CBG MEB

Public Assessment Report

Scientific discussion

Emtricitabine/Tenofovirdisoproxil DOC Generici, 200 mg/245 mg film-coated tablets

(emtricitabine/tenofovir disoproxil succinate)

NL/H/3490/001/DC

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This module reflects the scientific discussion for the approval of Emtricitabine/Tenofovirdisoproxil DOC Generici, 200 mg/245 mg film-coated tablets. The procedure was finalised on 21 March 2016. 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
EDQM	European Directorate for the Quality of Medicines
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
Ph.Int.	WHO International Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Emtricitabine/Tenofovirdisoproxil DOC Generici, 200 mg/245 mg film-coated tablets, from DOC Generici S.r.l.

The product is a fixed dose combination of emtricitabine and tenofovir disoproxil succinate. It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infected adults aged 18 years and over.

The demonstration of the benefit of the combination emtricitabine and tenofovir disoproxil in antiretroviral therapy is based solely on studies performed in treatment-naïve patients (see SmPC section 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 registered in the EEA by Gilead Sciences International Limited through centralised procedure EU/1/04/305/001 since 21 February 2005. Emtricitabine/Tenofovirdisoproxil DOC Generici contains the phosphate salt of the prodrug tenofovir disoproxil while the originator Truvada contains the fumarate salt.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Emtricitabine/Tenofovirdisoproxil DOC Generici is a blue coloured, capsule shaped film-coated tablet, plain on both sides. Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil as 300.6 mg of tenofovir disoproxil succinate.

The product is packed in a High Density Polyethylene (HDPE) bottle containing a silica gel desiccant.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), pregelatinised maize starch, croscarmellose sodium and magnesium stearate (E470b)
Tablet coating - indigo carmine aluminium lake (E132), titanium dioxide (E171), poly(vinyl alcohol) (E1203), macrogol 4000 (E1521) and talc (E553b)

II.2 Drug Substances

Emtricitabine
The active substance emtricitabine is an established active substance 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 a white to almost white crystalline powder, freely soluble in methanol and water, and practically insoluble in dichloromethane. The aqueous solubility is pH dependent, but is always >100 mg/ml in the pH range 1.2 - 6.8. Several polymorphic forms are known for emtricitabine. The manufacturer consistently produces crystalline form-1. Emtricitabine has two chiral centres, and is the cis enantiomer having the 2R, 5S absolute configuration.

The Active Substance Master File (ASMF) procedure is used for emtricitabine. 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 synthesis of emtricitabine is described in three steps. In the first step the first starting material is reacted with the second starting material. The third starting material is introduced in the second step of the synthesis. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the (pending) monograph in the USP and Ph.Int. with additional requirements for particle size. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
In the ASMF for emtricitabine stability data on 9 batches of emtricitabine have been provided that were stored at 30°C/65% RH (6-48 months) and 40°C/75% RH (6 months). No significant changes or trends were observed for the tested parameters. The claimed retest period of 4 years with storage conditions 'Do not store above 30°C. Protect from light. Protect from moisture.' is justified.

Tenofovir disoproxil succinate
The second active substance is tenofovir disoproxil succinate, an established active substance not described in the Ph.Eur. The related fumarate salt is described in the Ph.Int. and in a pending monograph for the USP. Tenofovir disoproxil succinate is a white to off white crystalline powder, very slightly soluble in water and dichloromethane, freely soluble in methanol, sparingly soluble in anhydrous ethanol, acetonitrile, isopropanol and tetrahydrofuran, slightly soluble in isopropyl acetate and practically insoluble or insoluble in n-heptane. Four polymorphs have been reported for tenofovir disoproxil succinate. The crystalline form is produced. Tenofovir disoproxil succinate has one chiral centre.

The Active Substance Master File (ASMF) procedure is used for tenofovir disoproxil succinate.

Manufacturing process
The synthesis of tenofovir disoproxil succinate starts with two starting materials that are used to synthesise an intermediate in a four step synthesis. The intermediate is then reacted with the third starting material. The last step in the synthesis is a purification step. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the (pending) monograph in the USP and Ph.Int. with additional requirements for particle size. Batch analytical data demonstrating compliance with this specification have been provided for 6 batches.

Stability of drug substance
In the ASMF for tenofovir disoproxil succinate stability data on 6 drug substance batches that were stored at 5°C (18-24 months) and 30°C/65% RH (6 months) have been provided. The batches were packed in double PE bags placed in a plastic drum, lined with an aluminium foil bag. An increase in impurities was seen at 30°C/65% RH. The long-term data showed no clear changes or trends. Based on the presented stability data the claimed retest period of 30 months when stored in a refrigerator at 2-8°C is 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 the excipients justified and their functions explained.
Emtricitabine/Tenofovirdisoproxil DOC Generici tablets were developed using an alternative salt of tenofovir disoproxil, tenofovir disoproxil succinate, whereas in the reference product Truvada tenofovir disoproxil fumarate is used. The MAH submitted a justification why the use of the succinate salt instead of the fumarate salt can be considered equivalent in terms of safety and efficacy and no further proof of the safety and/or efficacy of the two salts is considered necessary. The use of an alternative salt is acceptable since the amount of active moiety, tenofovir disoproxil, is identical.
The pharmaceutical development of the product has been adequately performed.

A bioequivalence study was carried out. The manufacture and composition of the bio-batch used in the bioequivalence study is identical to the formulation for marketing The dissolution profiles at various pH values of the reference batch and the test batch in the bioequivalence study were found to be similar.

Manufacturing process
The manufacturing process for the current drug product consists of preparing a granulate with both drug substances by wet granulation. Subsequently the granulate is dried and compressed into tablets, coated and packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The pharmacopoeial excipients all comply with the Ph.Eur. The colourant indigo carmine aluminium lake complies to Commission Regulation EU 231/2012 on food additives. The 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 and dimensions, identity of drug substances and colorants, assay, related substances, residual solvents, dissolution, uniformity of dosage units, uniformity of mass, water content 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 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 on three pilot scale batches, stored at 25°C/60% RH (18 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 intended HDPE bottles with desiccant. An increase in impurities was observed at both storage conditions. No clear trends or changes were seen for the other parameters. The product is not sensitive to light. The claimed shelf-life of 30 months with storage conditions ‘Store in the original package in order to protect from moisture. Keep the container tightly closed.’ is justified.

An in-use study where samples of the drug product were stored at 25°C/60% RH for 30 days showed an increase in water content as well as an increase in impurities. However, all parameters remained within the specified limits. Based on the results of the in-use studies, the claimed shelf-life after first opening of 30 days when stored below 25°C is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the excipients used in this formulation are of animal origin except lactose anhydrous and lactose monohydrate. Scientific data and/or certificates of suitability issued by the EDQM 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 Emtricitabine/Tenofovirdisoproxil DOC Generici, 200 mg/245 mg film-coated tablets 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 Emtricitabine/Tenofovirdisoproxil DOC Generici 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 disoproxil succinate 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Emtricitabine/Tenofovirdisoproxil DOC Generici, 200 mg/245 mg film-coated tablets (DOC Generici S.r.l., Italy) is compared with the pharmacokinetic profile of the reference product Truvada 200 mg/245 mg film-coated tablets (Gilead Sciences International Limited, United Kingdom).

The choice of the reference product
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.

Design
A single-dose, randomised, crossover, comparative bioequivalence study was carried out under fed conditions in 34 healthy male subjects, aged 19-59 years. Each subject received a single dose (200 mg/245 mg) of one of the 2 emtricitabine/tenofovirdisoproxil formulations. The tablet was orally administered with 240 ml water within 30 min after start of intake of a high fat, high caloric breakfast. There were 2 dosing periods, separated by a washout period of 14 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, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study under fed conditions to assess bioequivalence is acceptable. According to the SmPC, the tablets should be taken with food. As such, the fed 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.
Tenofovir instead of tenofovir disoproxil was analysed, as tenofovir disoproxil is very rapidly converted into tenofovir, which is agreed.

Results
One subject was withdrawn due to an adverse event (vomiting) after dosing in Period I. 33 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 emtricitabine under fed conditions.

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	9641 ± 1050	9890 ± 1057	1628 ± 336	2.0 (1.0 – 5.0)	13.4 ± 4.5
Reference	9823 ± 1344	10086 ± 1403	1763 ± 504	2.25 (0.75 – 6.0)	13.7 ± 6.3
***Ratio (90% CI)**	0.98 (0.96 – 1.01)	--	0.94 (0.89 - 1.00)	--	--
CV (%)	5.6	--	14.9	--	--

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
$t_{1/2}$	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=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2607 ± 426	2760 ± 456	266 ± 73	1.75 (0.5 – 5.0)	18.2 ± 2.3
Reference	2583 ± 559	2739 ± 601	270 ± 79	2.0 (0.75 – 6.0)	18.2 ± 2.6
***Ratio (90% CI)**	1.02 (0.98 – 1.05)	--	0.99 (0.92 - 1.07)	--	--
CV (%)	8.4	--	18.6	--	--

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
$t_{1/2}$	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 for both active substances. Based on the submitted bioequivalence study Emtricitabine/Tenofovirdisoproxil DOC Generici is considered bioequivalent with Truvada under fed conditions.

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 Emtricitabine/Tenofovirdisoproxil DOC Generici.

Summary table of safety concerns as approved in RMP:

Important identified risks	- Post-treatment hepatic flares in hepatitis B or C virus co-infected patients - Lactic acidosis and severe hepatomegaly with steatosis - Lipodystrophy - Renal toxicity - Bone events due to proximal renal tubulopathy/loss of bone mineral density - Interaction with didanosine - Pancreatitis
Important potential risks	None
Missing information	- Safety in children (including long-term safety) - Safety in elderly patients - Safety in pregnancy - Safety in lactation - Safety in patients with renal impairment

An additional risk minimisation measure is required relating to renal toxicity and has been laid down in line with the reference product. It concerns a renal educational brochure, including a creatinine clearance slide ruler, for all physicians who are expected to prescribe/use emtricitabine/tenofovirdisoproxil. The following key elements should be included:

- That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil-containing products such as emtricitabine/tenofovirdisoproxil.
- That emtricitabine/tenofovirdisoproxil should only be used in patients with impaired renal function if the potential benefits of treatment are considered to outweigh the potential risks.
- The importance of dose interval adjustment of emtricitabine/tenofovirdisoproxil in patients with creatinine clearance of 30-49 ml/min.
- That emtricitabine/tenofovirdisoproxil is not recommended for patients with severe renal impairment (creatinine clearance <30 ml/min).
- That use of emtricitabine/tenofovirdisoproxil should be avoided with concomitant or recent use of nephrotoxic medicinal products. If tenofovir/emtricitabine is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule.

- That patients should have their baseline renal function assessed prior to initiating emtricitabine/tenofovirdisoproxil therapy.
- The importance of regular monitoring of renal function during emtricitabine/tenofovirdisoproxil therapy.
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment.
- That if serum phosphate is <1.5 mg/dl or creatinine clearance decreases during therapy to <50 ml/min then renal function should be reevaluated within one week. If creatinine clearance is confirmed as <50 ml/min or serum phosphate decreases to <1.0 mg/dl then consideration should be given to interrupting emtricitabine/tenofovirdisoproxil therapy.
- Instructions on the use of the creatinine clearance slide ruler.

The renal educational brochure should be submitted to the national competent authority for assessment and should be available before the launch of the product.

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

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 2 participants, followed by two rounds with 10 participants each. The 15 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Emtricitabine/Tenofovirdisoproxil DOC Generici, 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 Emtricitabine/Tenofovirdisoproxil DOC Generici with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 March 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached