COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ezetimibe Biohorm 10 mg tablets

(ezetimibe)

NL/H/4378/001/DC

Date: 20 August 2019

This module reflects the scientific discussion for the approval of Ezetimibe Biohorm 10 mg tablets. The procedure was finalised at 3 April 2019. 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
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 Biohorm 10 mg tablets from Biohorm S.L.

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 the 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.

Prevention of Cardiovascular Events
Ezetimibe is indicated to reduce the risk of cardiovascular events (see SmPC section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin.

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 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 the Netherlands by Merck Sharp & Dohme Ltd. since 18 April 2003 (NL License RVG 28626) through Mutual Recognition Procedure DE/H/0396/001.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe Biohorm 10 mg is a white, to off white capsule-shaped tablet debossed with "E 10" on one side and blank on the other side.

Each tablet contains 10 mg of ezetimibe.

The tablets are packed in an oPA-Al-PVC/Al blister.

The excipients used are croscarmellose sodium (E468), lactose monohydrate, magnesium stearate (E572), povidone K30 (E1201) and sodium lauryl sulphate (E487).

II.2 Drug Substance

The active substance is ezetimibe, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). Ezetimibe is a white crystalline powder. It is freely to very soluble in ethanol, methanol, acetonitrile and acetone, practically insoluble in water, and insoluble in hexane. Ezetimibe possesses three asymmetric carbons and consequently, it exhibits optical isomerism. The manufacturing process of ezetimibe results in the 3S, 3R, 4S isomer. Ezetimibe exhibits polymorphism. The anhydrous form (form A) is obtained by the manufacturing process.

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 eight steps of which six are actual synthetic steps. Starting materials are acceptable. Solvents of the last step are specified. No metal catalysts are used. The active substance was adequately characterized.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data have been presented for three pilot scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months) as well as for an additional 12 batches of larger batch sizes covering zero to 24 months at long term conditions and one to six months at accelerated conditions. No significant changes were observed. The drug substance does not need a temperature storage restriction. It was shown to be photostable. Based on the data submitted, a retest period could be granted of 48 months when stored in a tightly closed container to protect from moisture.

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 main development studies performed were the optimization of the formulation and performance of comparative dissolution studies complementary to the bioequivalence study. The choices of the packaging and manufacturing process are justified. The dissolution method for routine control.

A bioequivalence study has been performed against the reference product Ezetrol 10 mg. The test batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process at a representative scale. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are wet granulation, blending, compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scaled batches. The product is manufactured using conventional manufacturing techniques. Process validation for 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 appearance, water, uniformity of dosage units, dissolution, identification, assay, related substances and microbiological quality. Except for related substances, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three pilot scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product stable when exposed to light. No changes or trends were seen under both storage conditions. On basis of the data submitted, a shelf life was granted of 36 months without any special storage conditions is justified.

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

Only lactose monohydrate is of animal origin. 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 Biohorm 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 Biohorm 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 which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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 is a well-known active 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 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 Biohorm 10 mg tablets (J. Uriach & Cia S.A., Spain) is compared with the pharmacokinetic profile of the reference product Ezetrol 10 mg tablets (Merck Sharp & Dohme, Spain).

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 56 healthy subjects, aged 19-44 years. Each subject received a single dose (10 mg) of one of the two ezetimibe formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 18 days.

Blood samples were collected at 0.17, 0.33, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The conduct and design of the study is adequate and the study has been performed in accordance with GCP. A washout period of 18 days to prevent carry-over effects is appropriate.

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

Two subjects discontinued due to personal reasons (n=2). Three subjects did not report to the facility for 2nd period check-in. And one subject was withdrawn due to a complaint of fever with cough (n=1). Therefore, 50 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=50	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	84.6 ± 34.5	91.5 ± 39.3	4.3 ± 2.3	8.0 (0.5 - 16)	84.6 ± 34.5
Reference	89.8 ± 37.2	97.1 ± 42.7	4.6 ± 2.4	7.5 (0.5 - 16)	89.8 ± 37.2
***Ratio (90% CI)**	0.94 (0.89 - 1.01)	0.95 (0.89 - 1.01)	0.91 (0.85 - 0.98)	--	0.94 (0.89 - 1.01)

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study

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 Biohorm is considered bioequivalent with Ezetrol.

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 Biohorm.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Rhabdomyolysis/Myopathy • Abnormal liver function • Hypersensitivity • Drug interaction with warfarin, another

	coumarin anticoagulant, or fluindione • Drug interaction with ciclosporin
Important potential risks	• Cholecystitis/Cholelithiasis • Pancreatitis
Missing information	• Exposure during pregnancy • Limited exposure on long-term use in children age 10 to 17 and limited exposure in children less than 10 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. 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

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 Ezetrol. 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 Biohorm 10 mg tablets 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 Biohorm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 April 2019.

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