COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vaspit 1 mg, 2 mg and 4 mg film-coated tablets (pitavastatin calcium)

NL/H/5522/001-003/DC

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This module reflects the scientific discussion for the approval of Vaspit 1 mg, 2 mg and 4 mg film-coated tablets. The procedure was finalised on 26 January 2023. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FRCs	Functional-related characteristics
ICH	International Conference of Harmonisation
JP	Japanese Pharmacopoeia
LDL-C	Low-density lipoprotein-cholesterol
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TC	Total Cholesterol
TSE	Transmissible Spongiform Encephalopathy
USP-NF	United States Pharmacopeia- National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vaspit 1 mg, 2 mg and 4 mg film-coated tablets, from Medochemie Limited.

The product is indicated for the reduction of elevated total cholesterol (TC) and LDL-C, in adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, and combined (mixed) dyslipidaemia, when response to diet and other non-pharmacological measures is inadequate.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Livazo 1 mg, 2 mg and 4 mg film-coated tablets which has been registered in Portugal (PT/H/2350/001-003, before RMS transfer UK/H/1555/001-003) by Kowa Pharmaceutical Europe GmbH. In the Netherlands, Livazo 1 mg, 2 mg and 4 mg have been registered since 10 August 2010 by procedures RVG 106928, 103768 and 103769.

The concerned member states (CMS) involved in this procedure were Cyprus, Greece, Malta and Spain.

For this application, scientific advice has been given by the MEB.

II. QUALITY ASPECTS

II.1 Introduction

Vaspit 1 mg, 2 mg and 4 mg are film-coated tablets. Each film-coated tablet contains pitavastatin calcium equivalent to 1 mg, 2 mg or 4 mg pitavastatin. The film-coated tablets of the three strengths can be distinguished by the different sizes, colours and debossing and are as follows:

The 1 mg strength are white round, concave, film coated tablets, debossed with ‘10’ on one side and plain on the other side, with a diameter of approximately 6 mm.

The 2 mg strength are yellow round, concave, film coated tablets, debossed with ‘20’ on one side and plain on the other side, with a diameter of approximately 8 mm.

The 4 mg strength are white round, concave, film coated tablets, debossed with ‘MC’ on one side and plain on the other side, with diameter of approximately 10.3 mm.

The excipients are:
Tablet core - lactose monohydrate, low substituted hydroxypropyl cellulose, magnesium aluminometa silicate, hypromellose 2910 and magnesium stearate.
Film coating - opadry white 03O580007, hypromellose, titanium dioxide (E171), triethyl citrate (E1505), colloidal anhydrous silica and yellow iron oxide (E172) (only for the 2 mg tablets).

The composition of the three strengths (1, 2 and 4 mg) is dose proportional.

The film-coated tablets are packed in opaque PVC-PE-PVdC aluminium blisters in cardboard cartons.

II.2 Drug Substance

The active substance is pitavastatin calcium, an established active substance not described in the European Pharmacopoeia but in the Japanese Pharmacopoeia (JP). The drug substance is a white to off white powder. It is a chiral molecule which exhibits isomerism and polymorphism. The manufacturer consistently produced the same crystalline form. The solubility, hygroscopicity and other physicochemical properties of the drug substance have been adequately discussed.

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 applicant 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
The manufacturing process consists of two stages. Stage one is the synthesis of two advanced intermediate products. Stage two is the preparation of the pitavastatin calcium drug substance through several synthesis steps. After this, the material is milled or optionally micronized to meet particle size requirements. No class 1 organic solvents are used in the manufacturing process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is established in-house by the MAH, based on the specification as described in the ASMF. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the JP. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Stability data on the active substance have been provided for five (among which three validation batches) batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated package and storage conditions.

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 proposed formulation is an immediate release film-coated tablet containing pitavastatin calcium as an active substance in three strengths. The qualitative composition of the doses is identical except for the film-coating material. The ratio between the drug substance and the excipients is in all three doses the same. The drug substance content is approximately 1.2% of the total tablet mass. This is below 2%. Therefore, according to EMA/CHMP/CVMP /QWP/ BWP/70278/2012-Rev1,Corr.1, the medicinal product is not considered a standard dosage form.

A bioequivalence study was performed with the highest strength 4 mg. For the lower strengths, a biowaiver is applicable. To support the biowaiver, dissolution tests were performed (see section IV.2). For the pharmaceutical development, various development trials are described for determining the optimum functional-related characteristics (FRCs) grades for various excipients. By showing these differences it was also demonstrated that the proposed QC dissolution method can be considered as adequately discriminating.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches for each strength (nine batches in total) in accordance with the relevant European guidelines. The manufacturing process consists of wet granulation, blending, compression and film-coating. Although the processing steps are common for conventional solid oral dosage form, the drug substance content of 1.27% is below 2%, and herewith the manufacturing process is a non-standard process. Process validation studies have been performed for three batches for each strength produced at a medium scale. The results are acceptable. Process validation for full scaled batches will be performed post authorisation prior to marketing.

Control of excipients

Most excipients comply with Ph.Eur. requirements. For opadry, an in-house specification has been provided. However, the components of opadry also comply with Ph.Eur. requirements. Yellow iron oxide complies with the United States Pharmacopeia-National Formulary (USP-NF) and EU regulation 231/2012/EC. 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 description, disintegration, identification of drug substance and colorants, uniformity of dosage units, dissolution, related substances, assay and microbial quality. The release and shelf-life requirements are identical except for

one related impurity. The limits in the specification of the quality control of the product are acceptable with the commitment of the MAH to re-evaluate and tighten the shelf-life limit of a specific impurity and total impurities when the difference with actual results at the end of shelf life is more than 0.50%.

An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of three batches of each strength 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 batches of each strength stored at 25°C/ 60% RH (12 to 18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. The batches were stored in Alu-PVC/PE/PVdC blisters. Additionally, 12 to 18 months stability data has been submitted for two batches of each strength for the film-coated tablet bulk stored in double LDPE bags at 25°C/60% RH. Small increasing trends are seen for several related substances for all storage conditions. For the other parameters, no trends are observed and all results remain well within the stated shelf-life limits. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 30 months. The labelled storage conditions are “This medicinal product does not require any special temperature conditions. Keep blister in the outer carton to protect from light”.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided for the excipient lactose monohydrate and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vaspit 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 Vaspit is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Livazo which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Pitavastatin calcium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the single dose pivotal bioequivalence study, which is discussed below. Furthermore, pitavastatin can be converted to the metabolite pitavastatin lactone. The MAH submitted data confirming the lack of back conversion of the lactone form into parent drug during sample analysis.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test bio-batch product Vaspit 1 mg, 2 mg and 4 mg film-coated tablets (Medochemie Limited - Limassol, Cyprus) was compared with the pharmacokinetic profile of the reference product Livazo 4 mg film-coated tablets from Kowa Pharmaceutical Europe GmbH (Germany). For the lower product strengths, 1 mg and 2 mg, a biowaiver was applicable.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Comparative dissolution studies between the 4 mg test and reference bio-batches have been performed in 0.1N HCl (pH 1.2), acetate buffer pH 4.5 and phosphate buffer pH 6.8. Dissolution was very rapidly, >85% dissolved with 15 min, at all three pHs for all strengths. Herewith the dissolution profiles are considered similar and calculation of f_2 is not necessary. These results fully support the biowaiver for the 1 mg and 2 mg strengths.

Bioequivalence studies

Design

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions with 42 healthy male subjects, aged 19-49 years. Each subject received a single dose (4 mg) of one of the two pitavastatin calcium formulations. The tablet was orally administered with 240 mL water after an overnight fast of 10-12 hours and in the morning of the second day of each study period. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Pitavastatin calcium may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of pitavastatin calcium. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
42 subjects were enrolled. Three subjects withdrew from the study after the first drug dosing and prior to the second drug dosing due to a mild adverse event (myalgia, muscle pain) before the second drug dosing. A total of 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pitavastatin calcium 4 mg 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)**
Test	214 ± 188	234 ± 200	75 ± 61	1.0 (0.5 – 2.0)
Reference	206 ± 176	226 ± 182	73 ± 51	0.75 (0.33 – 1.67)
***Ratio (90% CI)**	1.04 (1.00 – 1.09)	-	1.01 (0.93 - 1.10)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Vaspit is considered bioequivalent with Livazo 4 mg film-coated tablets. Furthermore, the results of the bioequivalence study with the 4 mg formulation can be extrapolated to other strengths, 1 mg and 2 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Vaspit.

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

Important identified risks	- Rhabdomyolysis (including myalgia, muscle disorders, myopathy and associated renal disorder) - Liver disorder (including increased transaminases, hepatic function abnormal and jaundice)
Important potential risks	- Interstitial lung disease (class effect) - Thrombocytopenia /platelet count decreased
Missing information	- Long term use in children <18 years old - Use in children <6 years old

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 Livazo. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Livazo, film-coated tablets (PT/H/2350/001-003/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for and to Amisulprid Medochemie Romania, tablets (DK/H/2877/001-004/DC) for design and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vaspit 1 mg, 2 mg and 4 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Livazo 1mg, 2mg and 4mg film-coated tablets. Livazo 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 Vaspit with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 January 2023.

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
NL/H/5522/ 1-3/IA/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation	Yes	04-10-2023	Approved	N.A.