Public Assessment Report

Scientific discussion

Ezetimibe Mylan 10 mg, tablets (ezetimibe)

NL/H/2923/001/DC

Date: 6 November 2014

This module reflects the scientific discussion for the approval of Ezetimibe Mylan 10 mg, tablets. The procedure was finalised on 20 May 2014. 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 Mylan 10 mg, tablets from Mylan B.V.

The product is indicated for:

Primary hypercholesterolaemia
Ezetimibe Mylan, 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 Mylan 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 Mylan 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 Mylan is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

A beneficial effect of Ezetimibe Mylan 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 Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Poland, Portugal, Slovakia, Spain, Sweden 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 Mylan 10 mg is a white to off white capsule shaped, bevelled edge tablet debossed with ‘M’ on one side of the tablet and ‘EE1’ on the other side, approximately 8.2 mm in length and 4.1 mm in width.

The tablets are packed in clear/transparent PVC-Aclar Aluminium foil blisters, clear/transparent PVC-PVdC Aluminium foil blisters and HDPE bottles with polypropylene (PP) screw cap closure.

The excipients are: lactose monohydrate, sodium laurilsulfate (E487), croscarmellose sodium, hypromellose (E464), crospovidone (Type B), microcrystalline cellulose, magnesium stearate.

II.2 Drug Substance

The active substance is ezetimibe, an established active substance which is not described in the European Pharmacopoeia (Ph.Eur.), the British or United States Pharmacopoeia. The active

substance is a white to off-white crystalline powder, soluble in methanol. Ezetimibe has three chiral centres, polymorphism is described (crystalline forms).

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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 as employed by the first manufacturer consists of two parts and includes 5 stages, the manufacturing process as employed by the second supplier consist of 5 steps. The process is described in sufficient detail. The proposed starting material is acceptable. Solvents used in the final steps of the process are adequately controlled. Class I solvents are not used. Limit for residual metals are set in line with the guidance. The active substance is adequately characterized.

Quality control of drug substance
The drug substance specification as proposed by the ASMF holders is acceptable, it is in line with the general European guidance and Ph.Eur. requirements Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches by each supplier. Analytical methods are adequately described and validated. Batch analysis data by the drug product manufacturer have been provided on two batches of each drug substance supplier.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches, stored at 25°C/60% RH (9 months for one supplier; 24 months for the other) and 40°/75% RH (6 months). The batches were stored in the commercial packaging. No specific changes were seen in any of the parameters tested at 9/24 months, stability of the product at these conditions is shown. The proposed re-test period of 18 months and 36 months for the two manufacturers is considered acceptable, the proposed storage conditions: 'Preserve in tight containers at 25°C, not exceeding 40°C' for the first supplier and 'does not require any special storage condition' for the second are also acceptable.

II.3 Medicinal Product

Pharmaceutical development
The choices of the excipients, packaging and manufacturing process are justified. The innovator product was characterized and the development was based on these results. Relevant optimization studies on the excipients and manufacturing process were performed. Dissolution data in all common pH media were provided. The qualitative composition of the reference product Ezetrol and the test product is not identical. Similarity for dissolution could not be shown in all media. However, the results of the bioequivalence study prevail over the dissolution results. The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The manufacturing process is a standard process requiring process validation on pilot-scale batches. Process validation data on the product has been presented for three pilot-scale batches, showing compliance to the acceptance criteria. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, dissolution, uniformity of dosage units, assay, degradation products, water, microbial tests, resistance to crushing and friability. Release and shelf-life limits are the same with the exception of impurities and water. The specification is acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on several batches stored at 25°C/60% RH (12-36 months) and 40°/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging, *i.e*. PVC/Aclar blisters, PVC/PVdC blisters or HDPE bottles. No specific changes are noted at any of the conditions, the proposed shelf-life of 36 months is supported for the blister packs as well as the HDPE bottle pack. The tablets were shown to be photostable. The proposed storage condition (none) is justified. Results of an in-use stability study with the HDPE bottle showed no changes throughout the period of use (100 days). Therefore an in-use shelf life of 'use within 100 days of opening' is included in the SmPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose monohydrate, sodium laurilsulphate and magnesium stearate TSE/BSE certificates are provided. However, only lactose monohydrate is of animal origin. It is prepared from the milk sourced from healthy animals 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 Mylan 10 mg, tablets 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 MAH committed to perform process validation studies on the first three production-scale batches of tablets manufactured with proposed additional commercial batch sizes.
- The MAH committed to continue stability studies at long term stability conditions i.e. 25°C/60% RH as per provided stability protocol.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ezetimibe Mylan 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 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 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 Mylan 10 mg (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Ezetrol 10 mg, (MSD-SP Ltd UK).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition of reference product.
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 48 healthy male subjects, aged 22-43 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. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected at 0.16, 0.33, 0.50, 0.67, 0.83, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12, 16, 24, 36, 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. In plasma ezetimibe free and conjugated was determined.

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
One subject dropped out in the second period of his own accord. Forty-seven subjects were eligible for pharmacokinetic analysis.

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

Treatment N=47	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	70.6 ± 33.3	79.2 ± 38.1	4.08 ± 2.24	5.0 (0.67 – 36)	15.6 ± 9.3
Reference	72.1 ± 28.5	79.0 ± 30.0	4.20 ± 1.93	5.0 (0.5 – 16)	13.6 ± 4.6
***Ratio (90% CI)**	0.95 (0.89 - 1.02)	0.97 (0.90 - 1.05)	0.95 (0.87 - 1.03)	--	--
CV (%)	20	22	24	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe (free and conjugated) under fasted conditions.

Treatment N=47	AUC_{0-t} mg.h/ml	$AUC_{0-\infty}$ mg.h/ml	C_{max} mg/ml	t_{max} h	$t_{1/2}$ h
Test	905 ± 384	967 ± 410	114 ± 41	0.83 (0.5 - 2.5)	14.2 ± 7.1
Reference	886 ± 342	941 ± 356	113 ± 45	0.83 (0.5 - 4.0)	13.2 ± 5.0
***Ratio (90% CI)**	1.01 (0.95 - 1.07)	1.01 (0.95 - 1.07)	1.03 (0.96 - 1.10)	--	--
CV (%)	17	18	20	--	--

$AUC_{0-\infty}$ 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} for free ezetimibe and total ezetimibe are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ezetimibe Mylan 10 mg is considered bioequivalent with Ezetrol 10 mg tablets. The formulations were well tolerated, with no major side effects.

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 Mylan.

Summary table of safety concerns as approved in RMP

Important identified risks	• Rhabdomyolysis/myopathy • Abnormal liver function • Hypersensitivity • Drug interaction with ciclosporin • Drug interaction with warfarin, another coumarin anticoagulant, or fluindione
Important potential risks	• Cholecystitis/cholelithiasis • Pancreatitis
Important missing information	• Exposure during pregnancy • Limited exposure in children age 10 to 17 beyond 1 year and limited exposure in children less than 10 years of age.

The safety specification as submitted by the MAH is fully in line with the RMP for the reference product and considered acceptable. Routine pharmacovigilance activities for all important risks and missing information are considered sufficient.

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 2 participants, followed by two rounds with 10 participants each. The results showed that all participants correctly found all questions and also easily understood the answers. Therefore no weaknesses of the PL have been identified. 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

Ezetimibe Mylan 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 Mylan 10 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 May 2014.

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