COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe/Atorvastatine Althera Laboratories 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/5889/001-004/DC

Date: 18 June 2026

This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatine Althera Laboratories 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 3 September 2025. 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
ICH	International Conference of Harmonisation
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 Althera Laboratories 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg film-coated tablets, from Althera Laboratories Limited.

The product is indicated for:
Prevention of Cardiovascular Events
Ezetimibe/Atorvastatine Althera Laboratories is indicated to reduce the risk of cardiovascular events (see section 5.1 of SmPC) 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/Atorvastatine Althera Laboratories 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/Atorvastatine Althera Laboratories 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 by Organon N.V. via a decentralised procedure (DE/H/3895/001-004/DC)) since 17 October 2014.

The concerned member states (CMS) involved in this procedure were Portugal and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe/Atorvastatine Althera Laboratories 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg are film-coated tablets. The four strengths of the film-coated tablets can be distinguished by size, shape and debossing and are as follows:

Ezetimibe/Atorvastatine Althera Laboratories 10 mg/10 mg
Pink, oval (approximately 12.7 mm x 6.8 mm), debossed with "V1" on one side. Each tablet contains 10 mg of ezetimibe and 10 mg of atorvastatin (as calcium trihydrate) as active substances.

Ezetimibe/Atorvastatine Althera Laboratories 10 mg/20 mg
Pink, oval (approximately 14.2 mm x 7.2 mm), debossed with "V2" on one side. Each tablet contains 10 mg of ezetimibe and 20 mg of atorvastatin (as calcium trihydrate) as active substances.

Ezetimibe/Atorvastatine Althera Laboratories 10 mg/40 mg
Pink, oval (approximately 15.6 mm x 8.2 mm), no debossing. Each tablet contains 10 mg of ezetimibe and 40 mg of atorvastatin (as calcium trihydrate) as active substances.

Ezetimibe/Atorvastatine Althera Laboratories 10 mg/80 mg
Pink, capsule shaped (approximately 19.7 mm x 9.6 mm), debossed with "VII" on one side. Each tablet contains 10 mg of ezetimibe and 80 mg of atorvastatin (as calcium trihydrate) as active substances.

The excipients are:
Tablet core – lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium laurilsulfate, magnesium stearate, red iron oxide (E172), calcium carbonate, hydroxypropyl cellulose, polysorbate 80 and colloidal anhydrous silica.
Film-coating – hypromellose, titanium dioxide (E171), macrogol 4000 and red iron oxide (E172).

The drug product corresponds to a film-coated tablet intended for immediate release containing two active substances, atorvastatin calcium trihydrate and ezetimibe in separate layers in the same dosage form. The 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 weight proportional.

The film-coated tablets are packed in oriented polyamide/aluminium/polyvinyl chloride//aluminium (OPA/Alu/PVC//Alu) blisters.

II.2 Drug Substance

Ezetimibe
Ezetimibe is an active substance not described in the Ph.Eur. Ezetimibe is a white crystalline powder, which is freely soluble in ethanol, methanol and acetone but practically insoluble in water. The drug substance exhibits polymorphism. It has been adequately demonstrated by X-Ray diffraction studies that there is no change in active substance polymorphic form during manufacturing or storage of the drug substance or drug product. 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/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 a regulatory synthesis route. 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 is considered adequate to control the quality of the active substance. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
Stability data on the active substance have been provided for three lower scale and three higher scale batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 48 months when stored under the stated conditions.

Atorvastatin calcium trihydrate
Atorvastatin calcium trihydrate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). Atorvastatin calcium trihydrate has two chiral centres and therefore exhibits optical isomerism. Atorvastatin calcium trihydrate is a crystalline powder and is very slightly soluble in water. For this product, polymorphic form 1 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.

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. and the additional requirements of the CEP. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The choice of excipients is justified and their functions are explained. The main development studies were the characterisation of the reference product, formulation development, dissolution method development, manufacturing process development and performing comparative dissolution studies complementary to the bioequivalence (BE) study and comparative dissolution studies between the strength used in the BE study (i.e. 10 mg/80 mg) and the additional 10/10 mg, 10/20 mg and 10/40 mg strengths, in view of the biowaiver of strengths.
The pharmaceutical development has been adequately performed.

Manufacturing 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 per strength in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
In-house specification, including a description of the analytical methods, has been provided for the Opadry Pink coating material. Tests for Identification (by IR) and Ash content of Opadry Pink are performed according to the corresponding Ph. Eur. procedures. Compliance of iron oxide red with regulation 231/2012 is confirmed. All other excipients are in line with the Ph. Eur. requirements and the relevant functionality related characteristics. 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 of atorvastatin and ezetimibe, water content, assay, uniformity of dosage units, dissolution, related substances, identification test for ferric oxide and microbial load test. 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 pilot scaled batches per strength 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 pilot scaled batches per strength stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies show that the drug product is photostable. 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 Althera Laboratories 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)

At the time of submission of this application, before 1st of September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable yet. At the time of approval the conclusion for this medicinal product was:
Since Ezetimibe/Atorvastatine Althera Laboratories 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

Ezetimibe and atorvastatin calcium trihydrate are well-known active substances 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 bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ezetimibe/Atorvastatine Althera Laboratories 10 mg/80 mg film-coated tablets (Althera Laboratories Limited, Ireland) 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

For the additional strengths (Ezetimibe/Atorvastatine Althera Laboratories 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg) a biowaiver is claimed, based on the following general requirements (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 is the same and the composition of the strengths are quantitatively proportional.

The dissolution was investigated according to the EMA Bioequivalence guideline, complementary to the bioequivalence study. The calculated f2 similarity factor values were within criteria (>50%). An f2 value between 50 and 100% suggests that the two dissolution profiles are similar. The provided comparative dissolution data support the requested biowaiver, therefore the biowaiver for the additional strengths is granted.

Bioequivalence study

Study C21196

Design

A single-dose, open label, balanced randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 76 healthy male subjects, aged 20-43 years. Each subject received a single dose (10 mg/80 mg) of one of the two ezetimibe/atorvastatin calcium trihydrate formulations. The tablet was orally administered with 150 ml water after an overnight fast of at least 8 hours. There were two dosing periods, separated by a washout period of 14 days for one group of subjects and 15 days for the other group of subjects.

Blood samples were collected pre-dose and at 0.25, 0.33, 0.50, 0.67, 0.75, 1, 1.33, 1.50, 1.67, 2, 2.50, 3, 4, 5, 6, 6.50, 8, 12, 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
All 76 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=76	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	972 ± 409	988 ± 416	141 ± 55	1.00 (0.33 – 2.50)
Reference	1044 ± 447	1062 ± 453	160 ± 68	1.00 (0.33 – 3. 00)
***Ratio (90% CI)**	0.93 (0.89 – 0.97)	-	0.89 (0.84 – 0.94)	-

$AUC_{0-\infty}$	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 calcium trihydrate, 80 mg under fasted conditions.

Treatment N=76	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	366 ± 181	372 ± 181	80 ± 53	0.75 (0.50 – 6.00)
Reference	422 ± 230	428 ± 230	82 ± 54	1.50 (0.50 – 6.00)
***Ratio (90% CI)**	0.89 (0.83 – 0.94)	-	1.00 (0.88 – 1.14)	-

$AUC_{0-\infty}$	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 study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study

Ezetimibe/Atorvastatine Althera Laboratories 10 mg/80 mg is considered bioequivalent with Atozet 10 mg/80 mg.

The results of study C21196 with 10 mg/80 mg formulation can be extrapolated to other strengths 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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

IV.3 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 Althera Laboratories. At the time of approval, the most recent version of the RMP was version 0.2 dated 4 September 2024.

Table 3. 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. 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 3 participants, followed by two rounds with 10 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/Atorvastatine Althera Laboratories 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. 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 Althera Laboratories with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 September 2025.

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
N/A	N/A	N/A	N/A	N/A	N/A