CBG MEB

Public Assessment Report

Scientific discussion

Varistren 600 mg/300 mg, film-coated tablets

(abacavir sulfate/lamivudine)

NL/H/4038/001/DC

Date: 13 July 2018

This module reflects the scientific discussion for the approval of Varistren 600 mg/300 mg, film-coated tablets. The procedure was finalised on 4 May 2018. 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EEA	European Economic Area
ERA	Environmental Risk Assessment
HIV	Human Immunodeficiency Virus
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
USP	United States Pharmacopeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Varistren 600 mg/300 mg, film-coated tablets from Vocate Pharmaceuticals SA.

The product is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

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 Kivexa 600/300 mg film-coated tablets which has been registered in the EEA by ViiV Healthcare UK Limited since 17 December 2004 through a centralised procedure EMEA/H/C/000581. The individual active substances were registered as single component formulations in 1996 (lamivudine; centralised procedure) and 1999 (abacavir; centralised procedure).

The concerned member state (CMS) involved in this procedure was Greece.

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

II. QUALITY ASPECTS

II.1 Introduction

Varistren is an orange, film-coated, modified capsule shaped tablet debossed with “H” on one side and “A1” on the other side. Each tablet contains as active substances 600 mg abacavir (as sulfate) and 300 mg lamivudine.

The film-coated tablets are packed in OPA-Aluminium-PVC/Aluminium or PVC/PVDC- Aluminium blisters or HDPE bottles with a plastic child-resistant closure. Each bottle contains a silica gel desiccant canister.

The excipients are:
Tablet core – microcrystalline cellulose (E460), sodium starch glycolate (Type A), colloidal anhydrous silica (E551) and magnesium stearate (E470b).
Tablet coating – hypromellose (E464), macrogol (E1521), titanium dioxide (E171), sunset yellow FCF aluminium lake (E110) and polysorbate 80 (E433).

II.2 Drug Substances

The drug substances are abacavir (as abacavir sulfate) and lamivudine. The active substance abacavir sulfate is described in the European Pharmacopoeia (Ph.Eur.). Lamivudine is described in the Ph.Eur., USP and British Pharmacopoeia.

The CEP procedure is used for both active substances. 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 European Pharmacopoeia.

Abacavir
Abacavir sulfate is a white or almost white powder. The active substance is soluble in water, practically insoluble in ethanol and in methylene chloride. Abacavir sulfate exhibits isomerism and polymorphism. Enantiomeric purity and polymorphic form are controlled in the drug substance specifications. Polymorphic form II is produced.

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

Quality control of drug substance
The active substance specification is in accordance with the Ph. Eur. and the CEP with additional in-house tests for polymorphic form, optical rotation, content of sulfate, residual solvents, particle size and microbiological quality. The active substance specification is considered adequate to control the quality. The MAH has adopted the Ph. Eur. methods and additional in-house methods. The in-house methods are adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been provided for four commercial scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The batches were stored in the proposed packaging. No trends or significant changes were observed. The proposed re-test period of 36 months without any storage condition is acceptable.

Lamivudine
Lamivudine is a white or almost white powder and soluble in water, sparingly soluble in methanol and slightly soluble in ethanol. The active substance exhibits isomerism and polymorphism. Enantiomeric purity and polymorphic form are controlled in the drug substance specifications. Polymorphic form II is produced.

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

Quality control of drug substance
The active substance specification is in accordance with the Ph. Eur. and the CEP with additional requirements for polymorphic form, residual solvents, particle size and microbiological quality. The proposed limit for particle size is sufficiently justified and the proposed limits for residual solvents are acceptable. The additional test for microbial quality is adequately justified. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 are explained. The objective of the development was to create a stable formulation of abacavir and lamivudine in the form of a film-coated tablet comparable to that of the innovator product Kivexa. The same excipients as in the reference product were selected and development focussed on the optimisation of the compression and granulation method as well as on the optimisation of concentrations of disintegrant, lubricants and glidant.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Varistren 600 mg/300 mg, film-coated tablets and reference product, Kivexa 600/300 mg, film-coated tablets. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. The composition of the batch used in the bioequivalence trial is identical to the final formulation chosen.

The dissolution profiles of the test and reference product that were used in the bioequivalence study were compared at three different buffers (0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8). The results demonstrate that the test batch is *in vitro* similar to the innovator product Kivexa in the three buffers tested. The comparative impurity and assay results were also found to be comparable.

Manufacturing process
The manufacturing process consists of dry mixing, wet granulation, drying and sifting and milling of the dried granules (for both active substances separately), pre-lubrication, lubrication, followed by compression, film-coating, and packing. It is considered to be a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Acceptable process validation data were presented for two full scale batches. All predefined acceptance criteria were met and all batches complied with the proposed release specification.

Control of excipients
Apart from the coating material, all excipients comply with the Ph. Eur. Additional requirements for particle size and bulk density were laid down for microcrystalline cellulose and magnesium stearate and additional requirements for residual solvents were laid down for sodium starch glycolate. Acceptable specifications were proposed for the coating material.

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, identification, average weight, water content, uniformity of dosage units, dissolution, related compounds, assay, identification of colourants, and microbiological quality. 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 for two full scaled batches.

Stability of drug product
Stability data on the product have been provided for two full scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) in both types of proposed blisters and bottles. In addition, the batches packed in PVC/PVdC-Alu blister were stored at 30°C/65% RH (12 months). The tablets were stored at 25°C/60% RH for 12 months in bulk pack. The conditions used in the stability studies are according to the ICH stability guideline. No significant changes or trends were observed during the stability studies except for the PVC/PVdC-Al blister where significant changes occurred with respect to related substances after 6 months storage under accelerated conditions. Based on the provided stability data, the proposed shelf life of 24 months without storage conditions for the product stored in Alu/Alu blister and HDPE container is acceptable. For the product packaged in PVC/PVdC-Alu blister the proposed shelf life of 24 months is acceptable with the storage condition: “Store below 30°C”.
For the product packed in the bulk pack, the proposed shelf life of 12 months and storage condition “Store below 25°C” is acceptable.
Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Varistren 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 Varistren 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 Kivexa 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

Abacavir and lamivudine are well-known active substances 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 Varistren 600 mg/300 mg, film-coated tablets from (Vocate Pharmaceuticals SA, Greece) is compared with the pharmacokinetic profile of the reference product Kivexa 600/300 mg, film-coated tablets (ViiV Healthcare UK Limited, UK).

The choice of the reference product in the bioequivalence study is accepted, as Kivexa has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design
A single-dose, open-label, balanced, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 21-43 years. Each subject received a single dose (600 mg/300 mg) of one of the 2 active substance 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 9 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 5, 6, 8, 10, 12, 16, 24 and 36 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 conditions applied in the study are 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
Eight subjects were withdrawn from the study. Five subjects were withdrawn due to adverse events (vomiting), two subjects did no report to the facility in the second period and 1 subjects withdrew consent after the first dose. Therefore, a total of 40 subjects completed the study were eligible for pharmacokinetic analysis.

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

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	20259 ± 5064	20473 ± 5092	7473 ± 2365	1.1 (0.5 – 2.3)
Reference	19566 ± 4743	19765 ± 4775	6977 ± 1844	1.3 (0.5 – 2.3)
***Ratio (90% CI)**	1.04 (1.00 – 1.07)	1.04 (1.00 – 1.07)	1.06 (0.99 – 1.14)	--
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lamivudine under fasted conditions.

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	16377 ± 3888	16655 ± 3866	2813 ± 783	2.3 (0.8 – 4.0)
Reference	16624 ± 3983	16897 ± 3975	2871 ± 764	2.3 (1.0 – 5.0)
***Ratio (90% CI)**	0.98 (0.93 – 1.04)	0.99 (0.94 – 1.04)	0.97 (0.91 – 1.04)	--
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**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 Varistren is considered bioequivalent with Kivexa.

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 Varistren.

- Summary table of safety concerns as approved in RMP

Important identified risks	- ABC hypersensitivity reaction (including reduced vigilance following HLA-B*5701 testing) - Use in subjects with hepatic impairment
Important potential risks	- Use in subjects with moderate/severe hepatic impairment - Long term risk of carcinogenicity and long term exposure to NRTIs - Use in pregnancy - Ischaemic cardiac events - Possible interaction of ABC/3TC with tenofovir disoproxil fumarate - Risk of shorter time to virological failure
Missing information	None

It is considered that the following additional risk minimisation measures are necessary for the safe and effective use of the product:

- Educational materials for healthcare professionals to address the risk of abacavir hypersensitivity (website and slide set) covering the key points as stated in Annex II for Kivexa. The educational material should contain the following key elements:

  1. Major symptoms associated with ABC HSR are fever (~80%), rash (~70%), gastrointestinal symptoms (>50%) such as nausea, abdominal pain, vomiting, and diarrhoea, generalise malaise, fatigue, and headache (~50%) and other symptoms (~30%) such as respiratory, mucosal, and musculoskeletal symptoms.
  Based on the above patients are advised to contact their physician immediately to determine whether they should stop taking abacavir:
  - in the presence of skin rash; or
  - when developing 1 or more symptom from at least 2 of the following groups:
    - fever
    - shortness of breath, sore throat or cough
    - nausea or vomiting or diarrhoea or abdominal pain
    - extreme tiredness or achiness or general ill feeling

  2. Risk factors for ABC HSR
  HLA-B*5701 is the only identified pharmacogenetic marker that is consistently associated with clinical diagnosis of an ABC HSR reaction. However, some patients with a suspected ABC hypersensitivity reaction may not have the HLA-B*5701 allele.

  3. Recommendations for HLA-B*5701 screening
  Before initiating abacavir therapy, clinicians should screen for HLA-B*5701 (in settings where validated screening methods are available). Clinical diagnosis of suspected hypersensitivity to ABC remains the basis for clinical decision making. HLA-B*5701 screening for risk of ABC hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving ABC. If ABC hypersensitivity cannot be ruled out on clinical grounds, ABC should be permanently discontinued and should not be restarted, regardless of the results of HLAB*5701 screening. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.

  4. Information on HLA-B*5701 testing
  The one-time HLA-B*5701 test identifies people at high risk for this serious allergic reaction. The gold standards for HLA-B*5701 screening are sequence-based genotyping and polymerase chain reaction sequencing of specific oligonucleotide

probes. Blood or saliva samples are collected and tested for genetic sequences coding for the HLA-B*5701 allele. Results of PREDICT-1 and SHAPE studies show that the presence of the HLA-B*5701 allele is associated with increased risk of ABC hypersensitivity, regardless of race, screening for HLA-B*5701 before starting treatment with ABC may identify subjects at increased risk of a HSR, avoiding treatment with ABC in subjects with the HLA-B*5701 allele was shown to significantly reduce the incidence rate of clinically diagnosed cases of hypersensitivity. Data from these studies do not support the use of skin patch testing in routine clinical practice. Only patients found to lack the HLA-B*5701 allele should begin therapy with ABC.

5. Management of ABC HSR reaction
Symptoms can occur at any time during treatment with ABC, but usually occur within the first 6 weeks of therapy. Symptoms are initially mild and evolve over days, becoming more severe with continued ABC therapy. Symptoms improve on cessation of ABC. Rechallenge can result in a more rapid and severe reaction, which can be fatal, therefore rechallenge is contraindicated.

6. Hypersensitivity case studies
The educational material includes 3 case studies to demonstrate different clinical scenarios and their management

- Patient alert card. Each pack of abacavir/lamivudine medication contains an Alert Card for patients and information on the risk in the packet leaflet (PL).

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Kivexa. 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.
For bridging the content, the applicant provided a rationale that the content and wording of the PL for Varistren is identical to the PL of Kivexa, with the exception of changes related to the QRD template and differences in pharmaceutical composition. Bridging for content is acceptable, since the differences.
For bridging the design and lay-out, the applicant has included a comparison demonstrating that the design and lay-out of the PL for Varistren is identical to the PL of Levetiracetam Hetero – another product of the Applicant. For Levetiracetam Hetero a full user testing report has been included in the dossier.
The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Varistren 600 mg/300 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Kivexa 600 /300 mg film-coated tablets. Kivexa 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 Varistren with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 May 2018.

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