Public Assessment Report
Scientific discussion

Atorvastatin Almus Pharma 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets

Atorvastatin Calcium Trihydrate

Registration number in Spain:82627 ï 82628 ï 82629 - 82630

This module reflects the scientific discussion for the approval of **Atorvastatin Almus Pharma 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets**. The procedure was finalised on September 2017. For information on changes after this date please refer to the module óUpdateô.

INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sortis film-coated tablets by pharmaceutical form as the reference product (Pfizer Pharma GmbH, Germany). Sortis film-coated tablets have been registered since in January 09th, 1997 in Germany.

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

The Concerned Member States involved in this procedure are France and Italy.

The efficacy and safety of atorvastatin calcium trihydrate has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Atorvastatin Almus Pharma 10 mg, 20 mg, 40 mg and 80 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 study against the reference product.

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Atorvastatin is furthermore indicated for prevention of cardiovascular events in adult patients 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 **Atorvastatin Almus Pharma 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets** for Almus Farmacéutica, S.A.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

DRUG SUBSTANCE

Atorvastatin calcium trihydrate is a known active substance described in Ph.Eur. The supplier of active substance has been submitted a CEP in order to support the quality of the active ingredient.

The re-test period of the substance indicated in the CEP is 60 months if stored in double polyethylene bags in a triple laminated polybag, placed in a polyethylene container.

DRUG PRODUCT

Description of the product

The finished product is formulated as tablets containing 10, 20, 40 and 80 mg of Atorvastatin calcium trihydrate. All film-coated tablets are white, round, biconvex tablets with bisection line on one side and debossed with 10, 20, 40 and 80 on other side respectively. The difference between tablets strengths is the dimensions ranging from 7 mm to 20 mm and the different strengths are debossed to state the strength on the tablet.

The qualitative composition of the tablets is as follows:

Tablet core:

- Atorvastatin calcium trihydrate
- Calcium carbonate, E170
- Microcrystalline cellulose, E460
- Lactose monohydrate
- Croscarmellose sodium
- Copovidone
- Crospovidone type B
- Magnesium stearate, E572
- Sodium laurilsulfate
- Silica, colloidal anhydrous
- Talc

Tablet coating:

- Hypromellose, E464
- Macrogol 400
- Titanium dioxide, E171
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The product is packed in PVC/PE/PVdC Alu blister.

Pharmaceutical development

The pharmaceutical development has been properly described.

The function of the excipientes has been discussed. Selection of the dissolution method has been justified and the discriminatory power of dissolution method has been demonstrated.

Manufacture of the product and process controls

The manufacturing process is divided in two parts, the production of common blend for all strengths of atorvastatin film-coated tablets and compression of the common blend into tablet cores followed by coating. The process has been satisfactorily validated on three batches of each strength and process validation results have been provided from both manufacturing sites.

Excipients

The information provided is adequate. The analytical procedures used to control the excipients are performed according to the European Pharmacopoeia monographs.

Product specification

Specifications proposed are adequate. The limits proposed for the different parameters have been adequately justified.

All analytical methods have been correctly validated following the ICH Q2 (R1) Guideline.

Container closure system

Atorvastatin film-coated tablets are packed in:

PVC/PE/PVdC Alu blister.

The components of the container closure system comply with the requirements of European Pharmacopoeia 3.1.11.

Stability

Stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

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

Atorvastatin calcium trihydrate 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 80 mg strength (please refer to section of results). These data can be extrapolated (i.e., 10 mg, 20 mg and 40 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 a bioequivalence study ña single centre, randomized, single-dose, 3-period crossover reference-replicate BA study to compare the bioavailability of the test Atorvastatin versus and the reference Sortis (Pfizer Pharma GmbH), under fasting conditions.

The clinical part of the study was performed from December 28th, 2010 to January 27th, 2011 at University of Skopje, Medical Faculty, Department of Preclinical and Clinical Pharmacology & Toxicology, 50 Divizija b.b., 1000 Skopje, Republic of Macedonia and the principal investigator was Nikola Labacevski, MD, Ph.D.

The study periods were:

- Period I (dosing): December 28th, 2010
- Period II (dosing): January 11th, 2011
- Period III (dosing): January 25th, 2011

The analytical portion was conducted at Anapharm Europe S.L.U., C/ Encuny 22 - 08038 Barcelona (Spain) from February 02nd, 2011 to March 01st, 2011.

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 a single centre, randomized, single-dose, 3-period crossover reference-replicate BA study to compare the bioavailability of the test Atorvastatin versus the reference Sortis (Pfizer Pharma GmbH), under fasting conditions with a washout period of 14 days.

Atorvastatin PK parameters are shown to be more than proportional and the innovator SmPC recommends that atorvastatin can be taken with our 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 14 days is considered adequate since the drug has a half-life of approximately 14 hours and this wash-out exceeds 5 elimination half-lives.

Considering the elimination half-life of atorvastatin, the sampling schedule and the sampling time period of 48 hours seems long enough to estimate PK parameters. The mean percentage of extrapolated area under the curve was lower than 20% for all subjects indicating that the duration of sampling was sufficient.

Considering the expected time to peak concentration (1.0-2.0 hours), sampling is reasonably frequent over the first 3 hours and should be sufficient to allow an accurate measurement of t_{max} and C_{max}.

Test Product: Atorvastatin 80 mg film-coated tablets manufactured by Alkaloid AD, Skopje, Republic of Macedonia. Batch number: 30528 0710. Batch size: 100,000 film-coated tablets. Proposed batch size: 200,000-400,000 film-coated tablets. Manufacturing day: July 2010. Expiry date (re-test date): July 2012. Assay (content): 98.21 % of label claim.

Reference Product: Sortis® 80 mg film-coated tablet, manufactured by Parke-Davis (Pfizer Pharma GmbH, Germany). Batch number: 0629040D. Expiry date: March 2013. Assay (content): 99.04% of label claim.

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

Randomization of the test and the reference dosage form administration over the subject and the study session was performed using the random number generator. Subjects were randomly assigned to one of the following sequences: ABB, BAB, or BBA.

According to the Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604/2008), if a 3 period design is to be used to justify a widening of the limits for C_{max} subjects the most efficient study design would randomise subjects to receive treatments in the following order: RRT, RTR or TRR. This design is the most efficient as all subjects receive the reference product twice and hence an estimate of the within subject variability is based on data from all subjects.

In this study, 45 subjects signed the ICF, were randomized, and dosed in this study; of these 44 subjects completed the study. Although, subject No. 25 had not available concentration in Period 3, the subject was included in the pharmacokinetic and statistical analyses since data for the test and the reference product is available.

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 statistical analyses using the GLM procedure and including data from Subject no. 25 were performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. The results are summarized in the table below.

PK Parameter	90% Confidence Intervals			
	Point estimate%	Lowe limit %	Upper Limit %	Intra-subject CV%
C_{max}	92.74%	83.28%	103.27%	33.89%
AUC_{0-t}	98.93%	93.97%	104.15%	17.24%
$AUC_{0-Đ}$	98.90%	94.06%	103.99%	16.81%

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 atorvastatin the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-t} 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 substance atorvastatin 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 September 2017.