CBG MEB

# Public Assessment Report

# Scientific discussion

# Ezetimibe Glenmark 10 mg, tablets

# (ezetimibe)

# NL/H/3139/001/DC

# Date: 25 April 2016

**This module reflects the scientific discussion for the approval of Ezetimibe Glenmark 10 mg Tablets. The procedure was finalised on 8 May 2015. 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 |
| 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 |
| 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 Glenmark 10 mg tablets, from Glenmark Pharmaceuticals Europe Limited.

The product is indicated for:

**Primary Hypercholesterolaemia**
Ezetimibe, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone.

Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

**Homozygous Familial Hypercholesterolaemia (HoFH**)
Ezetimibe co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

**Homozygous Sitosterolaemia (phytosterolaemia)**
Ezetimibe is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

A beneficial effect of Ezetimibe Glenmark 10 mg on cardiovascular morbidity and mortality has not yet been demonstrated.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ezetrol 10 mg tablets, which has been registered in Germany by MSD-SP Limited since 17 October 2002. The Dutch reference product is Ezetrol 10 mg tablets (NL License RVG 28626), registered by MSD Limited since 18 April 2003 through Mutual Recognition Procedure DE/H/0396/001.

The concerned member states (CMS) involved in this procedure were Czech Republic, Germany, Denmark, Ireland, Sweden, Slovakia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Ezetimibe Glenmark 10 mg is a white to off-white, capsule shaped, flat, bevelled edged uncoated tablet engraved with ‘G’ on one side and “44” on the other side. Each tablet contains 10 mg of ezetimibe.

The tablets are packed in PVC/Aclar-Aluminium blisters and HDPE bottles with child-resistant cap.

The excipients are: lactose monohydrate, sodium lauryl sulphate, croscarmellose sodium, povidone K-30 and magnesium stearate.

## II.2 Drug Substance

The active substance is ezetimibe, an established active substance which is not described in any pharmacopoeia. The active substance is practically insoluble in water. The molecule contains 3 chiral centres. Polymorphic form X is manufactured.

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 proposed process consists of three chemical steps and one purification step. No class 1 solvents or heavy metal catalysts are used. The active substance has been adequately characterized as absolute stereo-specific configuration and polymorphic form have been demonstrated. Acceptable specifications have been adopted for the starting materials, solvents and reagents used in the process.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph of various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for two full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months).
Based on the data submitted, a re-test period of 30 months has been granted. The storage condition of "store in airtight container, protected from moisture at controlled room temperature below 25 °C" has been adopted by the ASMF-holder, although this is not considered necessary in view of the stability data.

## 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 explained.
The dissolution method has been adequately developed and is sufficiently discriminative. A bioequivalence study has been performed with the reference product Ezetrol 10 mg tablets obtained from the UK market. The test batch used in the bioequivalence study was of appropriate size, and represents the commercial formulation and production process. Dissolution profiles of the test and reference batches have been provided in three media with pH 1, pH 4.5 and pH 6.8, all containing sodium lauryl sulphate as the drug substance is practically insoluble in water. The batches showed > 85% dissolution in 15 min in the three media and are therefore considered similar. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a standard wet-granulation process in which the ingredients are sifted, mixed, granulated, dried, sieved, blended, lubricated and compressed prior to packaging. The manufacturing process had been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches. Process validation for additional three full scaled 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, identity, average weight, disintegration time, uniformity of dosage units, degradation products, dissolution, water content, assay and microbial enumeration (non-routine test).
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 has been provided for three full scaled batches stored at 25°C/60% RH (up to 12 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging. No changes are seen. The proposed shelf-life of 24 months without specific storage restrictions, is justified for both the PVC/Aclar -Aluminium blisters and the HDPE bottles.
Stability data has been provided demonstrating that the product remains stable for 100 days following first opening of the container. The data for the 100 days can be extrapolated to an in-use period of 200 days. Further testing for in-use stability will be done at the end of the shelf-life of the unopened product and will encompass a period of 200 days.
The photostability study has been carried out in accordance with Note for Guidance on the Photostability testing of Medicinal products. The result of this study confirms that no significant change observed in the quality of product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies.
Certification statements of BSE/TSE absence have been provided. Magnesium stearate is of vegetable origin. Lactose monohydrate has been produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption

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

Based on the submitted dossier, the member states consider that, Ezetimibe Glenmark 10 mg, 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 Glenmark 10 mg is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ezetrol 10 mg tablets, which is available on the European market. Reference is made to preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology had been provided, which is based 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 is a well-known substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a 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 (Glenmark Pharmaceuticals Europe Limited, United Kingdom) is compared with the pharmacokinetic profile of Ezetrol 10 mg (MSD, UK).

The choice of the reference product in the bioequivalence study has been justified.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 22-38 years. Each subject received a single dose (10 mg) of one of the 2 ezetimibe formulations. The tablet was orally administered with 240 ± 2 ml water after an overnight fast for at least 10 hours until their scheduled dosing time. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16, 20, 24, 36, 48, 72 and 96 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. As this product can be taken regardless food intake, a study under fasting conditions is justified.

*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 36 subjects completed the study and were eligible for pharmacokinetic analysis. There were no withdrawals.

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

| **Treatment N=36** | **$AUC_{0-t}$** pg.h/ml | **$AUC_{0-\infty}$** pg.h/ml | **$C_{max}$** pg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 66868.63 | 70527.19 | 3977.96 | 5.00 (1.25 – 12.00) | 12.72 ± 4.83 |
| **Reference** | 65349.70 | 68478.99 | 4144.67 | 5.00 (0.50 – 12.00) | 11.43 ± 3.41 |
| ***Ratio (90% CI)** | 1.02 (0.96-1.09) | 1.03 (0.96-1.10) | 0.96 (0.86-1.07) | -- | -- |
| **CV (%)** | 16.60 | 16.84 | 27.61 | -- | -- |

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|---|---|
| **$AUC_{0-\infty}$** | 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 hours |
| **$C_{max}$** | maximum plasma concentration |
| **$t_{max}$** | time for maximum concentration |
| **$t_{1/2}$** | half-life |
| **CV** | coefficient of variation |

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ for ezetimibe are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ezetimibe Glenmark 10 mg is considered bioequivalent with Ezetrol 10 mg.

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 Glenmark.

**Summary table of safety concerns as approved in RMP**

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|---|---|
| Important identified risks | – Rhabdomyolysis/myopathy: rhabdomyolysis, myopathy, myalgia, and blood creatine phosphokinase increased<br>– Abnormal liver function: hepatitis, aspartate aminotransferase increased, and alanine aminotransferase increased<br>– Hypersensitivity: anaphylaxis, angioedema, rash, urticaria, and hypersensitivity<br>– Drug interaction with cyclosporin<br>– Drug interaction with warfarin, another coumarin anticoagulant, or fluindione |
| Important potential risks | – Cholecystitis/cholelithiasis: cholecystitis and cholelithiasis<br>– Pancreatitis: pancreatitis |
| Missing information | – Exposure during pregnancy and lactation<br>– Exposure in children (limited experience in 10 – 17 years of age) |

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 Ezetrol 10 mg. No new clinical studies were conducted. 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 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 proposed leaflet and questionnaire were subjected to pilot testing with six volunteers. The results indicated that changes were required to the leaflet and one change to the questionnaire.
The leaflet was amended and subjected to two stages of testing, with 10 subjects each. This resulted in a success rate of greater than 90% for all 15 questions in terms of subjects being able to locate the information (traceability).
During both stages of testing, there was only one case where a subject correctly located the information but did not adequately explain the meaning in their own words. Overall, the leaflet is considered to meet the required standard in terms of the quality aspects: comprehension and applicability.

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

Ezetimibe Glenmark 10 mg has a proven chemical-pharmaceutical quality and is a generic form of Ezetrol 10 mg tablets. Ezetrol 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 Glenmark 10 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 May 2015.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| After finalisation of the initial procedure the MAH requested for a change in the name and/or address of: a manufacturer (including where relevant quality control testing sites) and the activities for which the manufacturer/importer is responsible do not include batch release. | NL/H/3139/ IA/001/G | IA/G | 19 -12-2015 | 01-02-2016 | Approval | No |

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