COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe/Atorvastatine axunio 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets (ezetimibe and atorvastatin (as atorvastatin calcium trihydrate))

NL/H/5682/001-004/DC

Date: 22 May 2024

This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatine axunio 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets. The procedure was finalised on 29 November 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
HoFH	Homozygous Familial Hypercholesterolaemia
ICH	International Conference of Harmonisation
LDL	Low-density lipoprotein
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

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

The product is indicated for:
Prevention of Cardiovascular Events
Ezetimibe/atorvastatin axunio is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease and a history of acute coronary syndrome, either previously treated with a statin or not.

Hypercholesterolaemia
Ezetimibe/atorvastatin axunio 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 axunio 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).

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP), Atozet 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets, which has been registered in Germany via decentralised procedure (DE/H/3895/001-004/DC) since 12 September 2014.

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

Scientific advice
Scientific advice was sought prior to this application from Member State Germany.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Atorvastatine axunio is a white to off white, capsule shaped, biconvex film-coated tablet. Each tablet contains 10 mg ezetimibe and 10 mg, 20 mg, 40 mg or 80 mg atorvastatin

(as atorvastatin calcium trihydrate).

10 mg/10 mg tablet: dimension of approximately 13 mm x 5 mm, one side debossed with “1T” and plain on the other side.
10 mg/20 mg tablet: dimension of approximately 15 mm x 6 mm, one side debossed with “2T and plain on the other side.
10 mg/40 mg tablet: dimension of approximately 16 mm x 6 mm, one side debossed with “4T” and plain on the other side.
10 mg/80 mg tablet: dimension of approximately 19 mm x 8 mm, biconvex, one side debossed with “8T” and plain on the other side.

The excipients are:
Tablet core Ezetimibe Layer - lactose monohydrate, croscarmellose sodium, povidone, sodium laurilsulfate (E487), cellulose (microcrystalline) and magnesium stearate.

Tablet core Atorvastatin Layer - lactose monohydrate, cellulose (microcrystalline), calcium carbonate, croscarmellose sodium, hydroxypropylcellulose, polysorbate 80, silica (colloidal anhydrous) and magnesium stearate.

Film-coating – Hypromellose, lactose monohydrate, titanium dioxide, macrogol and talc.

The tablet core layers are manufactured separately. The ezetimibe layer remains the same at the different strengths, however the atorvastatin layer varies at the different strengths and is dose proportional.

The tablets are packed in Alu-Alu (aluminium-aluminium) blisters.

II.2 Drug Substance

The active substances are atorvastatin calcium trihydrate and ezetimibe.

Atorvastatin calcium trihydrate
The active substance is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder of polymorphic form I, and is very slightly soluble in water. For this product, polymorphic form I is consistently produced.

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

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included. A description of the micronisation process is provided as the responsible site for micronisation is stated.

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. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for seventeen production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 months. Based on the data submitted, a retest period could be granted of 4 years when stored under the stated conditions.

Ezetimibe

The active substance is an established active substance described in the US Pharmacopeia (USP). Ezetimibe is a white to off-white crystalline powder, which is soluble in methanol but practically insoluble in water. The drug substance exhibits polymorphism, the manufacturer produces polymorphic form X. Ezetimibe contains three asymmetric carbon atoms and therefore exhibits optical isomerism. For this product, polymorphic form X is consistently produced.

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

Manufacturing process

The manufacturing process consists of five stages. Four starting materials and, in the last step, two solvents are used. No class 1 organic solvents or heavy metal catalysts are used during the manufacture. Micronisation is performed by the drug substance manufacturer. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and contains tests for description, identification, water determination, specific optical rotation, melting range, sulphated ash, assay, related substances, chiral purity, residual solvents and particle size. The specification acceptable. No test for microbiological quality is included as omission

is adequately justified. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for nine production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of five years when stored under the stated conditions.

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 development of the product has been described, the choice of excipients is justified, and their functions explained. The main development studies were formulation and process development, dissolution method development and the performance of comparative dissolution studies at three pHs complementary to the bioequivalence study carried out on ezetimibe/atorvastatin 10 mg /80 mg strength and in support of the biowaiver of strengths claimed for the additional 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg strengths. The pharmaceutical development of the product has been adequately performed. The provided comparative dissolution data support the requested biowaiver.

Manufacturing process
The manufacturing process of Ezetimibe/Atorvastatin film-Coated tablets, which includes manufacturing of Ezetimibe granules (dispensing, sifting, binder solution preparation, granulation, sifting, blending, lubrication), manufacturing of Atorvastatin granules (dispensing, sifting, binder solution preparation, granulation, sifting, wet milling, drying, sifting, milling, blending, lubrication), tablet formation (compression, coating) and packing is considered to be a conventional process.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph. Eur. requirements. 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 description, identification, assay, average mass, content uniformity, water content, dissolution, related substances and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three commercial scale batches stored at 25°C/ 60% RH (6 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability study has been performed in accordance with the ICH Q1B. The proposed product is not photosensitive. On basis of the data submitted, a shelf life was granted of 30 months. No specific storage conditions needed to be included in the SmPC or on the label.

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

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate 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 axunio 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 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe/Atorvastatine axunio is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Atozet which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Atorvastatin calcium trihydrate and ezetimibe are well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one pivotal and one pilot bioequivalence study, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted one pivotal and one pilot bioequivalence study in which the pharmacokinetic profile of the test product Ezetimibe/Atorvastatine axunio 10 mg/80 mg film-coated tablets (axunio Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Atozet 10 mg/80 mg film-coated tablets (Organon Healthcare GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The MAH provided comparative dissolution data to justify biowaivers for the lower strengths of 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg (ezetimibe/atorvastatin), based on these criteria (according to the EMA Bioequivalence guideline):

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 pharmaceutical products are manufactured by the same manufacturing process, the qualitative composition of the different strengths/layers is the same and the composition of the strengths/layers are quantitatively proportional.

Comparative dissolution experiments in three dissolution media (pH 1.2, 4.5 and 6.8) with the lower strengths were submitted by the MAH. The MAH adequately substantiated that sink conditions during the comparative dissolution experiments are not met for the tablet with the

highest strength of atorvastatin (ezetimibe/atorvastatin 10/80 mg) in the pH 1.2 and 4.5 media, resulting in F2-values <50. Therefore, the comparative dissolution experiments were repeated with equivalent doses of atorvastatin (e.g. ezetimibe/atorvastatin 8x10 mg/10 mg, 4x10 mg/20 mg and 2x10 mg/40 mg vs 1x10/80 mg). These experiments comparing equivalent doses of atorvastatin demonstrated F2-values >50 in pH 1.2 and 4.5 media for all lower strengths. Furthermore,. all tablets had a dissolution time <15 minutes in the pH 6.8 medium.

Therefore, it can be concluded that a waiver for the lower strengths of ezetimibe/atorvastatin 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg is justified.

Bioequivalence studies

Pivotal study

Design

An open label, randomised, four-period, two-treatment, two-sequence (TRTR/RTRT), fully replicate, crossover, balanced, single dose oral bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-44 years. Each subject received a single dose (10 mg/80 mg) of one of the two ezetimibe and atorvastatin formulations. The tablet was orally administered with 240 mL water after an overnight fasting of at least 10 hours. There were four dosing periods, separated by a washout period of at least 12 days.

Blood samples were collected pre-dose and at 0.25, 0.33, 0.42, 0.5, 0.67, 0.75, 0.83, 1.0, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Ezetimibe and atorvastatin calcium trihydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ezetimibe and atorvastatin calcium trihydrate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

One subject was discontinued from the study, because of positive testing during the urine scan for drugs of abuse (benzodiazepines) on check-in day of period 3. Therefore this subject only completed two periods and was excluded for the intra-subject variability calculations (SWR). Another subject was discontinued only for period 3 (subject withdrew his consent due to personal reason on check-in day of period 3) and completed three periods of the study of which two periods with the reference product. Therefore all 40 subjects were included in the

pharmacokinetic and statistical analyses for bioequivalence and 39 subjects were included for the statistical analysis for intra-subject variability.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ezetimibe, 10 mg under fasted conditions.

Treatment N=40	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	794 ± 237	828 ± 264	107 ± 28	0.83 (0.50- 3.00)
Reference	840 ± 303	873 ± 328	122 ± 39	0.83 (0.50- 5.00)
***Ratio (90% CI)**	0.96 (0.92 – 1.04)	-	0.89 (0.92 – 1.13)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atorvastatin, 80 mg under fasted conditions.

Treatment N=40	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	221 ± 102	226 ± 102	58 ± 30	1.00 (0.50- 4.50)
Reference	227 ± 107	231 ± 107	59 ± 39	1.67 (0.50- 4.52)
***Ratio (90% CI)**	0.98 (0.92 – 1.04)	-	1.02 (0.92 – 1.13)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ezetimibe/Atorvastatine axunio, 10/80 mg is considered bioequivalent with Atozet, 10/80 mg. The results of the pilot study will be considered as supportive data.

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 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 axunio.

Table 5. 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.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Atozet. No new clinical studies were conducted. The MAH demonstrated through a pivotal and a pilot 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Atozet 10 mg/10 mg, 10mg/20 mg, 10 mg/40 mg, 10 mg/80 mg film-coated tablets, DE/H/3895-98/001-004/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezetimibe/Atorvastatine axunio 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

Atozet 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets. Atozet is a well-known medicinal product 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ezetimibe/Atorvastatine axunio with the reference product, and have therefore granted a marketing authorisation. The decentralised/mutual recognition procedure was finalised with a positive outcome on 29 November 2023.

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
-	-	-	-	-	-