IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ezetimibe 10mg Tablets
Ezetimibe
PA23176/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6438/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12th September 2019 under procedure number IE/H/1049/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0343/001/001
Marketing Authorisation Holder: Key Pharmaceuticals Ltd.

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Ezetimibe 10 mg Tablets(PL 34424/0005; UK/H/6438/001/DC) could be approved.

This is a decentralised abridged application submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product, Ezetrol 10mg Tablets, which was granted a Marketing Authorisation to Merck Sharp & Dohme Limited on 03 April 2003 following a national procedure (PL 00025/0609).

Ezetimibe 10 mg Tablets is a 'prescription only medicine' (legal status "POM") containing the active substance ezetimibe which is indicated for the treatment of:

- *Primary Hypercholesterolaemia E*zetimibe, 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 nonfamilial) 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 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.

Ezetimibe is a class of lipid-lowering compounds selectively inhibiting the intestinal absorption of cholesterol and phytosterols by targeting the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1). Although ezetimibe is rapidly absorbed and is extensively metabolised to an active phenolic glucuronide, which reaches the systemic circulation after oral administration, its action is localized at the brush border of the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This results in a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Therefore, Ezetimibe and statins have distinct mechanisms of action that provide complementary cholesterol reduction.

A single bioequivalence study was performed, which compared the pharmacokinetics of the test product Ezetimibe 10 mg Tablet to those of the reference product Ezetrol 10mg Tablets (Merck Sharp & Dohme Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical or non-clinical studies were conducted which is acceptable given that the application was based on being a generic medicinal product of reference product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application, and these are satisfactory.

The United Kingdom acted as RMS and Ireland was the CMS.

All Member States agreed to grant a Market Authorisation for the above Ezetimibe 10 mg Tablets on 08 January 2018. Following a subsequent national phase, the UK granted a Market Authorisation (PL 34424/0005) for this product on 22 January 2018.

II. QUALITY ASPECTS

II.1 Introduction

Ezetimibe 10 mg Tablets contains 10 mg of ezetimibe. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, croscarmellose sodium, sodium lauryl sulphate, hypromellose, colloidal silicon dioxide, microcrystalline cellulose, hydrogenated castor oil, sodium stearyl fumerate.

The finished product is packaged in polyvinyl chloride / polyvinylidene chloride transparent film / plain aluminium foil blisters strips packaged into cartons containing 28 tablets

Not all pack sizes may be marketed, however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

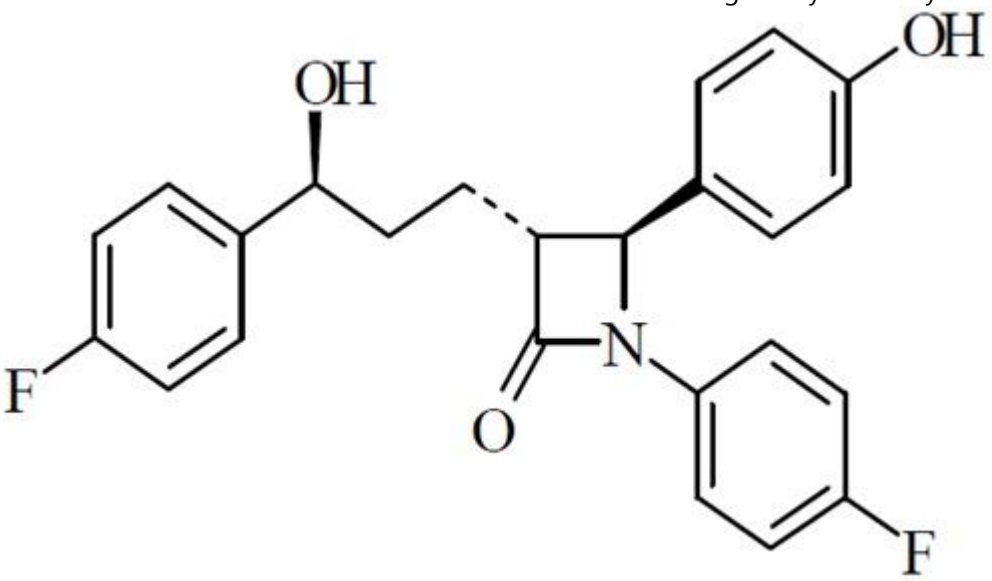
All primary product packaging complies with the current requirements. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 DRUG SUBSTANCES

Ezetimibe

Chemical Name:
(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one
1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)- hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone

Structure:



Molecular Formula: C24H21F2NO3

Molecular Mass: 409.43

Appearance: White to off-white crystalline powder

Solubility: Freely soluble in methanol and in acetone, soluble in ethanol, practically insoluble in water.

Ezetimibe is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data that comply with the proposed specification are provided. Satisfactory Certificates of Analysis have been provided for all working standards used.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to formulate safe, efficacious, stable, tablets, each containing 10 mg of Ezetimibe, which were comparable in performance to Ezetrol 10mg Tablets (Merck Sharp & Dohme Limited). Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The applicant has confirmed that the manufacturing process will be validated at commercial scale.

Finished Product Specifications
The finished product specification is acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specification have been provided. In-house working standards are used, which are compared to European Pharmacopoeia references, where available. Representative Certificates of Analysis have been provided.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months for the unopened product, with the storage condition, "Keep in the outer carton in order to protect from moisture.".

Suitable post approval stability commitments to continue stability testing on batches of the finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Ezetimibe 10 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance clofarabine are well-known. No new non-clinical data have been submitted for this application and none are required. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new pharmacology data were submitted and none are required for an application of this type.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted and none are required for an application of this type.

III.4 Toxicology
No new toxicology data were submitted and none are required for an application of this type.

III.5 Environmental Risk Assessment
Since this product will be used as a substitute for other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

III.6 Discussion on non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Ezetimibe 10 mg Tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction
No new clinical studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant.

IV.2 Pharmacokinetics

In support of the application, the Marketing Authorisation Holder has submitted results from the following bioequivalence study:

Open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of comparing the pharmacokinetics of the test product Ezetimibe 10 mg Tablets (Key Pharmaceuticals Ltd.) and Ezetrol 10 mg Tablets (Merck Sharp & Dohme Limited, UK) in healthy, adult subjects under fasting conditions.

After an overnight fast of 10 hours each subject received a single dose of the test formulation (1 x 10 mg) or a single dose of the reference medicine (1 x 10 mg), administered with 240mL of drinking water. Blood samples were collected before dosing and up to and including 72 hours after dosing.

A washout period of 14 days was kept between each dosing period.

Summary statistics for pharmacokinetic parameters for the test and reference product are shown in the tables below:

Table 1. Pharmacokinetic parameters for Ezetimibe (unconjugated) obtained by a Non-Compartmental Model (N=38) (non-transformed values; arithmetic mean±SD, tmax median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	69.3182 ± 38.25036	93.0349 ± 64.67668	4.5101 ± 2.15231	6.836 ± 4.4106
Reference	67.6534 ± 32.80137	83.6428 ± 41.24223	4.8697 ± 2.64193	6.178 ± 3.1777
*Ratio (90% CI)	97.00 (86.66, 108.57)	N/A	95.23 (85.91, 105.56)	N/A

AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$	does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Table 2. Pharmacokinetic parameters for total Ezetimibe (ezetimibe+ ezetimibe glucuronide) obtained by a Non-Compartmental Model (N=38) (non-transformed values; arithmetic mean±SD)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	735.8830 ± 359.98696	813.9642 ± 439.26576	87.9888 ± 46.46178	14.9173 ± 9.21379
Reference	742.5084 ± 240.53840	807.1618 ± 278.95902	91.6558 ± 39.19911	14.4581 ± 7.78436
*Ratio (90% CI)	93.96 (87.16, 101.30)	N/A	91.54 (80.45, 104.15)	N/A

AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

ln-transformed values

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for ezetimibe and ezetimibe glucuronide lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Based on the data provided the applicant's test product, Ezetimibe 10 mg Tablets can be considered bioequivalent to the reference product, Ezetrol 10 mg Tablets (Merck Sharp & Dohme Limited).

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy

No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical Safety

No new data on clinical safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an 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 10 mg Tablets.

A summary of safety concerns, as approved in the RMP, are listed below:

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity to active substance or any other ingredient of the medicine • Skeletal muscle pain / myopathy and rhabdomyolysis • Abnormal liver function • Drug interactions with ciclosporin and Drug interaction with warfain, another coumarin anticoagulant or fluindione.
Important potential risks	• Cholelithiasis/cholecystitis • Risk of pancreatitis (inflammation of the pancreas)
Missing information	• Pregnancy and lactation • Paediatric population- Limited clinical trial experience in children age 10-17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical trial experience in children less than 6 years of age.

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Ezetimibe 10 mg Tablets.

V. OVERALL CONCLUSIONS

User Consultation

A user consultation with target patient groups on the package leaflet has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

OVERALL CONCLUSIONANDBENEFITRISKASSESSMENTAND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ezetimibe is considered to have demonstrated the therapeutic value of the compound. As the product consists of an aqueous IV solution containing the same active substance and same concentration as the currently approved product Evoltra 1 mg/ml Concentrate for solution for infusion, and the excipients are not known to interact with the drug substance nor to otherwise affect the disposition of the drug substance, bioequivalence studies are not needed.

The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

May 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6438/001/DC to IE/H/1049/001/DC	N/A	N/A	N/A	Approved 12/09/2019
MA Transfer	CRN00C5D5	SmPC Section 7, 8, 10 Leaflet New MA Holder: Lexon Pharmaceuticals (Ireland) Limited New PA number: PA23176/001/001	16/04/2021	16/04/2021	Approved