LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Atorvastatin Krka
(Atorvastatin calcium)

SE/H/642/05-07/DC

This module reflects the scientific discussion for the approval of Atorvastatin Krka. The procedure was finalised at 2011-03-10. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Krka, d.d., Novo mesto has applied for a marketing authorisation for Atorvastatin Krka, film-coated tablet, 30 mg, 60 mg and 80 mg claiming essential similarity to Lipitor, film-coated tablet, 10 mg marketed the EU by Pfizer. 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, film-coated tablet, 80 mg marketed by Pfizer in EU.

II. QUALITY ASPECTS

II.1 Introduction

Atorvastatin Krka is presented in the form of tablets containing atorvastatin calcium corresponding to 30, 60 and 80 mg of atorvastatin. The excipients are sodium hydroxide, hydroxy-propylcellulose, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polysorbate 80, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol and talc.

II.2 Drug Substance

The scientific information on drug substance has been submitted in a frame of an Active Substance Master File.

The structure of atorvastatin calcium has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substances specifications include 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

Atorvastatin Krka film-coated tablets are formulated using excipients described in the current Ph Eur. Only lactose monohydrate is of animal origin. 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 (EMEA/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, with no special temperature storage precautions.

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

Bioequivalence was evaluated in one single-dose cross-over bioequivalence study under fasting conditions, comparing Atorvastain Krka 80 mg film-coated tablet with Sortis 80 mg, film-coated tablet (Pfizer). Plasma concentrations of atorvastatin and 2-hydroxyatorvastatin were determined with a validated HPLC-method with MS/MS-detection.

The available data on atorvastatin and metabolite PK indicate linear pharmacokinetics for parent compound, but give conflicting data on metabolite with possibly more than proportional increase in exposure for active metabolites. In this situation, the highest dose is most sensitive to detect potential differences between formulations, and a biowaiver for the lower strengths 30 and 60 mg is acceptable.

Bioequivalence was demonstrated for C_{max} and AUC for both atorvastatin and 2-hydroxyatorvastatin. Bioequivalence has been sufficiently 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 consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Atoris 10mg, 20mg and 40mg film-coated tablets, DCP/MRP number SE/H/642/01-03/E01, SE/H/757/01-03/E01 and SE/H/758/01-03/E01. The bridging report submitted by the applicant has been found 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 Atorvastatin Krka, film-coated tablet, 30 mg, 60 mg and 80 mg is recommended for approval.

Specific obligations (Quality)

- It is committed that the process validation will be performed on three consecutive batches for each scale up.

VI. APPROVAL

The Decentralised procedure for Atorvastatin Krka, film-coated tablet, 30 mg, 60 mg and 80 mg was successfully finalised on 2011-03-10.

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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)

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