Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Ezetimibe 10 mg Tablets

ezetimibe

PL 49565/0031

Rudipharm Limited

LAY SUMMARY

Ezetimibe 10 mg Tablets
ezetimibe

This is a summary of the Public Assessment Report (PAR) for Ezetimibe 10 mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Ezetimibe 10 mg Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Ezetimibe 10 mg Tablets and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Ezetrol 10 mg Tablets.

Ezetimibe 10 mg Tablets is a medicine to lower increased levels of cholesterol.

This medicine lowers levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, Ezetimibe 10 mg Tablets raises levels of "good" cholesterol (HDL cholesterol).

Cholesterol is one of several fatty substances found in the bloodstream. The total cholesterol is made up mainly of LDL and HDL cholesterol. LDL cholesterol is often called "bad" cholesterol because it can build up in the walls of the arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke. HDL cholesterol is often called "good" cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease.

Triglycerides are another form of fat in the blood that may increase the risk for heart disease. It is used for patients who cannot control their cholesterol levels by cholesterol lowering diet alone. Patients should stay on cholesterol lowering diet while taking this medicine.

Ezetimibe 10 mg Tablets is used in addition to the cholesterol lowering diet if patients have:

- a raised cholesterol level in their blood (primary hypercholesterolaemia [heterozygous familial and non-familial])
    - together with a statin, when the cholesterol level is not well controlled with a statin alone.
    - alone, when statin treatment is inappropriate or is not tolerated.
- a hereditary illness (homozygous familial hypercholesterolaemia) that increases the cholesterol level in the blood. The patient will also be prescribed a statin and may also receive other treatments.
- a hereditary illness (homozygous sitosterolaemia, also known as phytosterolaemia) that increases the levels of plant sterols in the blood.

If the patients have heart disease, Ezetimibe 10 mg Tablets combined with cholesterol-lowering medicines called statins reduces the risk of heart attack, stroke, surgery to increase heart blood flow, or hospitalisation for chest pain.

Ezetimibe 10 mg Tablets does not help to lose weight.

How does Ezetimibe 10 mg Tablets work?
Ezetimibe, the active ingredient of Ezetimibe 10 mg Tablets, works by reducing the cholesterol absorbed in your digestive tract. Ezetimibe adds to the cholesterol-lowering effect of statins, a group of medicines that reduce the cholesterol your body makes by itself.

How is Ezetimibe 10 mg Tablets used?
The pharmaceutical form of this medicine is a tablet, and the route of administration is oral (by mouth).

The recommended dose is one Ezetimibe 10 mg Tablet once a day.

This medicine can be taken at any time of the day, with or without food.

- Before starting Ezetimibe 10 mg Tablets, the patient should be on a diet to lower their cholesterol.
- The patient should stay on this cholesterol lowering diet whilst taking this medicine.

If the patient's doctor has prescribed Ezetimibe 10 mg Tablets along with a statin, both medicines can be taken at the same time. In this case, patient should read the dosage instructions in the package leaflet of that particular medicine.

If the patient's doctor has prescribed Ezetimibe 10 mg Tablets along with another medicine for lowering cholesterol containing the active ingredient colestyramine or any other medicine containing bile acid sequestrant, they should take Ezetimibe 10 mg Tablets at least 2 hours before or 4 hours after taking the bile acid sequestrant.

The patient should continue taking the other cholesterol-lowering medicines unless their doctor tells them to stop.

For further information on how Ezetimibe 10 mg Tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Ezetimibe 10 mg Tablets have been shown in studies?
Because Ezetimibe 10 mg Tablets is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Ezetimibe 10 mg Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can

be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Ezetimibe 10 mg Tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Ezetimibe 10 mg Tablets approved?
It was concluded that, Ezetimibe 10 mg Tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Ezetimibe 10 mg Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Ezetimibe 10 mg Tablets. The RMP details the important risks of Ezetimibe 10 mg Tablets, how these risks can be minimised, any uncertainties about Ezetimibe 10 mg Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Ezetimibe 10 mg Tablets:

Summary of safety concerns	
Important identified risks	• Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases. • Ezetimibe should not be used during lactation. Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation. • Contraindicated in case of hypersensitivity to the active substance or to any of the excipients.
Important potential risks	• In patients receiving fenofibrate and Ezetimibe, there is a possible risk of cholelithiasis and gallbladder disease. • Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations. • Risk of myopathy and rhabdomyolysis in most patients when taking a statin concomitantly with Ezetimibe. However, rhabdomyolysis has been reported very rarely with Ezetimibe monotherapy and very rarely with the addition of Ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. • Risk of increased International Normalised Ratio (INR) in patients who had Ezetimibe added to warfarin or fluindione.
Missing information	• Ezetimibe has not been studied in patients younger than 6 years of age. • Long-term efficacy of therapy with Ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood. • Effects of ezetimibe for treatment periods > 12 weeks in patients aged 6-10 years. • Safety and efficacy of Ezetimibe co-administered with doses of simvastatin above 40mg daily in patients 10 to 17 years of age. • Effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment. • Effects of ezetimibe for a treatment period > 33 weeks on growth and sexual maturation. • Use of Ezetimibe during pregnancy.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Ezetimibe 10 mg Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Ezetimibe 10 mg Tablets
A marketing authorisation for Ezetimibe 10 mg Tablets was granted in the United Kingdom (UK) on 16 June 2022.

The full PAR for Ezetimibe 10 mg Tablets follows this summary.

This summary was last updated in June 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Ezetimibe 10 mg Tablets (PL 49565/0031) could be approved.

The product is approved for the following indications:
Primary Hypercholesterolaemia
Ezetimibe 10 mg Tablets 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 10 mg Tablets 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)
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 10 mg Tablets is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemic patients, Ezetimibe inhibited intestinal cholesterol absorption by 54 %, compared with placebo.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Ezetrol 10 mg Tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

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

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

A marketing authorisation for Ezetimibe 10 mg Tablets was granted in the United Kingdom (UK) on 16 June 2022.

II QUALITY ASPECTS

II.1 Introduction

The active substance is ezetimibe.
Each Ezetimibe 10 mg Tablet contains 10 mg ezetimibe.

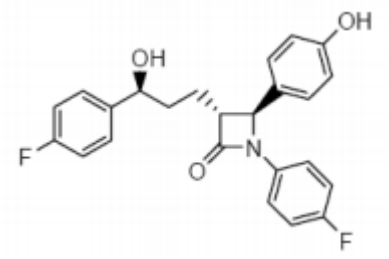
In addition to ezetimibe, this product also contains the following excipients:
Mannitol, butylhydroxyanisole, povidone (K-30), sodium laurilsulfate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate.

The finished product is packaged in Alu/PVC/ACLAR and Alu/PVC/PVDC blister packs and are available in pack-sizes of 7, 10, 14, 20, 28, 30, 50, 98, 100, or 300 tablets.
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: ezetimibe
Chemical Name: 1-(4-fluorophenyl)-3(R)-[3-(4- fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone
Molecular Formula: $C_{24}H_{21}F_2NO_3$
Chemical Structure:



Molecular Weight: 409.4
Appearance: White crystalline powder
Solubility: Soluble in ethanol, methanol, acetonitrile and acetone and practically insoluble in water and hexane.

The information related to the active substance was provided in an 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 specifications 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 specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in 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

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

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. Based on the results, a shelf-life of 3 years, without any special storage conditions, is acceptable.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of ezetimibe are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of ezetimibe is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

Bioequivalence Study 1

This study was an open label, balanced, randomized, two-treatment, two-sequence, four-period, single oral dose, fully replicate, crossover bioequivalence study comparing the test product, Ezetimibe 10 mg Tablets, with the reference product, Ezetrol 10 mg Tablets in normal, healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single oral dose of either test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 14 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Relative Bioavailability Results for Total Ezetimibe (N = 16)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Acceptance Criteria (%)	Intra-subject CV of Reference Product-R (%)	Power (%)
	Test Product-T (N = 27 Observations)	Reference Product-R (N = 29 Observations)	Ratio (T/R) %				
$\ln C_{max}$	110.871	118.940	93.2	86.24 - 100.76	80.00 - 125.00	18.1	99.8
$\ln AUC_{0-72}$	1053.219	1117.946	94.2	86.45 - 102.67	80.00 - 125.00	22.6	99.5

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application, and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND 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. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**