

Public Assessment Report

Scientific discussion

Atorvastatin Krka
10mg, 20mg and 40mg film coated tablets

(Atorvastatin calcium)

SE/H/642/01-03/DC

This module reflects the scientific discussion for the approval of Atorvastatin Krka. Please note that the marketing authorisation was first approved with the name “Atostin” and therefore this name is used throughout the document. The procedures were finalised at 2008-03-13. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

Jacobsen Pharma AS has applied for a marketing authorisation for Atostin film coated tablets, 10 mg, 20 mg and 40 mg claiming essential similarity to Lipitor, film coated tablets 10 mg, 20 mg and 40 mg marketed in Sweden by Pfizer AB. The product contains Atorvastatin calcium as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Sortis 40 mg marketed by Pfizer in Germany.

II. QUALITY ASPECTS

II.1 Introduction

Atostin is presented in the form of tablets containing 10.36, 20.72 or 41.44 mg of atorvastatin calcium which corresponds to 10, 20 and 40 mg, respectively, of the atorvastatin. The excipients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, crospovidone, sodium laurilsulfate, sodium hydroxide, magnesium stearate and Opadry II HP white 85F28751. The tablets are packed in OPA/Al/PVC-aluminium blisters.

II.2 Drug Substance

Atorvastatin calcium does not have a monograph in the Ph Eur.

Atorvastatin calcium is a white or slightly white powder sparingly soluble in DMSO, soluble in methanol, practically insoluble in water and 10% HCl. The structure of Atorvastatin calcium has been adequately proven and its physico-chemical properties sufficiently described. The substance is amorphous and shows non-crystalline properties. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Atostin, film coated tablets, 10 mg, 20 mg and 40 mg are formulated using excipients described in the current Ph Eur. Only lactose monohydrate is of animal origin and compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01) has been demonstrated.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored in the original package in order to protect from light and moisture.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

One bioequivalence study comparing the pharmacokinetic profiles of Atostin 40 mg tablets with Sortis 40 mg tablets, Pfizer was performed. The study design was an open, 2 periods, 2-way crossover study performed in healthy, adult, male human subjects under fasting conditions. Plasma samples were analyzed for atorvastatin, orthohydroxy atorvastatin (2-OH-atorvastatin) and parahydroxy atorvastatin (4-OH-atorvastatin) by a validated LC-MS/MS method. Pharmacokinetic parameters were calculated using conventional non-compartmental methods. ANOVA was performed on the ln-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$.

Pharmacokinetic results are shown in the tables 1-3 below.

Table 1. Atorvastatin pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	111.7 $\pm$ 144.8	117.5 $\pm$ 145.0	23.64 $\pm$ 23.88	0.75 (0.5-3.0)	12.2 $\pm$ 3.1
Reference	99.97 $\pm$ 78.21	106.0 $\pm$ 78.34	22.48 $\pm$ 24.15	0.75 (0.25-4.0)	13.0 $\pm$ 4.2
*Ratio (90% CI)	102.4 (97.3-107.7)	102.2 (97.2-107.4)	109.9 (97.9-123.4)	NS	
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration T_{max} time for maximum concentration $T_{1/2}$ half-life NS no statistically significant difference					

*ln-transformed values

Table 2. 2-OH-atorvastatin pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range)

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h	T _{1/2} h
Test	102.0 $\pm$ 71.9	109.4 $\pm$ 71.7	13.8 $\pm$ 9.7	1.0 (0.5-4.0)	13.2 $\pm$ 4.5
Reference	94.48 $\pm$ 52.7	102.1 $\pm$ 52.3	12.5 $\pm$ 13.6	1.0 (0.5-4.0)	16.2 $\pm$ 5.2
*Ratio (90% CI)	104.9 (100.1-109.8)	104.9 (99.8-110.3)	112.5 (100.9-125.529)		
AUC _{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration T _{max} time for maximum concentration T _{1/2} half-life					

**In-transformed values*

Table 3. 4-OH-atorvastatin pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range)

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h	T _{1/2} h
Test	13.5 $\pm$ 15.6		0.52 $\pm$ 0.65	6.0 (5.0-36)	
Reference	12.7 $\pm$ 10.5		0.62 $\pm$ 1.1	16 (0.25-48)	
*Ratio (90% CI)	100.6 (87.5 – 115.6)		101.4 (90.0-114.3)		
AUC _{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration T _{max} time for maximum concentration T _{1/2} half-life					

**In-transformed values*

Bioequivalence between the two products, in terms of rate (C_{max}) and extent of absorption (AUC), was adequately demonstrated.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The SPC, package leaflet and labelling are acceptable

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Atostin, 10 mg, 20 mg and 40 mg film coated tablets, are recommended for approval.

VI. APPROVAL

The Decentralised procedures for Atostin, film coated tablets, 10 mg, 20 mg and 40 mg were successfully finalised on 2008-03-13.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)