LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Simvastatin Brown (simvastatin)

SE/H/598/01-04/DC

This module reflects the scientific discussion for the approval of Simvastatin Brown. Please note that the marketing authorisation was first approved with the name "Simvastatin Morningside" and therefore this name is used throughout the document. The procedure was finalised at day 210 (18/7-2007). For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Morningside Healthcare Ltd, UK, has applied for a marketing authorisation for Simvastatin Morningside, film-coated tablets, 10 mg, 20 mg, 40 mg and 80 mg claiming essential similarity to Zocord, film-coated tablets, 10 mg, 20 mg, 40 mg and 80 mg marketed in Sweden by MSD (The Netherlands). The product contains simvastatin as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Zocor, tablets, 80 mg, Merck, Sharp & Dohme Ltd, taken from the UK market.

II. QUALITY ASPECTS

II.1 Introduction

Simvastatin Morningside is presented in the form of film-coated tablets containing 10 mg, 20 mg, 40 mg or 80 mg of simvastatin. The excipients are lactose anhydrous, pregelatinized maize starch, microcrystalline cellulose, butylated hydroxyanisole, magnesium stearate and purified talc. The simvastatin tablets are packed in blisters of printed aluminium foil and a triplex film of PVC/PE/PVDC.

II.2 Drug Substance

Simvastatin with butylated hydroxyanisole 0.01% has a monograph in the Ph Eur.

Simvastatin is a white or almost white crystalline powder. The structure of simvastatin 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 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

Simvastatin Morningside, film-coated tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin or have demonstrated 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).

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 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 a single dose, cross-over study in healthy, male, fasting subjects, comparing the 80 mg generic tablet with Zocor 80 mg tablet from the UK market. A single-dose, fasting study with one tablet strength is appropriate from a pharmacokinetic point of view, as the application concerns an immediate-release formulation, the pharmacokinetics of simvastatin are linear over the clinical dose range and are unaffected by food. From a quality point of view, the dissolution profiles of the different tablet strengths applied for are similar, their composition is proportional and they are manufactured at the same production site.

The analytical method for simvastatin and simvastatin acid in plasma has been adequately validated.

The study protocol stated that bioequivalence would be concluded if the 90% CI for AUC_{0-t} and AUC_{∞} for simvastatin as well as simvastatin acid were within 80-125%, and the 90% CI for C_{max} for both analytes were within 175-133%. The widening of the acceptance criteria for C_{max} was prospectively justified by suggesting that efficacy and safety of simvastatin depends on AUC, representing amount absorbed, and not on C_{max}, representing rate of absorption.

The predefined criteria were met. For the active form, simvastatin acid, the 90% CI for C_{max} as well as AUC were within 80-125%. For simvastatin, the 90% CI for the AUC parameters were within 80-125% and for C_{max} it was 78.5-106% (Tables 1 and 2). The two products were therefore concluded to be bioequivalent.

Table 1. Pharmacokinetic parameters for *simvastatin* (non-transformed values; presented as arithmetic mean ± SD, except for t_{max}, which is presented as mean, range) after a single 80 mg dose

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	179.2±100.4	218.0 ± 146.5	36.5 ± 25.3	1.9 (0.5-5.0)	8.8 ± 8.9
Reference	181.6 ± 114.4	197.2 ± 123.6	42.1 ± 35.7	2.2 (0.5-12)	5.9 ± 3.1
T/R Ratio (90% CI)*	100.6 (90.4 - 111.9)	108.7 (97.0 - 121.8)	91.2 (78.5 - 106.0)	na	na
CV (%)	37.4	39.9	54.5	50.6	59.8

$AUC_{0-\infty}$	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
CV	intra-subject residual coefficient of variation

*ln-transformed values

Table 2. Pharmacokinetic parameters for *simvastatin acid* (non-transformed values; presented as arithmetic mean ± SD, except for t_{max}, which is presented as mean, range) after a single 80 mg dose

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	62.5 ± 29.2	73.1 ± 40.4	9.7 ± 5.1	4.3 (1.5-8.0)	5.7 ± 4.9
Reference	67.7 ± 48.2	78.0 ± 53.4	11.4 ± 8.1	4.0 (1.0-8.0)	6.5 ± 16.6
Ratio (90% CI)*	100.0 (89.4 - 111.8)	98.8 (88.2 - 110.7)	90.5 (80.9 - 101.2)	na	na
CV (%)	39.2	40.0	39.4	33.1	71.9

$AUC_{0-\infty}$	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
CV	intra-subject residual coefficient of variation

*ln-transformed values

In addition, the Applicant submitted results from a bioequivalence study performed with a related formulation, for the US market, determined against the US reference product. Comparison of the qualitative formulations of the UK and US reference products showed that they are identical, and the US labelling states that the US product is manufactured in the UK. The European test product and the US test product only display minor formulation differences that are suggested not to cause any differences in either *in vivo* or *in vitro* behaviour. The *in vitro* dissolution profiles were comparable. In the US bioequivalence study, confidence limits for C_{max} as well as AUC of simvastatin and simvastatin acid were within the normal acceptance criteria of 80-125%. Although a full assessment of the US study or the comparability of the different test and reference products could not be made within the 210 days procedure, the US study was considered to be supportive.

IV.2 Discussion on the clinical aspects

The justification of wider acceptance criteria for C_{max} was closely discussed during the procedure, and especially the risk of widening the acceptance criteria for C_{max} upwards, i.e. accepting a higher C_{max} than for the originator. However, it was agreed that a potentially lower C_{max} of simvastatin prodrug for a generic simvastatin product, as indicated by the observed 90% confidence limits in the bioequivalence study, does not constitute a problem for either efficacy or safety. Although the Applicant may not have provided fully convincing arguments for why a higher C_{max} will not increase the risk for rhabdomyolysis, widening the lower acceptance limit for C_{max} to 75% is acceptable as C_{max} is not important for efficacy. As the simvastatin dose is not individually titrated and the risk for rhabdomyolysis at a certain dose is estimated based on data from a study population who has received the originator product with a potentially higher C_{max}, it should be acceptable to switch from Simvastatin Morningside to the originator as well as from the originator to Simvastatin Morningside. In addition, the deviation of the confidence limits for simvastatin C_{max} from the normal acceptance criteria was only minor, and based on the results of the US bioequivalence study it might have been a random result.

No clinical studies regarding efficacy and safety have been submitted with the present application, which is acceptable, as the application concerns a generic drug and bioequivalence with the originator has been demonstrated.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

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 Simvastatin Morningside, film-coated tablets, 10 mg, 20 mg, 40 mg and 80 mg, are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Simvastatin Morningside, film-coated tablets, 10 mg, 20 mg, 40 mg and 80 mg was successfully finalised on 2007-07-18.

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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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