COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tenofovirdisoproxil Vocate 245 mg film-coated tablets (tenofovir disoproxil fumarate)

NL/H/5622/001/DC

Date: 21 March 2024

This module reflects the scientific discussion for the approval of Tenofovirdisoproxil Vocate 245 mg film-coated tablets. The procedure was finalised on 18 August 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
ICH	International Conference of Harmonisation
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
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 Tenofovirdisoproxil Vocate 245 mg film-coated tablets, from Vocate Pharmaceuticals S.A.

The product is indicated for:
HIV-1 infection

- the treatment of HIV-1 infected adults (in combination with other antiretroviral medicinal products).
- the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to <18 years.

Hepatitis B infection

- the treatment of chronic hepatitis B in adults with:
  - compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.
  - evidence of lamivudine-resistant hepatitis B virus.
  - decompensated liver disease.
- the treatment of chronic hepatitis B in adolescents 12 to <18 years of age with compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis.

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 Viread 245 mg film-coated tablets, which has been registered in the EU via a centralised procedure (EU/1/01/200/001-002) since 4 February 2002.

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

II. QUALITY ASPECTS

II.1 Introduction

Tenofovirdisoproxil Vocate is a white coloured, almond shaped, film-coated tablet, debossed on one side with 'H' and on the other side with '123'.

Each tablet contains as active substance 245 mg of tenofovir disoproxil (as 300 mg of tenofovir disoproxil fumarate).

The excipients are:
Tablet core - sodium croscarmellose (E468), lactose, magnesium stearate (E470b), microcrystalline cellulose (E460) and starch (pregelatinised).

Film-coating - triacetin (E1518), HPMC 2910/Hypromellose 15 mPas (E464), lactose and titanium dioxide (E171).

The tablets are packed in a high density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing a silica gel desiccant or aluminium (Alu/Alu) blister.

II.2 Drug Substance

The active substance is tenofovir disoproxil fumarate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is slightly soluble in water. The active substance contains one stereogenic centre which is adequately controlled in the manufacturing process for this product. The active substance exhibits polymorphism, polymorphic Form-I is consistently manufactured.

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 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 of tenofovir disoproxil fumarate is a five step process starting with two starting materials in addition to two intermediates. In the last step of the synthesis, three solvents are used. No class I solvents are used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification has been established in-house by the MAH and is based on the specification of the ASMF-holder. The specification of the ASMF-holder is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided by the drug substance manufacturer on three full scale batches and by the drug product manufacturer on two full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 3 years. Based on the data submitted, a retest period could be granted of 5 years when stored under the stated 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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials and comparative dissolution studies at three pH levels, compared with the reference product. Dissolution profiles and raw numerical data for 12 tablets per pH are submitted for both the test and reference product at 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. In all cases, for both the test and reference product, more than 85% dissolution is observed within 15 minutes. A bioequivalence study has been performed versus the reference product. The test product batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablet is manufactured with a wet granulation process which consist of sifting, dry mixing, granulation, drying, compression and film coating. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for two full scale batches in accordance with the relevant European guidelines. Process validation for a third full scale batch will be performed post-authorisation.

Control of excipients

The excipients comply with their corresponding Ph. Eur. monographs and their 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, identity, water, average weight, disintegration time, dissolution, uniformity of dosage units, related compounds, assay, microbiological examination and identification of colourant. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Because the risk for formation of nitrosamines is negligible, no controls for nitrosamines are deemed required on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from eight batches (five batches of small size and three batches of large size) 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 two batches stored at 25°C/ 60% RH (36 months), 30°C/65% RH (12 months, blister only) and 40°C/75% RH (6 months). In addition, 18 month long term condition data has been provided for one batch. The stability was tested in accordance with the ICH stability guideline.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

The shelf-life of 24 months, with the storage condition 'this medicinal product does not require any special storage conditions', for the drug product packaged in HDPE containers is acceptable. For the product packaged in blisters the shelf-life of 24 months is acceptable, with the storage condition 'store below 30°C'.

In-use stability has been studied and no significant changes to the product were observed at the end of shelf-life, therefore no in-use shelf-life was required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided 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 Tenofovirdisoproxil Vocate 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 Tenofovirdisoproxil Vocate 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 Viread 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

Tenofovir disoproxil fumarate 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 bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tenofovirdisoproxil Vocate 245 mg film-coated tablets (Vocate Pharmaceuticals S.A., Greece) was compared with the pharmacokinetic profile of the reference product Viread 245 mg film-coated tablets (Gilead Sciences International Limited, United Kingdom).

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.

Bioequivalence studies

Design

An open label, balanced, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study was carried out under fed conditions in 34 healthy male subjects, aged 26-41 years. Each subject received a single dose (245 mg) of one of the two tenofovir disoproxil formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, tablets should be taken with food, as it enhances the bioavailability of tenofovir disoproxil fumarate.

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
All 34 subjects completed the study and subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tenofovir disoproxil, 245 mg under fed conditions.

Treatment N=34	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3796 ± 988	4076 ± 1070	351 ± 109	2.0 (1.0 – 3.5)
Reference	3673 ± 856	3925 ± 952	357 ± 99.9	2.25 (0.75 – 3.5)
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	1.03 (0.99 – 1.07)	0.97 (0.92 – 1.03)	-

$AUC_{0-\infty}$	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 = 72 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 Tenofovirdisoproxil Vocate is considered bioequivalent with Viread.

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 Tenofovirdisoproxil Vocate.

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

Important identified risks	• Renal toxicity • Bone events due to proximal renal tubulopathy/loss of bone mineral density
Important potential risks	None
Missing information	• Safety in pregnancy and lactation • Safety in patients with renal impairment

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 Viread. 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 Viread, EU/1/01/200/001-002. 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

Tenofovirdisoproxil Vocate 245 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Viread 245 mg film-coated tablets. Viread 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 Tenofovirdisoproxil Vocate with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 August 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
-	-	-	-	-	-