CBG MEB

Public Assessment Report

Scientific discussion

Ezetimibe Uriach 10 mg tablets

(Ezetimibe)

NL/H/3191/001/DC

Date: 6 April 2016

This module reflects the scientific discussion for the approval of Ezetimibe Uriach 10 mg tablets. The procedure was finalised at 26 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 Uriach 10 mg tablets from J. Uriach y Compañía, S.A..

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

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

The concerned member states (CMS) involved in this procedure were Bulgaria, Greece, Spain and Romania.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe Uriach 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 not described in the European, British or United States Pharmacopoeia (Ph.Eur, BP, USP). The drug substance is a white to off-white crystalline powder, practically insoluble in water and soluble in methanol. Ezetimibe has three chiral centres, polymorphism is described (crystalline forms). A discussion on potential forms is provided and

concerns the anhydrous form of Ezetimibe (form A), hydrate form of Ezetimibe (form B) and tert-butanol solvate. The first two forms are most likely to form in the process or during storage, the anhydrous form is obtained by the manufacturing process. The MAH has sufficiently justified that control for polymorphic form in the active substance specification is not necessary.
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 consisting of 5 steps is described in sufficient detail. The proposed starting material is acceptable, solvents used in the process are adequately controlled and the active substance is sufficiently characterized.

Quality control of drug substance
The drug substance specification laid down by the ASMF holder is acceptable; it is in line with the general European guidance and Ph.Eur. requirements. The MAH includes and additional test for particle size distribution. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance
Stability data on the drug substance have been provided for three batches, stored at 25°C/60% RH (9 months) and 40°/75% RH (6 months). No specific changes were seen in any of the parameters tested at 9 months. Stability of the substance at these conditions is shown. The proposed re-test period of 18 months is considered acceptable. Furthermore the proposed storage conditions "preserved in tight containers at 25°C, not exceeding 40°C' are acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product is sufficiently described, the choice of excipients is justified and their functions explained. The impact of several manufacturing process parameters were studied on the pharmaco-technical aspects of the formulation and compressibility properties (e.g. tablet hardness, dissolution); the values found were also compared with those of an innovator batch. The choice of the packaging and manufacturing process are justified.

A bioequivalence study was submitted to demonstrate bioequivalence between Ezetimibe Uriach 10 mg and the reference medicinal product, Ezetrol 10 mg. The test batch used in the bioequivalence study was manufactured according to the finalized manufacturing process and composition. Comparative *in vitro* dissolution profiles between the bioequivalence batch and reference batch at pH range 1.2 – 6.8 cannot be generated. Due to the low solubility of the drug substance, such profiles are not compulsory according to the Note for Guidance on the investigation of bioavailability and bioequivalence. Equivalence has been demonstrated *in vivo* (see section IV.2).

Manufacturing process
A wet granulation manufacturing process was selected, based on the drug substance physicochemical characteristics. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot batches from one of the manufacturing sites, which are also considered representative for the other site, considering the conventional techniques used. An acceptable process validation protocol is available, for post-authorization process validation of commercial full scale batches.

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

Quality control of drug product

The product specification includes tests for appearance, identity, uniformity of dosage units, water content, assay, degradation, dissolution and microbial quality. The proposed product specification is acceptable. The specification limit for dissolution ensures a sufficiently rapid dissolution, in compliance with the dissolution of the bio-batch. The analytical methods have been adequately described and validated.
Batch analytical data from both proposed product production sites have been provided for eight pilot batches from the production sites, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three pilot batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed container closure system. All parameters stayed well within the proposed specification limits. No specific trends are seen except a slight increasing trend for degradation products, with results remaining well within the limits. The tablets seem not susceptible to light as no significant changes were noted. The proposed shelf-life of 30 months without special storage conditions, is 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; for this excipient it is declared that the milk is sourced from healthy animals in the same conditions as milk for human. In the manufacturing process no TSE risk materials are used.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ezetimibe Uriach 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 Uriach 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 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

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of Ezetimibe Uriach 10 mg (J. Uriach y Compañía, S.A, Spain) is compared with the pharmacokinetic profile of the reference product Ezetrol 10 mg (Merck Sharp & Dohme Ltd., Spain).

The choice of the Spanish 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, open, two-sequence, two-period, randomised, crossover bioequivalence study was carried out under overnight fasting conditions in 56 healthy subjects (44 males, 6 females) , aged 19-44 years. Each subject received a single dose (10 mg) of one of the two ezetimibe formulations. The tablet was orally administered after an overnight fasting period. There were two dosing periods, separated by a washout period of 18 days.

Blood samples were drawn pre-dose and 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 the administration of each of the products.

The design of the study is acceptable, although the sampling scheme is sparse. For ezetimibe the expected C_{max} is around 4-12 hours (SmPC). However, the observed concentration time profiles, both mean and individual, indicate adequate characterisation of ezetimibe peak values. Therefore, this is issue is not further pursued.

Ezetimibe may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ezetimibe. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

50 subjects were eligible for pharmacokinetic analysis. Their samples were included in statistical data analysis and subsequent bioequivalence assessment. Discontinued subjects withdrew due to personal reasons (n=2), did not report to the facility for the second period check-in (n=3), or was withdrawn due to a complaint of fever with cough (n=1).

Table 1. Ezetimibe pharmacokinetic parameters under overnight fasting conditions (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment N=50	**AUC_{0-72}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	84.6 ± 34.5	91.5 ± 39.3	4.3 ± 2.3	8.0 (0.5-16)
Reference	89.8 ± 37.2	97.1 ± 42.7	4.6 ± 2.4	7.5 (0.5-16)
***Ratio (90% CI)**	0.94 (0.89-1.01)	0.95 (0.89-1.0)	0.91 (0.85-0.98)	--

AUC_{0-72} area under the plasma concentration curve from administration to last observed concentration at time 72h.
$AUC_{0-\infty}$ area under the plasma concentration curve extrapolated to infinite time.
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**In-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ezetimibe Uriach 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 (RMP), 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 Uriach 10 mg tablets.

Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
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 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 the 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 test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Results were measured quantitatively and qualitatively. The results showed that all participants correctly found all questions and also easily understood the answers.

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 Uriach 10 mg has a proven chemical-pharmaceutical quality and is a generic form of Ezetrol 10 mg. 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 Uriach 10 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 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