CBG MEB

Public Assessment Report

Scientific discussion

Ezetimibe CF 10 mg, tablets

(ezetimibe)

NL/H/3516/001/DC

Date: 3 May 2017

This module reflects the scientific discussion for the approval of Ezetimibe CF 10 mg, tablets. The procedure was finalised on 27 July 2016. 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
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
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 CF 10 mg, tablets from Centrafarm B.V.

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.

Prevention of cardiovascular events
Ezetimibe CF 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 states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Hungary, Italy, Luxembourg, Portugal, Sweden and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe CF is a white to off-white, oval, capsule-shaped tablet.

Each tablet contains 10 mg of ezetimibe.

The tablets are packed in PVC/PCTFE/PVC-Al blisters

The excipients are lactose monohydrate, microcrystalline cellulose (E 460), povidone (E 1201), croscarmellose sodium (E 468), sodium lauryl sulphate and magnesium stearate (E 470b).

II.2 Drug Substance

The active substance is ezetimibe, an established active substance described in the European Pharmacopoeia (Ph.Eur.). A United States Pharmacopoeia (USP) monograph on ezetimibe is available since 1 December 2015. Ezetimibe is a white to off-white crystalline powder. It is soluble in N,N-dimethyl formamide, acetone and acetonitrile, and insoluble in water. Ezetimibe possesses three asymmetric carbons; consequently it exhibits optical isomerism. The manufacturing process of ezetimibe, consistently produces the (R,S,S) isomer. Ezetimibe exhibits polymorphism. The manufacturing process consistently produces the anhydrous crystalline form.

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
Three manufacturing process consists of 7 steps and is described in sufficient detail. Starting materials are accepted. For all steps adequate controls are applied.

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 3 commercial scale batches.

Stability of drug substance
Three lower scale batches have been stored for 5 years at 2-8°C and 6 months at 40°C/75% RH. In addition three higher scale batches have been stored for 4 years at 2-8°C and 6 months at 40°C/75% RH. All stability results were in accordance with the set drug substance specification. Based on the provided stability data the claimed retest period of 4 years if stored at 2-8°C in the proposed packaging can be accepted.

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 same excipients as in the reference product were selected and development focused on a homogenous distribution of the drug substance. Due to the low flowability of the drug substance, a fluid bed granulation approach was chosen.

A bioequivalence study was submitted to demonstrate bioequivalence between Ezetimibe CF 10 mg and the reference medicinal product, Ezetrol 10 mg. Comparative dissolution profiles of the biobatches at pH 1.2, 4.5, and 6.8 support bioequivalence.

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 full scale batches among which the biobatch of the test product in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the Ph.Eur. 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 and includes tests for appearance, identification, average mass, uniformity of dosage units, dissolution, assay, related substances, and microbiological quality. The release and shelf life specifications differ with regard to the acceptance criteria for a specified impurity and total

impurities. The drug product specification is acceptable. 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 three commercial scale batches among which the biobatch of the test product from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product is provided for three full scale batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in the proposed packaging. No significant changes or trends were observed in the currently available stability data. Photostability was demonstrated under ICH Q1B conditions. Based on the provided stability data, the proposed shelf life of 36 months and storage condition “Store in original package in order to protect from moisture” are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
No excipient of human or animal origin is used, with the exception of lactose monohydrate. Scientific data and/or certificates of suitability issued by the EDQM 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 CF has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The ongoing long term stability studies will be continued up to 60 months.
- The MAH has committed to place the first three production batches on stability if the production batch size differs from batches presented in the dossier.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe CF 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

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ezetimibe CF 10 mg, tablets (Centrafarm B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Ezetrol 10 mg tablets (Merck Sharp & Dohme Ltd., Germany).

The choice of the reference product

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.

Design

A single-dose, two-period, two-stage, two-treatment, randomised cross-over bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 20-43 years. Each subject received a single dose (10 mg) of one of the 2 ezetimibe formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 48 and 72 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

A total of 2 subjects were withdrawn from the study; 1 due to vomiting and 1 due to a fall down and abrasion on the forehead. 58 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=58	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	85.2 ± 37.8	94.8 ± 40.0	5.3 ± 2.4	5.0 (0.5 - 16.0)
Reference	87.9 ± 37.1	94.2 ± 42.3	5.6 ± 2.4	5.0 (0.5 - 12.0)
***Ratio (90% CI)**	0.96 (0.88 - 1.04)	--	0.94 (0.85 - 1.03)	--

$AUC_{0-\infty}$ 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

**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 CF 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 CF.

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 fluindone • Drug interaction with ciclosporin
Important potential risks	• Cholecystitis/Cholelithiasis • Pancreatitis
Missing information	• Exposure during pregnancy • Limited exposure in children less than 6 years of age • Long-term efficacy of ezetimibe to reduce morbidity and mortality in adulthood in patients below 17 years • Safety and efficacy of ezetimibe administration with fibrates

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

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 test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The participants were males and females between 23 and 75 years of age. Each round consisted of 15 questions about key safety issues in the PL and 4 questions regarding the layout/design. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezetimibe CF 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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 July 2016.

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
Secondary packaging site added	NL/H/3516/ 1/IA/1	IA	2-12-2016	19-12-2106	Approved	No