IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ezetimibe/Atorvastatin DOC Generici
Ezetimibe
Atorvastatin calcium trihydrate
PA2244/003/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ezetimibe/Atorvastatin DOC Generici 10mg/10mg tablet from DOC Generici S.r.l., on 05/06/2026 for

Prevention of Cardiovascular Events
Ezetimibe/Atorvastatin DOC Generici 10mg/10mg tablets is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Hypercholesterolaemia
Ezetimibe/Atorvastatin DOC Generici 10mg/10mg tablets is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate.
- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetimibe/Atorvastatin DOC Generici is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g. low-density lipoprotein [LDL] apheresis).

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a "generic' application.

This means that Marketing Authorisation Holder Organon France registered on the 12th of September 2014 for LIPTRUZET comprimé pelliculé, Atozet 10 mg/10 mg, film-coated tablets as an authorised medicinal product in Europe containing the active substances Ezetimibe and Atorvastatin.

DOC Generici S.r.l. with Ireland as the Reference Member State (RMS) in this Decentralized Procedure, Doc Generici S.r.l. is applying for the Marketing Authorisations for Atozet 10mg/10mg film-coated tablets with CSM as Italy.

Ezetimibe/Atorvastatin DOC Generici 10mg/10mg tablets has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as for LIPTRUZET comprimé pelliculé, Atozet 10 mg/10 mg film-coated tablets.

Subject to prescription which may be renewed is proposed. This is in line with the reference medicinal product in Ireland and is acceptable to the RMS.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Ezetimibe/Atorvastatin DOC Generici 10mg/10mg
Name(s) of the active substance(s) (INN)	Ezetimibe, Atorvastatin calcium trihydrate
Pharmacotherapeutic classification (ATC code)	C10BA05
Pharmaceutical form and strength(s)	10mg/10mg
Marketing Authorisation Number(s) in Ireland	PA2244/003/001
Marketing Authorisation Holder	DOC Generici S.r.l.,
MRP/DCP No.	IE/H/1354/001-004/DC
Reference Member State	IE
Concerned Member State	IT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Ezetimibe/Atorvastatin 10mg/10mg tablets.

II.2 Drug substance

The active substances are established active substance described in the European Pharmacopoeia and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substances specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specifications has been provided.

II.3 Medicinal product

P.1 Composition

The tablets contain either 10mg/10mg of Ezetimibe/Atorvastatin.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Ezetimibe/Atorvastatin 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Liptruzet comprimé pelliculé, Atozet 10 mg/10 mg film-coated tablets by Organon France registered since the 12th of September 2014 on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of ezetimibe and atorvastatin calcium trihydrate are well known.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Ezetimibe/Atorvastatin DOC Generici 10mg/10mg Tablet is intended for generic substitution, this will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of ezetimibe and atorvastatin calcium trihydrate are well known. As ezetimibe and atorvastatin calcium trihydrate are widely used, well-known active substances, the applicant has not provided additional studies, and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ezetimibe and Atorvastatin are both well-known active substances with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product in the RMS Atozet 10mg/10mg film-coated tablets marketed by IE MAH.

For this generic application, the applicant has submitted one pivitol bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatin + Ezetimibe 80 mg/ 10
mg film-coated Tablet is compared with the pharmacokinetic profile of the reference product Atozet 80 mg/ 10 mg film coated Tablet.

A Randomized, Open Label, Balanced, Two-Treatment, Two-Sequence, Two-Period, Single Dose, Crossover Oral Comparative Bioequivalence Study was carried out comparing Atorvastatin + Ezetimibe 80 mg/ 10 mg film-coated Tablet of ELPEN Pharmaceutical Co Inc., Greece and Atozet 80 mg/ 10 mg film coated Tablet of MSD Sharp & Dohme B.V., Haar, Germany in Healthy Adult Human Subjects Under Fasting Conditions.

Atorvastatin in Project 20-VIN-0123

Treatment	**AUC_{0-t}** xg/ml/h	**C_{max}** xg/ml
Test	318.900 ± 197.5845	91.786 ± 86.5647
Reference	323.430 ± 198.0091	91.894 ± 78.5304
***Ratio (90% CI)**	99.92 (94.71 - 105.42%)	100.64 (91.54 - 110.63%)
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} canbe reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products **$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported whenAUC_{0-72h} is reported instead of AUC_{0-t} **C_{max}**Maximum plasma concentration **t_{max}** Time until Cmax is reached		

**ln-transformed values*

Total Ezetimibe in Project 20-VIN-0123

Treatment	**AUC_{0-t}** xg/ml/h	**C_{max}** xg/ml
Test	1146.647 ± 553.8922	143.130 ± 58.5513
Reference	1189.544 ± 539.8966	164.367 ± 63.4483
***Ratio (90% CI)**	93.65 (89.49% - 98.00%	85.53 (81.26% - 90.02%)
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} canbe reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products **$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported whenAUC_{0-72h} is reported instead of AUC_{0-t} **C_{max}**Maximum plasma concentration		

t_{max} Time until Cmax is reached		

Based on the pharmacokinetic parameters of active substances these drug products are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Biowavier of strength
Similarity at all lower strengths is again stated by the applicant to been demonstrated against the higher strength the biobatch. A biowaiver, based on the criteria outlined in the Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr, has been proposed for the 10 mg/10 mg, 10mg /20 mg and 10mg /40mgstrengths. This is considered acceptable.

Atorvastatin and Ezetimibe are well known active substances with established efficacy and tolerability. This medicinal product is the same as Atozet 10mg/10mg film-coated tablets on the European market.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Atozet 10mg/10mg film-coated tablets marketed by IE MAH.

Compliance with GCP
The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

No new Pharmacokinetics data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy

No new efficacy data were submitted and none are required for an application of this type.

IV.5 Clinical Safety

No new safety data were submitted and none are required for an application of this type.

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 DOC Generici 10mg/10mg film-coated tablets.

Safety specification

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)

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This application concerns a generic medicinal product Ezetimibe/Atorvastatin DOC Generici 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg tablets referencing LIPTRUZET comprimé pelliculé, Atozet 10 mg/10 mg, 20 mg/10 mg, 40 mg / 10 mg & 80 mg/ 10mg film-coated tablets as an authorised medicinal product in Europe containing the active substances Ezetimibe and Atorvastatin since the 12th of September 2014.

Bioequivalence with the reference medicinal product has been demonstrated. No clinically relevant differences in efficacy or safety are anticipated in the proposed indication. The benefit–risk balance is favourable.

V. OVERALL CONCLUSIONS

Ezetimibe/Atorvastatin DOC Generici 10mg/10mg tablets is a generic form of LIPTRUZET comprimé pelliculé, Atozet 10 mg/10 mg film-coated tablets. LIPTRUZET comprimé pelliculé, Atozet 10 mg/10 mg film-coated tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Ezetimibe/Atorvastatin DOC Generici 10mg/10mg tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted marketing authorisations.

Following MRP/DCP procedure:

None

VI. REVISION DATE

11.05.2031