CBG MEB

Public Assessment Report

Scientific discussion

Ezdivule 10 mg coated tablets (ezetimibe)

NL/H/3693/001/DC

Date: 2 November 2017

This module reflects the scientific discussion for the approval of Ezdivule 10 mg coated tablets. The procedure was finalised on 8 February 2017. 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 Ezdivule 10 mg coated tablets from Laboratoires SMB S.A.

The product is indicated for:

Primary hypercholesterolaemia
Ezdivule, 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.

Ezdivule 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
Ezdivule is indicated to reduce the risk of cardiovascular events 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)
Ezdivule 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)
Ezdivule 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 Germany by MSD-SP Limited since 17 October 2002. The Dutch reference product is Ezetrol 10 mg tablets (NL License RVG 28626), registered by Merck Sharp & Dohme Limited since 18 April 2003 through Mutual Recognition Procedure DE/H/0396/001.

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Ezdivule 10 mg is a green oblong coated tablet with a score line. The tablet can be divided into equal doses.

The coated tablets are packed in PCTFE/PVC–Aluminium blisters or PVdC/PE/PVC–Aluminium blisters.

The excipients are:
tablet core – lactose monohydrate, microcrystalline cellulose (E460), povidone (E1201), crospovidone (E1202), sodium laurilsulfate, magnesium stearate (E470b)
tablet coating – hypromellose (E464), gelatin, Brilliant blue FCF (E133), yellow iron oxide (E172), titanium dioxide (E171)

II.2 Drug Substance

The active substance is ezetimibe, an established active substance which is not described in the European Pharmacopoeia (Ph.Eur.). A monograph in the United States Pharmacopoeia (USP) is available. 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. Ezetimibe exhibits polymorphism. The anhydrous form (form A) is obtained.

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. No metal catalysts are used. The active substance was adequately characterized.

Quality control of drug substance
The drug substance specification of the ASMF holder was established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analysis data were provided of three commercial scale batches demonstrating compliance with the drug substance specification of the ASMF holder. The drug substance specification of the MAH contains an additional requirement for particle size distribution. The proposed acceptance criteria are justified based on the pharmaceutical development data.

Stability of drug substance
Primary stability data have been presented for three pilot scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) as well as for an additional 12 batches of larger batch sizes covering up to 24 months at long term conditions and one up to 6 months at accelerated conditions. No significant changes were observed. The claimed re-test period of 48 months is justified. The drug substance does not need a temperature storage condition. It was shown to be photostable. As the drug substance is hygroscopic, the proposed storage condition 'Store in a tightly closed container to protect from moisture' is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The choice of the excipients was based on the reference product with the differences that crospovidone is used instead of croscarmellose and the fact that the product at issue is coated. It corresponds to a tablet coated by a gelatin capsule. Moreover, the product at issue contains score line which allows breaking of the tablet in equal doses. Divisibility was demonstrated in accordance with the Ph.Eur. test on subdivision of tablets.
Sufficient information has been provided on formulation and manufacturing process development.
A bioequivalence study was carried out comparing the test product to the reference product taken from the Belgian market. The concomitant comparative dissolution data at pH 1.2, 4.5, and 6.8 were initially determined with the use of a surfactant in the medium. It turned out that dissolution without the use of a surfactant is too low to quantify in both the test and the reference product.
The proposed method for routine dissolution testing is adequate. The proposed acceptance criterion of NLT 80% (Q) dissolved after 15 minutes sufficiently reflects the dissolution profile of the biobatch of the test product. The method was shown to be discriminatory with regard to the particle size of the drug substance. The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The manufacturing process includes blending, wet granulation, drying, calibration, blending and lubrication, tableting, sub-coating, gelatin coating, and packaging. The manufacturing process is regarded as a standard process and has been adequately described.
The manufacturing process was successfully validated with three pilot scale batches. An acceptable process validation scheme for industrial scale batches was provided.

Control of excipients
With the exception of the gelatin capsules, all excipients are controlled according to the Ph.Eur. An acceptable in-house specification is provided for the (hard) gelatin capsules.

Quality control of drug product
The product specification includes tests for appearance, uniformity of dosage units, identification, assay, related substances, dissolution, and microbiological quality. Average mass, hardness, and thickness are tested in-process. The release and shelf life specifications are identical. The proposed drug product specifications are acceptable. Analytical methods were adequately described and validated.
Batch analysis data showing compliance with the proposed release specification were provided for the three process validation batches among which the biobatch of the test product.

Stability of drug product
Stability data on the product is provided for three pilot scale batches stored at 25°C/60% RH (12 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 PCTFE/PVC-Aluminium blisters and PVdC/PE/PVC-Aluminium blisters. A decreasing trend for dissolution was observed at accelerated conditions. However, no significant changes were seen. Photostability was shown under ICH conditions. Based on the provided stability data the claimed shelf life of 24 months and storage condition 'Store below 30°C'are justified.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
CEPs are provided for the gelatin sources used by the supplier of the gelatin capsules. The supplier of lactose monohydrate certified that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and that the lactose is prepared without the use of other ruminant materials. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ezdivule 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 Ezdivule 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 Ezdivule 10 mg coated tablets (Laboratoires SMB S.A., Belgium) is compared with the pharmacokinetic profile of the reference product Ezetrol 10 mg tablets (Merck Sharp & Dohme Limited UK, obtained from Belgium).

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 44 healthy subjects (25 males/19 females), aged 19-39 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 14 days.

Blood samples were collected pre-dose and at 45 minutes, 1:30, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 5:30, 6:00, 6:30, 7:00, 7:30, 8:00, 09:00, 10:00, 12:00, 24:00, 48:00 and 72:00 hours after administration of the products.

The design of the study is acceptable. As ezetimibe should be taken regardless of food intake, a study under fasting conditions is acceptable. The washout period of 14 days is adequate considering the half-life 0f 20 hours.

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.
It is known for ezetimibe that there is possible *in-vitro* and/or *ex-vivo* (back-) conversion of ezetimibe phenolic glucuronide and ezetimibe benzylic glucuronide to (free) ezetimibe. The analytical method showed sufficiently that there is no in-vitro conversion during the storage and handling of the samples.

Results
Seven subject dropped out of the study due to several non drug-related reasons and only one was replaced before the start of the study. Thirty eight subjects completed the whole study and were statistically evaluated.

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

Treatment N=38	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	88.7 ± 43.3	129 ± 98.9	3.50 ± 2.27	5.5 (0.75 - 24)	--

Reference	89.5 44.4	137.5 ± 120.9	3.84 ± 2.33	5.5 (0.75 – 48)	--
***Ratio (90% CI)**	1.01 (0.94 - 1.08)	0.98 (0.85 - 1.12)	0.94 (0.83 - 1.08)	--	--

$AUC_{0-\infty}$ 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 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 Ezdivule 10 mg coated tablets is considered bioequivalent with Ezetrol 10 mg tablets.

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 Ezdivule.

- 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 in children age 10 to 17 beyond 1 year 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

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. Before the actual test one preliminary round of testing was performed on 4 participants. Weaknesses in the PL not identified. The actual test consisted out of two rounds with 10 participants each. The test consisted of 17 questions concerning addressing the key safety issues addressed in the PL and additionally 3 questions were asked concerning the layout/design. Results were measured quantitatively and qualitatively. The results showed that each and every question meets pre-defined criterion of 81% correct answers. Therefore, no weaknesses of the PL have been identified. The success criteria are met and the test is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ezdivule 10 mg coated 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 Ezdivule with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 February 2017.

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