target population has not been described, current robust evidence is available demonstrating the relationship between LDL-C lowering and CV event prevention. Furthermore, the indication of ezetimibe "indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), when added to existing statin therapy or initiated with a statin at the same time" has been extrapolated in a similar manner for the use with other statins (and not restricted to simvastatin). Considering the available clinical evidence and taking into account decisions of other member states in Europe regarding the CV prevention indication for similar products, it was accepted to include the CV indication statement of ezetimibe.

IV.5 Clinical safety

A general description of the safety profile and adverse events of atorvastatin has been described based on labelling data from the FDA and Pfizer. Furthermore, several review/meta-analysis publications compared the safety profile of atorvastatin to other statins. Similarly, for ezetimibe, a general description of the safety profile and adverse events has been described based on labelling data of MSD, MHRA, and Sandoz. Other review articles and specific studies have been referenced to further describe safety aspects of ezetimibe in different type of patients. The adverse events profile as described for the mono-components is applicable to the combination. Reviews/meta-analysis type of studies,

specific studies, and case reports have been presented based on references to inform on the safety profile of the combination in different type of patients.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ezetimibe/Atorvastatine Stada.

Table 4. Summary 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

For this authorisation, reference is made to the clinical studies and experience with the individual mono-component products Ezetrol 10 mg, tablets and Lipitor 10, film-coated tablets 10 mg. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of these reference products; the fixed dose combination can be used instead of the separate mono-components. Sufficient evidence was presented to demonstrate the relationship between LDL-C lowering and CV event prevention and this indication was approved for the combination product. Risk management is adequately addressed and safety data regarding the mono-components can be extrapolated to the combination.

V. USER CONSULTATION

A package leaflet draft (PL) was evaluated via a user consultation study, in which the key safety messages were identified by the participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. However, the tested PL did not contain information on the indication of “prevention of cardiovascular events”. For this reason, the MAH submitted a comparison with several products. In the Netherlands several ezetimibe/simvastatine-containing products are registered with “prevention of cardiovascular events” included as indication. From the new proposal, not patient-friendly wording (“coronary heart disease (CHD)” and “a history of acute coronary syndrome (ACS)”)

was deleted and, instead, the use of 'heart disease' was accepted for the PL. Regarding the interaction with daptomycin, the wording could be bridged to the approved PL of Atozet (atorvastatin/ezetimibe in film-coated tablets), hence no additional reader testing was deemed necessary for this text.

The user testing and bridging information submitted by the MAH has been found acceptable; the PL has been approved.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezetimibe/Atorvastatine Stada 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 considered approvable fixed dose combinations. Ezetimibe and atorvastatin are well known, established active substances, which are used as a combination in clinical practice.

The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate products of Ezetrol 10 mg, tablets (ezetimibe) and Lipitor, film-coated tablets (atorvastatin) of 10 mg, 20 mg, 40 mg, or 80 mg, respectively. The efficacy and safety profile of this new product is considered the same as for the mono-components.

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 these fixed dose combinations are approvable and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 March 2022.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5301/1-4/IA/001	Change in test procedure for the finished product – Minor changes to an approved test procedure	No	28-10-2022	Approved	N/A