Public Assessment Report
Scientific discussion

Rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg Film-coated Tablets

Rosuvastatin calcium

ES/H/0376/001-004/DC

Applicant: Macleods Pharma UK Limited

Registration number in Spain:xxx

This module reflects the scientific discussion for the approval of **Rosuvastatin Macleods 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets.** The procedure was finalised on January 2017. For information on changes after this date please refer to the module ôUpdateô.

INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Crestor film-coated tablets by pharmaceutical form as the reference product (AstraZeneca B.V., The Netherlands). Crestor film-coated tablets have been registered since in November 6th, 2002 via the mutual recognition procedure (NL/H/0343/001-004/MR).

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

The Concerned Member States involved in this procedure are DE, FR, IT, NL and UK.

The efficacy and safety of rosuvastatin calcium has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Rosuvastatin Macleods 5, 10, 20 and 40 mg film-coated tablets are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, safety and efficacy has been carried out besides the bioequivalence studies against the reference product.

Rosuvastatin is indicated in adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate, in homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate and in the prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Rosuvastatin Macleods 5, 10, 20 and 40 mg film-coated tablets** for Macleods Pharma UK Limited.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance

The active substances Rosuvastatin is a known drug substance which are described in the European Pharmacopoeia.

The active substance manufacturer uses ASMF procedure. The Letter of Access has been provided.

General properties of the drug substance and manufacture are well described.

Sufficient information about specifications and analytical methods has been provided.

The re-test period for the drug substance is acceptable.

Drug product

The finished product is formulated as film-coated tablets containing 5 mg, 10 mg, 20 mg and 40 mg of rosuvastatin. The 4 strengths are dose proportional; the amount of active substance is about 10% w/w. The different strengths can be distinguished by color, debossing, size and tablet dimensions.

The product is packed in OPA/Al/PVC blisters and in HDPE containers. The excipients used in the formulation are well-established for solid-dosage forms and comply with relevant pharmacopoeial monographs. The pharmaceutical development has been properly described.

The applicant provides enough information on development of the dissolution method and discriminatory power of the dissolution has been demonstrated.

The manufacturing process are described in detail, in-process controls are adequate. The manufacture involves a direct compression. The manufacturing process is considered a standard process.

Specifications are considered acceptable. All the analytical methods are sufficiently described and have been acceptably validated in accordance with ICH requirements.

Stability data including accelerated and long term data are provided on the batches used for process validation and batch analyses. The available long term data cover the proposed shelf life. The testing conditions and frequency were in line with the ICH requirements. A proposed shelf life period can be accepted.

A commitment to place the first three production batches with the maximum proposed batch size on long term stability studies through the proposed shelf life and on accelerated studies for 6 months has been provided.

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. The medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.

In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

II.3 Clinical aspects

Introduction

Rosuvastatin Calcium 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

The bioequivalence of test and reference products has been demonstrated for 40 mg strength (please refer to section of results). These data can be extrapolated (i.e., 5 mg, 10 mg and 20 mg) since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

Bioequivalence

To support the application, the Applicant has submitted one bioequivalence study (Study Protocol number: BEQ-1300-ROSU-2014) ñan open label, balanced, analyst blind, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of Rosuvastatin Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Crestor (rosuvastatin calcium) tablets 40 mg marketed by AstraZeneca UK Ltd, UK in healthy, adult, human subjects under fasting condition".

The clinical phase of the study was performed from February 12th, 2015 to March 09th, 2015 at Macleods Pharmaceuticals Ltd., Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai ï 400 093, India and the principal investigator was Dr. Ajay Surwase (M.B.B.S.).

The study periods were:

- Period 1: February 12th, 2015 ï February 16th, 2015
- Period 2: February 20th, 2015 ï February 24th, 2015

The analytical portion was conducted at Macleods Pharmaceuticals Ltd., Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai ï 400 093, India, from March 12th, 2015 to March 31st, 2015.

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 were inspected by Regulatory Authorities of the European Union without critical findings.

Design

This was an open label, balanced, analyst blind, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of Rosuvastatin tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Crestor (rosuvastatin calcium) tablets 40 mg marketed by AstraZeneca UK Ltd, UK in healthy, adult, human subjects under fasting condition with a wash out period of 8 days.

This approach is acceptable as the application concerns an oral immediate release formulation (film-coated tablets) and according to the SmPC the reference product may be taken with or without food, therefore, a single dose study under fasting conditions with the highest strength is considered acceptable to demonstrate bioequivalence with the reference product.

The wash-out period of 8 days is considered adequate since the drug has a half-life of approximately 19 hours and this wash-out exceeds 5 elimination half-lives and no pre-dose levels were detected.

Considering the elimination half-life of rosuvastatine, the sampling schedule and the sampling time period of 72 hours seems long enough to estimate PK parameters. Sampling after 72 hours is unnecessary for immediate release formulations.

Test Product: Rosuvastatin 40 mg film coated tablets, manufactured by Macleods Pharmaceuticals Ltd. India. Batch number: BRA3302D. Batch size: 125,000 film-coated tablets.

Proposed batch size: 125,000-1,250,000 tablets. Manufacturing date: December 2013. Expiry date: November 2015 (as per CoA). Assay (content): 100.3% of label claim.

Reference Product: Crestor 40 mg film-coated tablets, manufactured by Astra Zeneca. Batch number: KS540. Expiry date: February 2017. Assay (content): 100.4% of label claim.

The reference product is adequate with regards to expiry date, content and it was obtained from UK market.

In this study, the Applicant decided to include 40 healthy volunteers. Among these subjects, 39 subjects were enrolled. Of these 39 subjects, subject No. 07 dropped-out from the study due to personal reason in period 1 (pre-dose), subject No. 14 was withdrawn from the study in period 1 (post-dose) on principal investigator advice due to adverse event and subject No. 20 did not report to the facility due to personal reason for period 2, thus considered dropped-out from the study. A total of 36 subjects completed the study and were included in the PK and statistical analysis.

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 trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

The pharmacokinetic data were analysed by the statistical package integrated in the PROC GLM SAS® version 9.4 using the analysis of variance (ANOVA) of the logarithmically transformed kinetic parameters AUC and C_{max} and the application of 90% confidence intervals. This ANOVA takes 4 factors into account: sequence, subjects (sequence), period and formulation.

Following EMA criteria, the two formulations were classified as bioequivalent if the standard 90% confidence intervals of the pharmacokinetic parameters (AUC_{0-72} and C_{max}) with log transformation are within the 80.00-125.00 range.

Results

The 90% confidence intervals mean treatment T/R ratios are shown in the following table (N=36):

PK Parameter	90% Confidence Intervals			
	Point estimate%	Lowe limit %	Upper Limit %	Intra-subject CV%[1]
C_{max}	113.52	102.85	124.85	24.43
AUC_{0-t}	107.62	100.47	115.28	17.27

[1] Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

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 for rosuvastatin the 90%

confidence intervals for the ln-transformed C_{max} and AUC_{0-72} 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

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

Efficacy and safety of the active substances etoricoxib are well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results allow us to conclude bioequivalence with the reference.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence has been shown to be 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 January 2017.