COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fluvastatine 20 mg and 40 mg PCH, capsules

(fluvastatin sodium)

NL/H/4738/001-002/DC

Date: 30 January 2019

This module reflects the scientific discussion for the approval of Fluvastatine 20 mg and 40 mg PCH, capsules. The procedure was finalised on 6 May 2006 with the United Kingdom as RMS (UK/H/0977/001-002/DC). The current RMS since 31 December 2018 is the Netherlands (NL/H/4238/001-002/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fluvastatine 20 mg and 40 mg PCH, capsules, from TEVA UK Limited.

The product is indicated for in the treatment of primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb), as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Fluvastatine 20 mg and 40 mg PCH, capsules are also indicated for the secondary prevention of major adverse cardiac events (cardiac death, non-fatal myocardial infarction and coronary revascularisation) after coronary transcatheter therapy).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product of Lescol 20 mg and 40 mg capsules which has been registered in the United by Novartis since 23 August 1993.

The concerned member states (CMS) of the initial procedure were Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, The Netherlands, Norway, Portugal, Sweden and Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The 20 mg capsules have an ivory opaque body and pink opaque cap marked 93/7442, and are filled with an off-white to yellowish powder with small agglomerates. Each 20 mg capsule contains 20 mg fluvastatin (as fluvastatin sodium).
The 40 mg capsules have a yellow opaque body and pink opaque cap marked 93/7443, and are filled with an off-white to yellowish powder with small agglomerates. Each 40 mg capsule contains 40 mg fluvastatin (as fluvastatin sodium).

The capsules are packed in Aluminium – Aluminium blister packs and/or white HDPE bottles with white PP child-resistant closure and silica gel as desiccant.

The excipients are lactose monohydrate, colloidal anhydrous silica, crospovidone and magnesium stearate, red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin. The printing ink contains shellac, propylene glycol and black iron oxide (E172).

II.2 Drug Substance

The active substance is fluvastatin sodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.) but a monograph exists in the United Stated Pharmacopeia (USP). The drug substance is a white to pale-yellow, brownish–pale yellow or reddish–pale yellow, hygroscopic powder.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the MAH or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance fluvastatin sodium. The active substance specification provided is acceptable.
Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Active fluvastatin sodium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data have been provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.
Appropriate stability data have been generated supporting a shelf-life of 24 months with no specific storage conditions.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Dissolution and impurity profiles of drug product were found to be similar to those for the reference product.

Manufacturing process

A description and flow-chart of the manufacturing method has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture.

Control of excipients

All the ingredients within the body of the capsule comply with their relevant Ph. Eur. monographs. Red iron oxide (E172), yellow iron oxide (E172) comply with in-house specifications. Both shellac and propylene glycol comply with their relevant Ph. Eur. monographs and black iron oxide (E172) complies with in-house specifications. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their respective monograph/specifications. These specifications are acceptable.

Quality control of drug product

Validations of the analytical methods have been presented. Preliminary validation studies have been carried out on four pilot-scale batches with the commitment to provide the results for the first three consecutive full-scale batches; this is satisfactory. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

Stability of drug product

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Do not store above 30oC” for the blister packs and no specific storage conditions required for the HDPE bottles.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The only excipients used that contain material of animal or human origin are lactose monohydrate and gelatin. The MAH has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. A satisfactory TSE certificate of suitability has been provided for the supplier of gelatin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fluvastatine PCH has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fluvastatine 20 mg and 40 mg PCH, capsules is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Lescol which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fluvastatin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study.

IV.2 Pharmacokinetics

Biowaiver

The bioequivalence study has been conducted with the 40 mg strength. A biowaiver has been claimed for the lower 20 mg strength based on the standard criteria as detailed in the CPMP guidance note (CPMP/EWP/QWP/1401/98). The MAH and expert claim that the required criteria are fulfilled.

The biowaiver claim is accepted as the MAH has indeed fulfilled the criteria for biowaiver as specified in the guidance note. The manufacturer is the same, the composition of the two strengths is the same in terms of active/excipient ratios, the kinetics (drug input) of fluvastatin is linear within the dose range and the dissolution profiles demonstrated have been similar.

Bioequivalence study

Methods
Study design
Study number 2005-1016
A single dose, single centre, randomised, open label, crossover, two-period, bioequivalence study of two formulations of Fluvastatine PCH under fasting conditions.

Test and reference products
TEST [Treatment –A]; 40 mg capsules
REF [Treatment –B]; Lescol 40 mg capsules

The compositions of the test and reference products are qualitatively similar. Detailed information on the test formulation is found in module 3.

Overall 80 healthy male and female volunteers (75 M, 5 F) aged 18-55 years were included. All had to fulfil specific inclusion/ exclusion criteria. The mean age was 36±10 years (range of 20-54). Of these 65 were caucasian, 8 blacks and 7 were asian.

Study period;
Period -1; 16th Jan, 2006
Period 2; 23rd Jan, 2006
Washout; 7 days
Analytical Period; Feb 2006

Assessor's comment:
The 2x2 crossover study under fasting conditions using the 40 mg (higher strength) is acceptable. The Reference product is from the UK market (EU community authorised) and is thus appropriate. As discussed previously, the biowaiver criteria have been satisfactory addressed and the choice of the strength is acceptable with results extrapolatable to the lower strength. The healthy population included is appropriate. Healthy volunteer studies are acceptable for demonstration of bioequivalence and the results considered applicable to the general population or patients. The inclusion of females and racial groups are acceptable, although the distribution is frequently unequal as in this study. This however is unlikely to affect the results in the crossover, intra-individual comparison of pharmacokinetic parameters. The wash out period of 7 days should be sufficient to avoid any carry-over effect, as the β-elimination half-life is reported to be less than 3 hours. The study was conducted in accordance with GCP, local regulatory requirements and the Declaration of Helsinki.

Analytical methods
The plasma samples were assayed for fluvastatin using a validated assay method. In each period, 23 blood samples were obtained at 22 time points [pre-dose, 0.167, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours following drug administration].

Assessor's comment
The sample collection period covers the elimination half-life of fluvastatin adequately. Blood sampling points are appropriate to allow an accurate measurement of T_{max}. The sampling interval was sufficiently close in the first three hours to cover the period of anticipated Cmax / tmax. The method of collection the assay used and analysis appear to be appropriate.

Pharmacokinetic variables

The standard pharmacokinetic parameters were obtained using a non-compartmental approach. These included; AUC_t (0- last measurable time point), AUC_{inf}, C_{max}, Kel(λ) and $t_{1/2}$. $AUCi_{nf}$, Kel, and $t_{1/2}$ were not estimated from concentration-time profiles where the terminal linear elimination phase was not clearly defined.

Statistical methods

The statistical analysis was applied to the quality assured final data set from all subjects. The ANOVA method was applied to log transformed AUC_t, AUC_{inf} and C_{max} and to untransformed Kel and $t_{1/2}$ parameters. The significance of the sequence, period, and treatment effects were tested. In addition, the subject within sequence random effects was also tested. Using the same models, the least square means the differences between treatments LSM and the standard errors were estimated for log transformed parameters. Based on these the bioequivalence criteria were defined as below.

Bioequivalence criteria

90% geometric intervals of the ratio (A/B) of least square means from the ln-transformed values for AUC_{0-t} for fluvastatin should be within 80-125% and C_{max} was to be within 70-143% for fluvastatin.

The decision to use wider intervals for C_{max} was based on the efficacy and safety calculations. The reasons are presented in the protocol and are founded on the compendium of pharmaceuticals & Specialities (2004), a publication by Dujovne CA et al regarding similar efficacy /safety of fluvastatin administered at bedtime or 4 hours after an evening meal.

The MAH has presented data demonstrating that the dose at which non-linearity takes effect is beyond 40 mg. A number of publications do support this including the NDA file that the MAH discusses. It is considered that the MAH has addressed the issue of linearity. The results demonstrate that the two enantiomers are within the acceptability limits of 80-125%.

Sample size

Sample size of 76 was estimated from calculations using an in-house study indicating an intra-subject variability of ~42%. Further assumptions were used (50% variability and a treatment difference of <10%) a necessary sample for 95% probability to retain 90% CI within 70-143 was estimated to be 76 subjects. Four further subjects were added and thus 80 subjects were recruited.

Assessors comment
The PK variables are appropriate for a bioequivalence study. The statistical methods deployed follow the standard principles and are acceptable.

Results

Table 1. Pharmacokinetic parameters

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	400.38 435.55 (46)	358.22 395.21 (48)	111.77	106.07 - 117.78	20
AUCinf (ng*h/mL)	404.92 440.15 (45)	362.79 399.72 (48)	111.61	105.96 - 117.56	20
Cmax (ng/mL)	295.99 337.69 (57)	290.91 343.36 (61)	101.75	90.64 - 114.21	46
Tmax[a] (h)	1.10 (55)	0.78 (31)	-	-	-
Kel[a] (1/h)	0.3499 (42)	0.3461 (39)	-	-	-
Thalf[a] (h)	2.30 (39)	2.31 (37)	-	-	-

Safety results
There were a few adverse events reported for both formulations; 26 overall in 18 subjects. Of these, 17 were with the test and 9 with the REF formulation. All events were mild to moderate and only one needed further action/ intervention. Thirteen were considered possibly related to the study medication. The predominant ADR was headache. A summary table is included below.

There were 26 adverse events involving 18 subjects in the study.

	Severity			Relation to the Drug				Intervention	
Treatment Group	Mild	Mod	Severe	Unrelated	Unlikely	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A	17	0	0	7	0	10	0	0	1
B	9	0	0	6	0	3	0	0	0
Total	**26**	**0**	**0**	**13**	**0**	**13**	**0**	**0**	**1**

Assessor's comment
The study report provides a summary table that is represented above. Both the arithmetic mean and geometric mean are presented. 90% CI for both CI for both Cmax and AUC were within the conventional acceptance criteria of 80-125%.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study, Fluvastatine PCH capsules are considered bioequivalent with Lescol 40 mg and corresponding tablets in other nationally authorised brand leader products (Novartis Pharmaceuticals).

The results of study 2005-1016 with 40 mg formulation can be extrapolated to other strengths 20 mg, according to conditions in *Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4*.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lescol. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product.. This generic medicinal product can be used instead of the reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fluvastatine 20 mg and 40 mg PCH, capsules have a proven chemical-pharmaceutical quality and are generic forms of Lescol 20 mg and 40 mg capsules. Lescol is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fluvastatine 20 mg and 40 mg PCH, capsules with the reference product, and have therefore granted a marketing authorisation.

STEPS TAKEN AFTER THE FINALISATION OF THE PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse