COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe/Atorvastatin Hexal 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets
(ezetimibe and atorvastatin calcium trihydrate)

(NL/H/5209/001-004/DC)

Date:31-01-2022

This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatin Hexal. The procedure was finalised at 26 September 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

ACS	Acute coronary syndrome
ApoB	Apolipoprotein B
ASMF	Active Substance Master File
BE	Bioequivalence
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
CV	Cardiovascular
DM	Diabetes mellitus
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
Eg	Extensive gut wall extraction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ESC/EAS	Society of Cardiology/European Atherosclerosis Society
Fa	Intestinal absorption
FDA	Food and Drug Administration
FDC	Fixed dose combination
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference of Harmonisation
LDL	Low-density lipoprotein
LDL-C	LDL-cholesterol
MAH	Marketing Authorisation Holder
NPC1L1	Niemann-Pick C1-Like 1
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VLDL-C	Very low density lipoprotein cholesterol

I. INTRODUCTION

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

Ezetimibe/Atorvastatin Hexal is indicated 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.

Rationale

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

Decentralised procedure

This decentralised procedure concerns an application for the fixed dose combination (FDC) product of atorvastatin and ezetimibe. 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.

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 state (CMS) involved in this procedure was Germany.

Legal base
The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC. The clinical dossier (bioequivalence studies versus the mono products) is in line with the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017). The rationale and justification of the FDC product 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.

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.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Atorvastatin Hexal are film-coated tablets with the following specifications:

Ezetimibe/Atorvastatin Hexal 10 mg/10 mg
White, round, biconvex film-coated tablets.

Ezetimibe/Atorvastatin Hexal 10 mg/20 mg
White, ovaloid, biconvex film-coated tablets.

Ezetimibe/Atorvastatin Hexal 10 mg/40 mg
White, capsule shape, biconvex film-coated tablets.

Ezetimibe/Atorvastatin Hexal 10 mg/80 mg
Yellow, oblong, biconvex film-coated tablets.

Ezetimibe/Atorvastatin Hexal 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets contain as active substances 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg of ezetimibe and atorvastatin (as calcium trihydrate) respectively.

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

The excipients are:

All strengths
Tablet core - cellulose microcrystalline 101 (E460), mannitol (E 421), calcium carbonate (E170), croscarmellose sodium (E468), hydroxypropylcellulose (E463), polysorbate 80 (E433), iron oxide yelllow (E172), magnesium stearate (E470b), povidone K29/32 (E1201) and sodium laurilsulfate (E487).

10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg strengths
Tablet coating - lactose monohydrate, hypromellose 2910 (E464), titanium dioxide (E171) and macrogol 4000 (E1521).

10 mg/80 mg strength
Tablet coating - hypromellose 2910 (E464), titanium dioxide (E171), talc (E553b), macrogol 400 and iron oxide yellow (E172).

The four tablet strengths are dose proportional. The ezetimibe layer remains the same all over the different strengths; the atorvastatin layer is weight proportional.

II.2 Drug Substance

Ezetimibe
One of the active substances is ezetimibe, an established active substance described in the European Pharmacopoeia (Ph.Eur.). 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 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. 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/European Medicines Agency (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 chemical stages. The synthesis description is in sufficient detail and sufficient chemistry is part of the regulatory synthesis route. Specifications of starting materials and intermediates are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The specification of ezetimibe as applied by the applicant 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. 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.

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 polyethylene bags and in accordance with applicable European guidelines, demonstrating the stability of the active substance for 48 months. Based on the data submitted, a retest period has been granted of 48 months with no special temperature storage conditions.

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.

The CEP procedure is used for this active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The drug substance specification as applied by the drug product manufacturers is in general based on the Ph. Eur. monograph for atorvastatin calcium trihydrate and on the additional requirements of the CEP. The following tests are included: appearance, solubility, identification, enantiomeric purity, related substances, sodium, water, assay, residual solvents, residual catalyst, 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.

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 Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified. A quality target product profile (QTPP) and critical quality attributes (CQA) have been defined. The development was based on risk assessments performed in accordance with ICH Q8 (R2) guidance. An extensive and satisfactory description of the risk assessment performed at various development stages has been provided.

The development of the product has been described, 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, manufacturing process development and the performance of comparative dissolution studies complementary to the bioequivalence (BE) study with the 10 mg/ 40 mg, 10/ 20 mg and 10 mg/ 10 mg strengths. All those parts of the drug development were appropriately performed and described. The development of the dissolution method was sufficiently addressed. Bioequivalence studies were carried out on the highest strength (10 mg/ 80 mg) of the product applied for. A biowaiver is requested for the additional 10/ 40 mg, 10/ 20 mg and 10/ 10 mg strengths. Since the provided in vitro dissolution data support the requested biowaiver, the biowaiver of strengths is considered acceptable from the chemical pharmaceutical point of view. During the manufacturing process development, all the process steps and the corresponding process parameters were investigated.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process of ezetimibe/atorvastatin film-coated tablets, which includes manufacturing of atorvastatin blend, manufacturing of ezetimibe blend, tablet formation, coating and packaging, is considered to be a standard process. The manufacturing process has been described in sufficient detail. Mixing/blending times, addition times, granulation times, 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. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average weight, disintegration time, content uniformity, identification, identification of colorants, 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 on twelve batches (three batches per strength), from the proposed production site have been provided, demonstrating compliance with the specification.

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

Stability of drug product

Stability data on the product have been provided for three batches per strength stored at 25°C/60% RH, (up to 18 months) and 30°/65% RH (up to 18 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product for 24 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 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 without 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 for lactose monohydrate 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/Atorvastatin Hexal 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

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.2 Pharmacokinetics

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 pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. The hepatic first-pass effect (Eh about 0.42) of atorvastatin is too small to fully explain the low bioavailability of 14%. It may be a consequence of incomplete intestinal absorption (fa) and/or extensive gut wall extraction (Eg). 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 atorvastatin-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.

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 one to two 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.

III.3 Toxicology

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.4 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe/Atorvastatin Hexal is intended to replace the usage of single component medicinal products containing the same active ingredients at the same dose, no increased in use is expected and no increase in environmental exposure is anticipated. No further ERA studies are considered necessary.

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 calcium trihydrate 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 Ezetimibe/Atorvastatin Hexal 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 European Society of Cardiology/European Atherosclerosis Society (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 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ezetimibe + Atorvastatin 80 mg/10 mg tablet (ELPEN Pharmaceutical Co Inc., Greece) is compared with the pharmacokinetic profile of the reference product Lipitor 80 mg film-coated tablets (Pfizer S.A. Belgium) and Ezetrol 10 mg tablets (Merck Sharp & Dohme, Greece).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions with the EU reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

One bioequivalence study was performed on the ezetimibe/atorvastatin 10/80 mg strength. A statement supporting biowaiver for the other strengths applied for 10/40 mg, 10/20 mg and 10/10 mg is given in the dossier. Ezetimibe/Atorvastatin tablets is a fixed combination product. Tablets are consisting of two layers (bilayer tablets). Each active ingredient is tableted in a separate layer of the tablet (one layer contains atorvastatin, the other layer contains ezetimibe). For the three remaining strengths a biowaiver (10/40 mg, 10/20 mg and 10/10 mg) justification is submitted.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. Therefore, atorvastatin shows linear pharmacokinetics.
According to the CPMP/EWP/QWP/1401/98 Rev1 /Corr** Guideline for the Investigation of Bioequivalence, the following criteria have to be fulfilled in order to meet the biowaiver criteria:

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, colouring agents and flavours are not required to follow this rule).
d. Appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing.

According to the same guideline and in order to support proportionality of the composition for bilayer tablets, each layer may be considered independently.

It was observed that the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths and the composition of the strengths are quantitatively proportional (within each layer).

In vitro dissolution data of the biobatch and all other strengths of the test product confirm the adequacy of waiving additional in vivo bioequivalence testing for the other strengths of the formulation than the one used in the bioequivalence study. It can be therefore concluded that the bioequivalence study with the highest strength can be used for waiving the lower strengths of the proposed formulations. This is due to the fact that all mentioned criteria (a-d) are fulfilled.

Bioequivalence studies

Design

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

Blood samples were collected within one hour before 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, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

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.

Results

Out of a total of 80, 75 subjects were eligible for pharmacokinetic analysis. Two subjects were withdrawn because of a positive drug test. Two other subjects were withdrawn because of a positive alcohol breath test and one subject was withdrawn because of an adverse event (vomiting).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atorvastatin calcium trihydrate (80 mg) 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)**	100.5 (95.4 - 106.0)	--	95.9 (87.0 - 105.8)	--

$AUC_{0-\infty}$ 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
CI confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ezetimibe unconjugated (10 mg) 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)**	91.2 (87.1 - 95.6)	--	78.9 (73.2 - 85.0)	--

$AUC_{0-\infty}$ 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
CI confidence interval

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe (10 mg) 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)**	91.2 (87.1 - 95.6)	--	78.9 (73.2 - 85.0)	--

$AUC_{0-\infty}$	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
CI	confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 80 – 125. Based on the submitted bioequivalence study Ezetimibe/Atorvastatin Hexal is considered bioequivalent with the mono-components Lipitor and Ezetrol.

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

Interaction
The MAH showed sufficiently that there is no significant interaction for ezetimibe and atorvastatin. According to the guideline on clinical development of fixed combination medicinal products (EMA/CHMP/58268/2017) a new FDC is therapeutically equivalent with the respective single drug products in free combination if it contains the same active substances or therapeutic moieties and, clinically, shows the same efficacy and safety as that products, whose efficacy and safety have been established. In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence. Since equivalence in biopharmaceutics quality between the FDC applied for and Sortis and Ezetrol was demonstrated in a respective bioequivalence study bridging of nonclinical and clinical trials associated with the respective reference medicinal products is allowed. No clinically significant pharmacokinetic interactions were seen when ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin. In this respect it needs to be pointed out that ezetimibe is indicated to be coadministered with a statin (Ezetrol SmPC). Furthermore the MAH provided a respective reference to a randomized, three-period, sixsequences cross over study conducted by Patiño-Rodríguez et al. who investigated the influence of ezetimibe on atorvastatin and conversely. Area under the concentration-time curve (AUC) and maximum plasma drug concentration (Cmax) were measured for each drug alone or together and tested for bioequivalence-based hypothesis. The estimation computed (90% confidence intervals) for AUC and Cmax, were 96.04% (85.88–107.42%) and 97.04% (82.36–114.35%), respectively for atorvastatin – ezetimibe combination versus atorvastatin 15/27 alone, while 84.42% (77.19–92.32%) and 95.60% (82.43–110.88%), respectively, for atorvastatin – ezetimibe combination versus ezetimibe alone were estimated. These results also show that atorvastatin and ezetimibe have no relevant pharmacokinetic drug–drug interaction.

IV.3 Pharmacodynamics

The pharmacodynamics of atorvastatin and ezetimibe is well-established. Atorvastatin is an antilipidemic agent, belonging to the drug class of statins which inhibit HMG-CoA reductase. Ezetimibe belongs to a class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. The two mono-components have a different mechanism of action which could provide a synergistic effect when combined. The combined effect of atorvastatin plus ezetimibe is described based on several studies. Also, other effects including other markers of the lipid profile and secondary effect on high-sensitivity C-reactive protein (hsCRP) are described. Further, a study on plaque regression is described. The use of ezetimibe in combination with statins is already included in the approved indication of ezetimibe. Improved LDL-C lowering with the combination of ezetimibe and atorvastatin has been referenced by review publications or meta-analyses. Addition of ezetimibe to other statins has also been mentioned including references of studies). Studies of combining ezetimibe with statins in heterozygous familial hypercholesterolemia (HeFH) have also been described. Also, a Japanese study, and a study in hyperlipidemia with type 2 diabetes mellitus (DM) have been described. These data provide sufficient support for the contribution of both components to the desired therapeutic effect.

IV.4 Clinical efficacy

The efficacy of the monocomponent atorvastatin has mainly been described based on 12 references evaluating comparison to other statins. Further, a placebo controlled study with atorvastatin has been described. Further, reference is made to 17 articles without further description. For ezetimibe, reference is made to the product information describing three randomised studies and references to seven other publications. Based on these references the efficacy of atorvastatin and ezetimibe have sufficiently been described. For the combination of statins with ezetimibe specific studies in patients with increased CV risk including hypercholesterolemia as a risk factor showing improved efficacy for LDL-C lowering have been described and/or referenced (Sweeney and Johnson, 2007, Bennett et al., 2004, Hamilton-Craig et al., 2010, SmPC reference, Inoue et al., 2010). Specific studies for the combination of atorvastatin with ezetimibe have also been mentioned as meta-analysis or combination of different studies (Mikhailidis et al., 2007, Bennett et al., 2004, Davidson et al., 2004), review article (Ai et al., 2018) or specific (post-hoc) studies (Blagden and Chipperfield, 2007, Athyros et al., 2008). Studies of combining ezetimibe with statins in HeFH 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 DM have been described.

According to the principles of the “Guideline on clinical development of fixed combination medicinal products” [EMA/CHMP/158268/2017] the basic scientific requirements for any fixed combination medicinal product are:
1. Justification of the pharmacological and medical rationale for the combination
2. Establishment of the evidence base for relevant contribution of all active substances to the desired therapeutic effect and a positive risk-benefit 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 pharmacologic 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, there is substantial clinical experience with the combination of atorvastatin and ezetimibe as demonstrated by description data of the use of the combination in France, Greece, Spain, Italy and Germany. Moreover, 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.

Relevant contribution of all active substances to the desired therapeutic effect
The use of ezetimibe in combination with statins is already included in the approved indication of ezetimibe. Improved LDL-C 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, T. Pearson et al., 2005; T. A. 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 HeFH 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 DM have been described. These data provide sufficient support for the contribution of both components to the desired therapeutic effect.

IV.5 Clinical safety

IV.5.1 Adverse events

Atorvastatin
A general description of the safety profile and adverse events of atorvastatin has been described based on labelling data from the Food and Drug Administration (FDA) and Pfizer. These adverse events are also listed in the SmPC of Sortis/Lipitor and can be found in table 4.

Table 4. Adverse drug reactions to atorvastatin

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

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

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

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).

Ezetimibe

Similarly, for ezetimibe, a general description of the safety profile and adverse events has been described based on labelling data of MHRA, and Sandoz. Further, some further review articles, (Sweeney and Johnson, 2007, or specific studies (Almutairi et al., 2009, Bays et al., 2001, Dujovne et al., 2002, Patel et al., 2007) have been referenced to further describe safety

aspects of ezetimibe in different type of patients. Adverse events associated with ezetimibe can be found in table 5.

Table 5. Tabulated list of adverse reactions (clinical studies and post-marketing experience) (Merck Sharp & Dohme Limited, 2016; MHRA, 2017)

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

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

Atorvastatin + Ezetimibe

The adverse events profile as described for the mono-components is also applicable to the combination. Further reviews/meta-analysis type of studies (Bennett et al., 2004, Lipka et al., 2004), particular 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 type of patients.

Table 6. : Drug-related clinical and laboratory adverse drug reactions.* (Teramoto et al., 2012).

System Organ Class	10 mg Ezetimibe + 10 mg Atorvastatin	20 mg Atorvastatin	2.5 mg Rosuvastatin
N	47	46	32
	←----------n (%)----------→		
	4 (8.5)	5 (10.9)	2 (6.3)
Eye disorders	1 (2.1)	0 (0.0)	0 (0.0)
Vision blurred	1 (2.1)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (2.1)	0 (0.0)	0 (0.0)
Stomatitis	1 (2.1)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (3.1)
Hepatic function abnormal	0 (0.0)	0 (0.0)	1 (3.1)
Infections and infestations	1 (2.1)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (2.1)	0 (0.0)	0 (0.0)
Investigations	3 (6.4)	4 (8.7)	1 (3.1)
Bilirubin conjugated increased	0 (0.0)	1 (2.2)	0 (0.0)
Blood bilirubin increased	0 (0.0)	1 (2.2)	0 (0.0)
Blood creatinine phosphokinase increased	2 (4.3)	0 (0.0)	0 (0.0)
Blood potassium increased	0 (0.0)	1 (2.2)	1(3.1)
Blood thyroid-stimulating hormone increased	1 (2.1)	1 (2.2)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	1 (2.2)	0 (0.0)
Platelet count decreased	0 (0.0)	1 (2.2)	0 (0.0)
White blood cell count increased	1 (2.1)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (2.2)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (2.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (2.1)	0 (0.0)	0 (0.0)
Muscle spasms	1 (2.1)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (2.1)	0 (0.0)	0 (0.0)
Tremor	1 (2.1)	0 (0.0)	0 (0.0)

*Adverse reactions were coded according to version 13.0 of the Medical Dictionary for Regulatory Activities system organ class and preferred terms.

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/Atorvastatin Hexal.

Table 7. Summary table of safety concerns as approved in RMP

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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lipitor and Ezetrol. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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

Ezetimibe/Atorvastatin Hexal 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 generic forms of Lipitor and Ezetrol. Lipitor and Ezetrol are well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ezetimibe/Atorvastatin Hexal with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 September 2021.

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

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