COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pravasor 40 mg coated tablets

(pravastatin)

NL/H/4614/001/DC

Date: 8 January 2020

This module reflects the scientific discussion for the approval of Pravasor 40 mg coated tablets. The procedure was finalised at 2 December 2019. 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 Pravasor 40 mg coated tablets, from Laboratoires S.M.B. S.A.

The product is indicated for:

- *Hypercholesterolemia*
  Treatment of primary hypercholesterolemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.
- *Primary prevention*
  Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia and at high risk of a first cardiovascular event, as an adjunct to diet.
- *Secondary prevention*
  Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors.
- *Post transplantation*
  Reduction of post transplantation hyperlipidaemia in patients receiving immunosuppressive therapy following solid organ transplantation.

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 Selektine 40 mg tablets (NL License RVG 20665) which was registered since 17 December 1996 by Bristol-Myers Squibb B.V. through a mutual recognition procedure (FR/H/0252/003). This product has been withdrawn on 31 December 2019 (after finalisation of this application).

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Pravasor is a green, oblong, coated tablet and can be divided into equal doses. Each tablet contains 40 mg of pravastatin sodium.

The coated tablets are packed in PVDC/PE/PVC/Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), povidone K29-32, sodium hydrogen carbonate, sodium starch glycolate type A and magnesium stearate (E470b).
Tablet coating - hypromellose (E464), gelatin, titanium dioxide (E171), yellow iron oxide (E172) and indigotin (E132).

II.2 Drug Substance

The active substance is pravastatin sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Pravastatin sodium is a white to yellowish white powder or crystalline powder, freely soluble in water and methanol, and soluble in anhydrous ethanol.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the CEPs. Batch analytical data demonstrating compliance with this specification have been provided for five full-scaled batches.

Stability of drug substance
For one manufacturer of the active substance a re-test period of 24 months when stored under the stated conditions is granted. Assessment thereof was part of granting the CEP and

has been granted by the EDQM. For the other drug substance manufacturer stability data on the active substance have been provided for four full-scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are acceptable. One bioequivalence study has been performed. Comparative dissolution profiles between the test bio-batch and reference bio-batch have been provided and are considered comparable. Overall, the pharmaceutical development is considered acceptable.

Manufacturing process

The manufacturing process consist of blending of the intragranular ingredients, granulation, blending granules with the extra granular ingredients, tabletting, pre-coating and gelatin coating and has been validated according to relevant European. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur or in-house requirements where applicable. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, uniformity of dosage units, identification, assay, related substances, dissolution, microbial limit test. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three pilot scaled batches stored at 25°C/60% RH (18 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the approved blisters. Photostability has been confirmed in line with ICH Q1B guideline. On basis of the data submitted, a shelf life was granted of 24 months if stored below 30°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The excipients gelatin and lactose monohydrate are of animal origin. Adequate TSE/BSE free declarations/statements have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pravasor has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pravasor 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 Selektine 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

Pravastatin 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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Pravasor 40 mg coated tablets (Laboratoires S.M.B. S.A., Belgium) is compared with the pharmacokinetic profile of the reference product Selektine 40 mg tablets (Bristol-Myers Squibb B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male and female subjects, aged 22-54 years. Each subject received a single dose (40 mg) of one of the 2 pravastatin formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of at least 3 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets can be taken with or without food. As such, the fasting condition applied in the study is considered adequate.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject withdrew from the study. A total of 39 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pravastatin under fasted conditions.

Treatment N=39	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	15108 ± 9134	15353 ± 9147	115 ± 81	1.0 (0.75 – 2.0)	--

Reference	14353 ± 8735	14669 ± 8731	114 ± 70	0.75 (0.5 – 1.5)	--
***Ratio (90% CI)**	1.06 (0.98 – 1.15)	--	0.98 (0.88 – 1.09)	--	--
CV (%)	20.3	-	28.1	--	--

$AUC_{0-\infty}$ 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 coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Pravasor is considered bioequivalent with Selektine.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pravasor.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Muscle disorders (myalgia, myopathy and rhabdomyolysis) - Hepatotoxicity (increased transaminases, hepatitis, jaundice) - Co-administration with fusidic acid - Pancreatitis - Peripheral polyneuropathy - Use in pregnancy and lactation
Important potential risks	- Co-administration with fibrates - Interstitial lung disease - Memory loss - Diabetes Mellitus - Depression - Muscle damage (Immune-mediated necrotizing

	myopathy)
Missing information	- Use in patients with homozygous familial hypercholesterolemia

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Selektine. 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. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pravasor 40 mg coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Selektine 40 mg tablets. Selektine 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 Pravasor with the reference

product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 December 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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