COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Valdevon 200 mg/245 mg film-coated tablets

(emtricitabine/tenofovir disoproxil fumarate)

NL/H/4666/001/DC

Date: 26 February 2021

This module reflects the scientific discussion for the approval of Valdevon 200 mg/245 mg film-coated tablets. The procedure was finalised on 23 December 2020. 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 Valdevon 200 mg/245 mg film-coated tablets from Vocate Pharmaceuticals SA.

The product is indicated for:

Treatment of HIV-1 infection
Valdevon is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infected adults (see SmPC section 5.1).

Valdevon is also indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents (see sections SmPC 4.2, 4.4 and 5.1).

Pre-exposure prophylaxis (PrEP)
Valdevon is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk (see sections SmPC 4.2, 4.4 and 5.1).

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 Truvada 200 mg/245 mg film-coated tablets which has been centrally registered in EEA by Gilead Sciences Ireland UC since 21 February 2005 (EU/1/04/305/001).

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

Valdevon is a blue, capsule shaped film-coated tablet de-bossed with 'H' on one side and 'E44' on the other side.

Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (corresponding to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir).

The film-coated tablets are packed in OPA-Alu-PVC/Alu blisters and white opaque HDPE bottles.

The excipients are:
Tablet core – croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, magnesium stearate, pregelatinised starch
Film-coating – hypromellose, lactose monohydrate, titanium dioxide (E171), triacetin, indigo carmine aluminium lake (E132)

II.2 Drug Substances

Emtricitabine
The active substance is emtricitabine, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.), but described in a pending monograph for the United States Pharmacopoeia (USP) and in the WHO International Pharmacopoeia (Ph.Int.). Emtricitabine is sparingly soluble in water. The substance shows polymorphism and is consistently manufactured in the same crystalline form. The opposite enantiomer is controlled as part of the drug substance specification.

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 four stages. Organic solvents used in the last step of the synthesis are sufficiently specified. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the solvents and reagents. The starting materials used in the manufacturing process of emtricitabine are acceptable.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. 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 two full scale and five pilot scale batches stored at 25°C/60% RH (up to 36 and 48 months respectively) and for one full scale and three pilot scale batches at 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 60 months without specific storage conditions.

Tenofovir disoproxil fumarate

The active substance tenofovir disoproxil fumarate is a well-known active substance. The substance is not described in the Ph.Eur. A monograph for this substance is included in the WHO international pharmacopoeia. The active substance is soluble in water (pH dependant) and sparingly soluble in methanol and ethanol. The active substance shows polymorphism and is consistently manufactured having the same crystalline form. An ASMF has been used for manufacturing tenofovir disoproxil fumarate.

Manufacturing process

The manufacturing process consists of four stages. The solvents used in the process are sufficiently specified. No Class I solvents are used. The process is adequately described.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. 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 three full scale batches stored at 5°C (60 months) and 25°C/60% RH (36 months). Based on the provided stability data, the claimed retest period of 60 months and storage condition 'Store in a refrigerator' are justified.

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 main development studies performed were the characterisation of the reference product, optimization of the formulation and manufacturing process and performance of comparative *in vitro* dissolution studies complementary to the *in vivo* bioequivalence study. The choices of the packaging and manufacturing process are justified. The drug product batch that was used in the bioequivalence study versus the reference product was manufactured according to the finalized composition and manufacturing process. Pharmaceutical development has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are sifting, blending and lubrication, compaction, extra granular material sifting, pre-lubrication and lubrication, compression and coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for a third full scale batch may be performed post authorisation.

Control of excipients

Except for the film-coating material, the excipients comply with their respective Ph.Eur. monographs. The film-coating material is controlled according to an in-house specification. 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, identification, average weight, water content, dissolution, uniformity of dosage units, related substances, assay and microbiological quality and identification of colourant. Except for water content and related substances, the release and shelf-life requirements are identical. 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 two full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.
The MAH carried out a risk assessment for elemental impurities according to ICH guideline Q3D. Based on this risk assessment, controls for specific elemental impurities are not required. The MAH also carried out a risk assessment for the presence of nitrosamines in the drug product and no risk was identified and no controls for nitrosamines are required for the drug product.

Stability of drug product

Stability data on the product has been provided on two full scale batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. An out of specification was observed for the product packed in blisters after three months storage at accelerated conditions. No significant changes were seen for the bottles at long term and accelerated conditions and for the blisters at long term and intermediate conditions.

On basis of the data submitted, a shelf life was granted of 24 months for the blisters and bottles. The blisters should be stored below 30°C while the bottles do not require a temperature storage condition. Due to the desiccant in the bottles, the tablets should be stored in the original package in order to protect from moisture.

The provided in use stability data for the bottles support the absence of a separate in use shelf life in the product information.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only component of animal origin used in the drug product is lactose monohydrate. It has been confirmed that the lactose is produced from milk sourced from healthy cows in the same condition as milk collected for human consumption. The lactose has been prepared without the use of other ruminant material than calf rennet according to the description as published in Public Statement EMEA/CPMP/571/02 of 27 February 2002.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Valdevon 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 Truvada, 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

Emtricitabine and tenofovir 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 Valdevon 200 mg/245 mg film-coated tablets (Vocate Pharmaceuticals SA, Greece) is compared with the pharmacokinetic profile of the reference product Truvada 200 mg/245 mg film-coated tablets (Gilead Sciences Ireland UC, Ireland).

The choice of the reference product in the bioequivalence study has been justified. 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 46 healthy male/female subjects, aged 18-43 years. Each subject received a single dose (200 mg emtricitabine and 245 mg tenofovir disoproxil) of one of the two formulations. The tablet was orally administered with 240 ml water within 30 mins after starting a high fat, high calorie breakfast. There were two dosing periods, separated by a washout period of 17 days.

Blood samples were collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.7, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The washout is long enough. The sampling schedule is adequate to estimate pharmacokinetic parameters. According to the SmPC, the tablets should be taken with food. As such, the fed conditions applied in the study is considered adequate. Tenofovir instead of tenofovir disoproxil was analysed, as tenofovir disoproxil is very rapidly converted into tenofovir.

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

Seven subjects were withdrawn from the study:

- One subject was found positive in alcohol breath test during admission of period 2.
- Five subjects did not report to the facility during admission of period 2
- One subject did not complete the high-fat; high-calorie breakfast in period 2

Therefore 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of emtricitabine under fed 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	10391 ± 1814	10717 ± 1836	1896 ± 466	2.0 (1.25 - 4.5)	7.47 ± 2.7
Reference	10378 ±1762	10680 ± 1785	1889 ± 441	2.25 (1.25 - 5.0)	6.76 ± 2.60
***Ratio (90% CI)**	1.00 (0.97-1.03)	1.00 (0.98-1.03)	1.00 (0.95-1.05)	--	--
CV (%)	7.16	7.05	12.8	--	--

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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tenofovir under fed 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	3221 ± 96	3411 ± 802	332 ± 96	2.0 (1.0 - 4.5)	17.8 ± 2.3
Reference	3243 ± 747	3464 ± 771	338 ± 99	2.25 (1.25 - 4.0)	18.4 ± 2.4
***Ratio (90% CI)**	0.99 (0.94 – 1.04)	0.98 (0.93 – 1.03)	0.98 (0.92 – 1.04)	--	--
CV (%)	13.6	13.3	15.7	--	--

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Valdevon is considered bioequivalent with Truvada.

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 Valdevon.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication) (TVD) • Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication) (TVD) • Renal toxicity (TDF) • Bone events due to proximal renal tubulopathy/loss of bone mineral density (TDF)
Important potential risks	--
Missing information	• Safety in pregnancy and lactation (TDF

The member states agreed that routine pharmacovigilance activities are sufficient for the other risks and areas of missing information.
The following additional risk minimisation measures are required to minimise risks of the product in line with the reference product:

- Physician educational pack containing the SmPC and an appropriate educational brochure for indication of “Pre-exposure prophylaxis (PrEP)” for the important identified risks of “HIV-1 Acquisition, including infection resulting from non-adherence” and “Development of resistance in patients with unrecognized or acute HIV-1 infection”.
- HIV paediatric renal educational brochure.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Truvada. 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 Truvada for content, and to Levetiracetam Hetero 750 mg film-coated tablets (PT/H/515/01-04/DC) for layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Valdevon 200 mg/245 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Truvada 200 mg/245 mg film-coated tablets. Truvada 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 Valdevon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 December 2020.

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