LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Altomib
(ezetimibe, atorvastatin calcium trihydrate)

SE/H/2513/01-04/DC

This module reflects the scientific discussion for the approval of Altomib. The procedure was finalised on 2025-02-19. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Altomib, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg, Film-coated tablet.

The active substance is ezetimibe, atorvastatin calcium trihydrate, atorvastatin. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Altomib, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg, Film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and ES, IE and IT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Atozet, 10 mg/10 mg, Film-coated tablet authorised in SE since 2014, with N.V. Organon as marketing authorisation holder.

The reference product used in the bioequivalence study is Atozet, 10 mg/80 mg, Film-coated tablet from BG with Organon Healthcare GmbH as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS ES: Atozet, 10 mg/ 10 mg, Film-coated tablet authorised in SE since 2014, with N.V. Organon as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of ezetimibe and atorvastatin are well known. As ezetimibe and atorvastatin are a widely used, well-known active substances, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Altomib is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Altomib from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Altomib (Ezetimibe/Atorvastatin) with the reference product Atozet.

Pharmacokinetic properties of the active substances

Ezetimibe
Absorption: After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high-fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as 10-mg tablets. Ezetimibe can be administered with or without food.

Elimination: Elimination half-life for ezetimibe and ezetimibe-glucuronide are approximately 22 hours.

Atorvastatin
Absorption: 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. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is

approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

The pharmacokinetics of atorvastatin is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the reference product.

Linearity: The SmPC of the reference product states that the extent of absorption increases in proportion to atorvastatin dose. However, it is not clear if this refers to atorvastatin or atorvastatin equivalents (atorvastatin + active metabolites).

Elimination: Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours.

Study C21196

Methods

This was a single-dose, two-way crossover study conducted in 76 healthy volunteers (76 completed), comparing Ezetimibe/Atorvasatin, 10 mg/80 mg, tablet with Atozet, 10 mg/80 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of ezetimibe, ezetimibe phenoxy β-D-glucuronide and atorvastatin were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 18-Jul-2022 and 12-Aug-2022.

Results

The results from the pharmacokinetic and statistical analysis are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for ezetimibe (unconjugated), n=76.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**91.552 ± 36.9726**	**13.799 ± 7.0241**	**0.670 (0.330-5.000)**
Reference	**97.747 ± 39.3078**	**14.987 ± 8.0096**	**0.843 (0.330-5.000)**
***Ratio (90% CI)**	**93.48 (88.93-98.26)**	**93.44 (86.21-101.28)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for total ezetimibe (ezetimibe + ezetimibe glucuronide), n=76.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**972.475 ± 409.0315**	**140.684 ± 54.9994**	**1.000 (0.330-2.500)**
Reference	**1044.391 ± 446.7881**	**160.368 ±67.8616**	**1.000 (0.330-3.000)**
***Ratio (90% CI)**	**92.51 (88.58-96.62)**	**89.09 (84.31-94.15)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for atorvastatin, n=76.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**365.505 ± 180.5916**	**79.790 ± 53.4380**	**0.750 (0.500-6.000)**
Reference	**422.111 ± 229.9793**	**81.656 ± 54.1380**	**1.500 (0.500-6.000)**
***Ratio (90% CI)**	**88.79 (83.43-94.48)**	**99.96 (87.69-113.96)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) and the Ezetimibe tablet 10 mg product-specific bioequivalence guidance (EMA/CHMP/802491/2018). The bioanalytical methods were adequately validated.

Ezetimibe undergoes extensive pre-systemic metabolism into ezetimibe-glucuronide. Because of extensive hepatic recirculation, the exposure of ezetimibe is less representative to evaluate the rate of absorption than the metabolite. Assessment of bioequivalence should be based on the total ezetimibe (parent ezetimibe + ezetimibe glucuronide) and the parent drug atorvastatin. Results for unconjugated ezetimibe can be considered supportive.

Based on the submitted bioequivalence study, Altomib is considered bioequivalent with Atozet.

Absence of studies with the additional strengths of 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled and since the pharmacokinetics of atorvastatin is linear between 10 mg and 80 mg. For quality aspects of biowaiver, see the quality assessment report.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan

The MAH has as requested by the RMS submitted an updated 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 Altomib.

Part II Safety specification, updated

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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)

These safety concerns are aligned to DE/H/6605/001-004 Atorimib, Apontis Pharma GmbH & Co. KG, Version 1.1 dated 16 Jan 2019.

RMS comment
The proposed updated summary table is identical with the table of safety concerns for Atorimib DE/H/6605/001-004, RMP Version 1.1 dated 16. Jan 2019. For Atorimib no *Important potential risks* are included. (url: Heads of Medicines Agencies: RMP (hma.eu))

Issue resolved.

Part III Pharmacovigilance Plan

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

Part V Risk minimisation measures
The safety information in the proposed product information is aligned to that of the individual active substances within the product

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 04 September 2024 is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 results show that the package leaflet 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

The quality of the generic product, Altomib is found adequate. There are no objections to approval of Altomib, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Altomib, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg, Film-coated tablet was positively finalised on 2025-02-19.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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