*CMDh/223/2005*
*February 2014*

# Public Assessment Report

# Scientific discussion

# Ezetimibe/atorvastatin Gobens 10 mg/20 mg tablets
# Ezetimibe/atorvastatin Gobens 10 mg/40 mg tablets

# (ezetimibe/atorvastatin calcium trihydrate)

# ES/H/0939/001-002/DC

# Date: 22/05/2025

**This module reflects the scientific discussion for the approval of Ezetimibe/Atorvastatin Gobens. The procedure was finalised at 16/04/2025. For information on changes after this date please refer to the module 'Update'.**

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ezetimibe/Atorvastatin Gobens 10 mg/20 mg and 10 mg/40 mg tablets, from Laboratorios Normon S.A.

The product is indicated for*:*

*Prevention of cardiovascular events*

Ezetimibe/atorvastatin is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

*Hypercholesterolemia*

This medicinal product is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolemia 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 hypercholesterolemia (HoFH)*

This medicinal product 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application, which has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

In this procedure the concerned member's states has been IS.

# II. QUALITY ASPECTS

## II.1 Introduction

The finished product is presented as tablets containing 10 mg/20 mg or 10 mg/40 mg of Ezetimibe/Atorvastatin (as atorvastatin calcium trihydrate) as active substances. The maximum daily dose is 10 mg Ezetimibe and 80 mg Atorvastatin.

The product is available in perforated unit dose blister of Aluminium/Polyamide-Aluminium-PVC.

## II.2 2.2Drug Substance

**Drug substance [Ezetimibe]**

The ASMF procedure has been used for the active substance Ezetimibe.

***General Information***

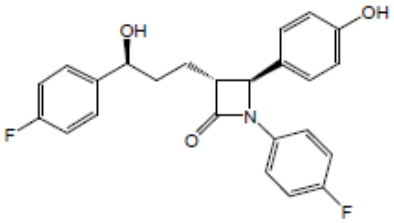
Nomenclature:

INN: Ezetimibe

Chemical name: (3R, 4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone

CAS-No: 163222-33-1

Structure:




MW: 409.43

Molecular formula: $C_{24}H_{21}F_2NO_3$

General Properties:

| | |
|---|---|
| Description: | Ezetimibe is a white to off-white powder |
| Solubility: | Ezetimibe is freely soluble in ethanol and methanol, soluble in acetonitrile, practically insoluble in water and aqueous solutions with pH value range from 1.0 to 11.0. |
| Melting point | 160 – 167°C |
| pH | 6.5 (1% in $H_2O$) |
| Optical rotation | -25.0° – 29.0° |
| Stereochemistry and isomerism: | 5 stereoisomers are routinely controlled in the drug substance specification. |
| Polymorphism: | Ezetimibe is crystal or amorphous. The crystals show polymorphous, and product ex Changzhou Pharma is crystal |
| Hygroscopicity | Hygroscopic |

***Manufacture, process controls and characterisation***

The description of the manufacturing process is properly detailed in the ASMF. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of

impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

***Specification, analytical procedures, batch analysis***

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

***Container closure system***

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

***Stability***

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

**Drug substance [Atorvastatin]**

The CEP procedure has been used for the active substance Atorvastatin.

***General Information***

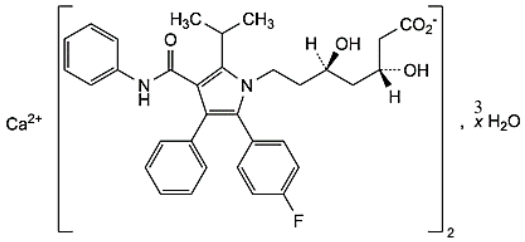
Nomenclature:

INN: Atorvastatin (*calcium trhihydrate*)

Chemical name: Calcium bis[(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate], trihydrate

CAS-No: 134523-03-8 (*Atorvastatin calcium*)

Structure:




MW: 1155 (*anhydrous substance*)

Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10},3H_2O$

General Properties:

White or almost white to yellowish, amorphous or crystalline powder, not hygroscopic to hygroscopic. Practically insoluble in water, very slightly soluble to very soluble in ethanol

(96 per cent), freely soluble to very soluble in methanol, practically insoluble to freely soluble in methylene chloride, freely soluble in dimethyl sulfoxide. It shows polymorphism.

***Manufacture, process controls and characterisation***

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

***Specification, analytical procedures, batch analysis***

Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

***Container closure system***

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

***Stability***

Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

## II.3 Medicinal Product

***Description of the product***

The drug product corresponds to uncoated tablets available in two strengths, Ezetimibe/Atorvastatin 10 mg/20 mg and 10 mg/40 mg. The tablets of different strengths can be distinguished by print. The excipients are: lactose monohydrate, croscarmellose sodium, povidone, sodium laurilsulfate, magnesium stearate, calcium carbonate, polysorbate 80, hydroxypropylcellulose and cellulose, microcrystalline. Tablets are packed in perforated unit dose blister of Aluminium/Polyamide-Aluminium-PVC.

***Pharmaceutical Development***

The development of the product has been described, the choice of excipients is justified and their functions explained.

The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified, and their control strategy is justified.

The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

***Manufacture of the product***

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided

***Excipients***

Excipients used are well known and of appropriate quality.

For lactose monohydratye, scientific data are presented to guarantee compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents for these excipients.

***Product specification, analytical procedures, batch analysis***

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

***Container closure system***

The finished product is packaged in perforated unit dose blister of Aluminium/Polyamide-Aluminium-PVC. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

***Stability***

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

**Shelf-life:** 2 years.

**Storage conditions:** This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

**In-use shelf life:** Not applicable.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

## III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of ezetimibe and atorvastatin are well known. As ezetimibe and atorvastatin are widely used, well-known active substances, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe/Atorvastatin Gobens 10 mg/20 mg, 10 mg/40 mg tablets is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Ezetimibe and atorvastatin are a well-known active substances with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted one bioequivalence study with the 10 mg/40 mg strength according to the Guideline on the investigation of bioequivalence, which is discussed below.

## IV.2 Pharmacokinetics

Biowaiver

Bioequivalence was demonstrated for 10 mg/40 mg strength.

The applicant claims that a biowaiver can be considered for 10 mg/20 mg strength since all conditions for biowaiving additional strengths according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) are fulfilled:

a) Both strengths are manufactured by the same manufacturing process.

b) The qualitative composition of both strengths is the same.

c) It is a bilayer tablets being excipients in atorvastatin layer proportional. Ezetimibe layer has the same composition in both strengths.

e) Ezetimibe/atorvastatin tablet exhibits linear pharmacokinetics.

d) In-vitro dissolution profiles are similar under identical conditions for the additional strengths.

Bioequivalence study

*Study code*
N-EZEATO-23-283

*GCP compliance*
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

*Clinical Study Site*
Clinical Trials Unit, Hospital Universitario de La Princesa. C/ Diego de León, nº 62. Madrid. Spain

*Bioanalytical Study Site*
Laboratorios Anapharm Europe S.L.U. C/ Encuny 22. Barcelona, Spain.

*Design*
The study was a randomised, two-treatment, four-period, four-sequence (TRTR, TRRT, RTRT or RTTR) single-dose crossover study conducted in 36 healthy volunteers under fasting conditions.
The replicate design was chosen because high variability (>30%) for Cmax was observed in previous studies for atorvastatin.
Each one of the four periods were separated by a wash-out period of 14 days.

*Analytical and statistical methods*

The analytical method for atorvastatin and total ezetimibe has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence.
Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*
36 subjects were included in the study. 33 subjects received a single dose of ezetimibe/atorvastatin 10 mg/40 mg in four periods of study, except: 3 subjects who did not perform some periods. However, as the study design was replicated 36 subjects were considered valid for pharmacokinetics and for evaluation of bioequivalence as all subjects had in every period at least one value for the test and another for reference product.

The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

*Summary of assessment bioequivalence studies.*

**Table 1. Pharmacokinetic parameters for total ezetimibe of ezetimibe/atorvastatin and Atozet (N=36)**
**(non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| **Treatment** | **$AUC_{0-72}$** **ng/ml/h** | **$C_{max}$** **ng/ml** | **$t_{max}$** **h** |
|---|---|---|---|
| **Test** | 749.12± 309.35 | 65.04 ± 29.65 | 1.00 (0.50-5.50) |
| **Reference** | 738.26 ± 292.87 | 72.61 ± 29.05 | 1.00 (0.50-4.00) |
| ***Ratio (90% CI)** | **102.15 (98.70 -105.71)** | **90.37 (84.89-96.20 )** | - |

*ln-transformed values

**Table 2. Pharmacokinetic parameters for atorvastatin of ezetimibe/atorvastatin and Atozet (N=36)**
**(non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| **Treatment** | **$AUC_{0-t}$** **ng/ml/h** | **$C_{max}$** **pg/ml** | **$t_{max}$** **h** |
|---|---|---|---|
| **Test** | 97309.43± 73933.21 | 21044.60 ± 21778.13 | 1.00 (0.50-6.00) |
| **Reference** | 91648.70 ± 56727.92 | 19845.24 ± 12926.85 | 1.00 (0.25-6.00) |
| ***Ratio (90% CI)** | **101.16 (96.53 -106.01)** | **93.31 (84.73-102.75 )** | - |

*ln-transformed values

Conclusion on bioequivalence study:

Based on the submitted bioequivalence study N-EZEATO-23-283, Ezetimiba/Atorvastatina Gobens 10 mg/40 mg tablets is considered bioequivalent with Atozet 10 mg/40 mg tablets.

The results of study N-EZEATO-23-283 with EzetimibaAtorvastatina Gobens 10 mg/40 mg tablets formulation can be extrapolated to other strength 10 mg/20 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

### IV.3 Pharmacodynamics/ Clinical efficacy/ Clinical safety

No original studies were submitted. This is acceptable in the context of a generic application, and no additional PD, efficacy or safety studies are deemed necessary. The efficacy and safety of ezetimibe and atorvastatin have been demonstrated in several clinical trials conducted with the reference product and during post-marketing experience. Therapeutic indication proposed for EzetimibaAtorvastatina Gobens 10 mg/20 mg, and 10 mg/40 mg tablets is the same as that authorized for the reference product, Atozet 10 mg/20 mg and 10 mg/40 mg tablets.

### IV.4 Risk Management Plan

The MAH has submitted a risk management plan (version 1.2, 28 October 2024), 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 Gobens 10 mg/20 mg tablets and Ezetimibe/atorvastatin Gobens 10 mg /40 mg tablets.

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Ezetimibe/atorvastatin Gobens 10 mg/20 mg tablets and Ezetimibe/atorvastatin 10 mg /40 mg tablets.

### IV.5 Discussion on the clinical aspects

*Please refer to section IV.2.*

## V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Atozet film-coated tablets DE/H/3895/00-003/DC (content) and Sugammadex Normon 100 mg/ml solution for injection ES/H/0829/001/DC (design). The bridging report submitted by the applicant has been found acceptable.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Ezetimibe/Atorvastatin Gobens 10 mg/20 mg, 10 mg/40 mg tablets is found adequate. There are no objections to the approval of

Ezetimibe/Atorvastatin Gobens 10 mg/20 mg, 10 mg/40 mg tablets 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.

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