CBG MEB

Public Assessment Report

Scientific discussion

Emtricitabine/Tenofovirdisoproxil CF 200/245 mg, film-coated tablets

(emtricitabine/tenofovir disoproxil succinate)

NL/H/3635/001/DC

Date: 30 January 2017

This module reflects the scientific discussion for the approval of Emtricitabine/Tenofovirdisoproxil CF 200/245 mg, film-coated tablets. The procedure was finalised on 30 June 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
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 Emtricitabine/Tenofovirdisoproxil CF 200/245 mg, film-coated tablets, from Centrafarm B.V.

The product is a fixed dose combination of emtricitabine and tenofovir disoproxil succinate and 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.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Denmark, Finland, France, Hungary, Ireland, Italy, Luxembourg, Poland, Sweden, and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Emtricitabine/Tenofovirdisoproxil CF blue coloured, capsule shaped film-coated tablet, plain on both sides. Each tablet contains 200 mg of emtricitabine and 300.6 mg tenofovir disoproxil succinate (equivalent to 245 mg of tenofovir disoproxil).

The tablets are packed in HDPE bottles with a polypropylene screw cap containing a silica gel desiccant in a separate HDPE canister.

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

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 off-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 this 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 synthesis of emtricitabine is described in three steps. The starting materials are acceptable. The final purification is a crystallisation. No class 1 solvents or heavy metal catalysts are used in the synthesis of emtricitabine. 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 three batches.

Stability of drug substance
Stability data on emtricitabine have been provided for 9 batches stored at 30°C/65% RH (6- 48 months) and 40°C/75% RH (6 months). No clear up- or downward trends are observed, under both long term and accelerated conditions. The proposed retest period of 48 months is with the storage condition "Do not store above 30°C. Protect from light. Protect from moisture" is acceptable.

Tenofovir disoproxil succinate
The second active substance is tenofovir disoproxil succinate, an established active substance not described in the Ph.Eur. The salt is described in the Ph.Int. and in a pending monograph for the USP. Tenofovir disoproxil succinate is a white to off-white 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, practically insoluble or insoluble in n-heptane. Five polymorphic forms have been reported and the crystalline form is consistently produced. Tenofovir disoproxil succinate has one chiral centre. The related fumarate salt is known as well.

The Active Substance Master File (ASMF) procedure is used for this active substance.

Manufacturing process
Tenofovir disoproxil succinate is manufactured in a four step synthesis. The last step in the synthesis is a purification step. No class 1 solvents or heavy metal catalysts are used in the synthesis of tenofovir disoproxil succinate. 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. The specification 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 for 6 batches.

Stability of drug substance
Stability data on tenofovir disoproxil succinate have been provided for 6 batches stored at 5°C (18-24 months) and 30°C/65% RH (6 months). An increase in impurities was seen at 30°C/65% RH. The long-term data showed no clear changes or trends. Based on the provided stability data the proposed retest period of 30 months with the storage condition "Store in a refrigerator at 2-8°C", is acceptable.

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 selected dissolution medium and method for quality control purposes is acceptable. The discriminative power of the dissolution method is insufficiently demonstrated. The presence or absence of a super disintegrant is not considered adequate for this purpose. However, considering the dissolution profiles of the tablets manufactured at high hardness, the discriminative power of the dissolution method in case of smaller changes is sufficiently demonstrated.

Emtricitabine/Tenofovirdisoproxil CF 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 use of a different salt form is acceptable based on the comparable drug product properties of the current product and the reference product.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process for the current drug product consists of preparing separate granulates for both drug substances by wet granulation, drying and milling. Subsequently the two granulates are mixed, 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 3 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

All the excipients comply with the Ph.Eur. However the colourant complies with European regulations on colourants. 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/dimensions, identity, assay, related substances, residual solvents, dissolution, uniformity of dosage units, uniformity of mass, water content and microbiological quality.

All limits in the specification have been justified and are considered appropriate for adequate quality control of the product. At release a test for description is defined, whereas at shelf-life this test is replaced by a test for appearance, this is sufficiently justified and is acceptable.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on 3 pilot scale batches, demonstrating compliance with the release specification. 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.

Stability of drug product

Stability data on the product has been provided on 3 pilot scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months), according to the ICH stability guideline. The product was stored in the proposed packaging. An increase in impurities was observed at both storage conditions. No clear trends or changes were seen for the other parameters. The drug product was shown not to be 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. In-use stability data has been provided demonstrating that the product remains stable for 30 days following first opening of the containers (bottles) when stored under 25°C.

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 Emtricitabine/Tenofovirdisoproxil CF 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 Emtricitabine/Tenofovirdisoproxil CF 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 CF 200/245 mg, film-coated tablets (Centrafarm, the Netherlands) is compared with the pharmacokinetic profile of the reference product Truvada 200 mg/245 mg, film-coated tablets (Gilead Sciences International Ltd., the United Kingdom).

The choice of the reference product in the bioequivalence studies is justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover 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 active substance formulations. The tablet was orally administered with 240 ml water 30 minutes after start of intake of a high fat, high caloric breakfast. The meal was compromised of approximately 240 ml of whole milk, 2 large eggs, 4 ounces hash brown potatoes (2 potato patties), 1 English muffin, 4.5 mg of butter and two slices of bacon. 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). A total of 33 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=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	10089 ± 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	--	--

$AUC_{0-\infty}$ 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=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	--	--

$AUC_{0-\infty}$ 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

**In-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. Based on the submitted bioequivalence study Emtricitabine/Tenofovirdisoproxil CF is considered bioequivalent with Travuda.

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 CF.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Post-treatment hepatic flares in human immunodeficiency virus/hepatitis B virus coinfected patients • Severe hepatomegaly with steatosis • 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 pregnancy • Safety in elderly patients • Safety in lactation • Safety in patients with renal impairment

In line with the reference product Truvada, an educational pack for healthcare professionals is required to address the risk of renal toxicity for the safe and effective use of the product. The additional risk minimisation measure should be submitted to the national competent authority for assessment and should be available before the launch of the product. A physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure should be included:

- HIV renal educational brochure
- PrEP educational brochure for prescribers entitled 'Important Safety Information for Prescribers About Emtricitabine/Tenofovirdisoproxil CF for a Pre-exposure Prophylaxis (PrEP) Indication'
- PrEP Checklist for prescribers
- PrEP educational brochure for the individual at risk entitled 'Important Information About Emtricitabine/Tenofovirdisoproxil CF to Reduce the Risk of getting Human Immunodeficiency Virus (HIV) Infection'
- PrEP reminder card.

HIV renal educational brochure
The HIV renal educational brochure should contain the following key messages:

- That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Emtricitabine/Tenofovirdisoproxil CF
- That Emtricitabine/Tenofovirdisoproxil CF should only be used in patients with impaired renal function if the potential benefits are considered to outweigh the potential risks
- That use of Emtricitabine/Tenofovirdisoproxil CF should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Emtricitabine/Tenofovirdisoproxil CF 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 CF therapy
- The importance of regular monitoring of renal function during Emtricitabine/Tenofovirdisoproxil CF therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- Instructions on the use of the creatinine clearance slide ruler.

PrEP educational brochure for prescribers:
- Reminder of the key safety information regarding the use of Emtricitabine/Tenofovirdisoproxil CF for PrEP
- Reminder of factors to help identify individuals at high risk of acquiring HIV-1
- Reminder on the risk of development of HIV-1 drug resistance in undiagnosed HIV-1–Infected individuals
- Provides safety information on adherence, HIV testing, renal, bone and HBV status.

PrEP Checklist for prescribers:
- Reminders for evaluations/counselling at the initial visit and follow-up.

PrEP educational brochure for the individual at risk (to be provided by healthcare provider [HCP]):
- Reminders on what the individual should know before and while taking Emtricitabine/Tenofovirdisoproxil CF to reduce the risk of getting HIV infection
- Reminder on the importance of strict adherence to the recommended dosing regimen
- Provides information on how to take Emtricitabine/Tenofovirdisoproxil CF
- Provides information on the possible side effects
- Provides information on how to store Emtricitabine/Tenofovirdisoproxil CF.

PrEP reminder card for the individual at risk (to be provided by HCP):
- Reminders to adhere to the dosing schedule
- Reminder to attend scheduled clinic visits.

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 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 20 questions sufficiently addressed key safety and usage messages. 3 additional questions were used to receive feedback on the format and user friendliness of the leaflet.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Emtricitabine/Tenofovirdisoproxil CF 200/245 mg, film-coated tablets, from Centrafarm B.V. 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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 June 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
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site.	NL/H/3635/ 001/IA/001	IA	03-11-2016	21-11-2016	Approved	No
Change in the (invented) name of the medicinal product	NL/H/3635/ 001/IB/002	IB	06-12-2016	05-01-2017	Approved	No