Public Assessment Report
Scientific discussion

Ezetimibe Accord 10 mg Tablets and Ezetimibe Astron 10 mg Tablets

Ezetimibe

ES/H/0329-0330/001/DC

Applicant: Accord Healthcare Limited & Astron Research Limited

This module reflects the scientific discussion for the approval of **Ezetimibe Accord 10 mg and Ezetimibe Astron 10 mg film-coated tablets**. The procedure was finalised on March 2016.

INTRODUCTION

This decentralised procedure concerns a generic application of ezetimibe, under Ezetimibe Accord 10 mg film-coated tablets and Ezetimibe Astron 10 mg film-coated tablets, claiming essential similarity with the innovator product Ezetrol 10 mg Tablets (MSD-SP Limited, UK). Ezetrol 10 mg Tablets have been registered in Germany since October 17th, 2002.

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

With Spain as the Reference Member State in this decentralised procedure, Accord Healthcare Limited and Astron Research Limited are applying for the Marketing Authorisations of Ezetimibe Accord 10 mg film-coated tablets and Ezetimibe Astron 10 mg film-coated tablets in:

- ES/H/0329/001/DC: AT, CZ, DE, DK, EE, FI, FR, IE, IS, LV, NL, NO, PL, PT, SE, SK and UK. CY, IT, RO and SI included in second wave.
- ES/H/0330/001/DC: CZ, DE, FR, HU, IT and NL. PL included in second wave.

Ezetimibe is a lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients.

Ezetimibe is a strong inhibitor of cholesterol and phytosterol absorption, lowering plasma cholesterol in humans by 15ï 20%. Radio-ligand binding investigations indicated that the direct target of ezetimibe is a Niemann-Pick C1-Like 1 transporter (NPC1L1). The NPC1L1, located in the brush border of enterocytes, is a critical protein in cholesterol transmembrane transport in the small intestine. Ezetimibe binds to its extracellular loop and blocks sterol absorption.

Ezetimibe is indicated for primary hypercholesterolaemia, homozygous familial hypercholesterolaemia and homozygous sitosterolaemia (phytosterolaemia). The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with ezetimibe. Route of administration is oral. The recommended dose is one ezetimibe 10 mg tablet daily. Ezetimibe can be administered at any time of the day, with or without food. When ezetimibe is added to a statin, either the indicated usual initial dose of that particular statin or the already established higher statin dose should be continued. In this setting, the dosage instructions for that particular statin should be consulted.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Ezetimibe Accord 10 mg film-coated tablets and Ezetimibe Astron 10 mg film-coated tablet**s for Accord Healthcare Limited and Astron Research Limited, respectively.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance
The drug substance is Ezetimibe. There is no Ph. Eur. monograph for this drug substance. The applicant has used the ASMF procedure.
Description of the manufacturing process is adequate. Elucidation and characterization of the drug substance are sufficient, including an acceptable proposal on impurities to control.
Specification for drug substance is considered adequate. Analytical methods are correctly described and their validation is performed according to ICH.
The proposed container for storage is similar than the one used in the stability studies.

Stability studies have been performed according to ICH/CPMP guidelines and guarantee the proposed retest period and storage conditions.

Drug Product
The drug product are immediate release, white to off white, capsule shaped, flat faced with beveled edge, uncoated tablets, debossed with "10" on one side and plain on the other side. Excipients are of Ph. Eur. quality and are commonly used in this dosage form.
All the manufacturers involved in the different steps of the drug product manufacture have been submitted. A flow chart of the manufacturing process, indicating critical steps and controls, is included.
Excipients specifications are according their respective Ph. Eur. monographs and are adequate for their function in the formulation.
The specification proposed is acceptable. Analytical methods are adequately described and their validation is performed according to ICH. Number and size of the analysed batches are considered sufficient.
Proposed packaging material is adequate for the proposed dosage form and coincides with the one used in the stability studies.
Stability studies have been performed according to ICH. The proposed shelf-life and storage conditions can be accepted.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.

The submitted application concerns film coated tablets with the active substances in the same form as the reference product.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. This was justified by the Applicant, since the proposed product Ezetimibe Tablets 10mg is generic version of Ezetrol® 10 mg tablets marketed by Merck Sharp & Dohme Limited, UK. The product is already available as generic product and the marketing authorization of the proposed product will not lead to any increased environmental risk. The risk assessment is based on following assumption.

- The proposed marketing authorisation will not lead to increase the use of this product; this would rather replace some of the products already available in market.
- There is no additional precautionary or safety measures required to be taken for this generic form, if the product is available in the market for more than 6/10 years.
- There is no specific requirement to be included on SPC and PIL in line with reference product.

II.3 Clinical aspects

Introduction

Ezetimibe is a well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. 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.

Biowaiver

Not applicable. The Applicant only applies for the 10 mg strength and this strenght is tested in vivo.

Bioequivalence

To support the application, the Applicant has submitted an open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of two products of ezetimibe tablets 10 mg in normal healthy, adult, human subjects under fasting condition.

The Clinical part of the study was performed at Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India and the principal investigator was Dr. Shashikant Sharma, MD.

The study was carried out from March 19th, 2013 to April 04th, 2013 and the study periods are described below:

- Period-I (dosing date): March 20th, 2013
- Period-II (dosing date): March 31st, 2013

The analytical portion was conducted at Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India from April 01st, 2013 to April 24th, 2013.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites have been inspected by Regulatory Authorities of the European Union without critical findings.

Design

This study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of two products of ezetimibe tablets 10 mg in normal healthy, adult, human subjects under fasting condition with a washout of 11 days.

This approach is acceptable as the application concerns an oral immediate release formulation (tablets). In addition, the administration of the reference product is irrespective of food intake. Therefore, a single dose study under fasting conditions is considered acceptable.

The wash-out period of 11 days (more than five times the half-life) is considered adequate since the drug has a half-life of approximately 22 hours and no pre-dose level was detected in the second period.

Considering the expected time to peak concentration (4-12 hours for ezetimibe) and the elimination half-life, the sampling schedule and the sampling time period of 96 hours seems long enough to estimate PK parameters.

Sampling is reasonably frequent over the first 12.00 hours and should be sufficient to allow an accurate measurement of t_{max}.

Test product: Ezetimibe 10 mg tablets manufactured by Intas Pharmaceutical Ltd., India. Batch number: N12127. Expiry date (Retest day): October 2014. Assay (content): 102.0% of label claim.

Reference product: Ezetrol 10 mg tablets manufactured by MSD-SP Limited-UK from the UK market. Batch number: 315036. Expiry date: September 2014. Assay (content): 99.1 % of label claim.

After an overnight fast of at least 10 hours, a single oral dose (10 mg) of either the test or the reference product was administered with 240 mL of drinking water at ambient temperature with the subjects in sitting posture.

The reference product is adequate with regards to expiry date, content and it was obtained from an European Union market (i.e. UK market).

A total of 56 subjects were included in this study and, after randomization, 51 subjects completed the study and were included in the pharmacokinetic and statistical analyses.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the linear trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.
According to the Guideline on investigation in bioequivalence, the evaluation of bioequivalence was based upon measured concentrations of the parent compound (free ezetimibe) as C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite.

Statistical analysis

The statistical analyses using the GLM procedure were performed on ln-transformed AUC_{0-t} and C_{max} of free ezetimibe (unconjugated). The results are summarized in the table below.

PK Parameter	90% Confidence Intervals			
	Point estimate%	Lowe limit %	Upper Limit %	Intra-subject CV%
C_{max}	94.9%	86.65%	103.91%	27.9%
AUC_{0-t}	100.1%	93.88%	106.68%	19.4%

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ratio test/reference of the ln-transformed C_{max} and AUC_{0-t} of ezetimibe are within the acceptance range of 80-125%.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Efficacy and safety of the active substance ezetimibe are well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results conclude bioequivalence with the reference product.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence has been shown in compliance with the requirements of European Union guidance documents.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in March 2016.