CBG MEB

Public Assessment Report

Scientific discussion

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

(emtricitabine/tenofovir disoproxil phosphate)

NL/H/3432/001/DC

Date: 20 January 2017

This module reflects the scientific discussion for the approval of Emtricitabine/Tenofovirdisoproxil Teva 200/245 mg, film-coated tablets. The procedure was finalised on 6 April 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
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 State3432
EDMF	European Drug Master File
EEA	European Economic Area
ERA	Environmental Risk Assessment
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 Teva 200/245 mg, film-coated tablets, from Teva Nederland B.V.

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

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Iceland, Italy, Latvia, Malta, Poland, Portugal, Romania, Sweden, Slovenia and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Emtricitabine/Tenofovirdisoproxil Teva is a green to light green, oval shaped film coated tablet, debossed with “E T” on one side and plain on the other side. Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil, equivalent to 291.22 mg of tenofovir disoproxil phosphate or 136 mg of tenofovir.

The film-coated tablets are packed in:

- OPA/Alu/PVC – Aluminium blister packs
- OPA/Alu/PE+ desiccant – Alu/PE blister packs
- 100 ml white HPDE heavy wall bottles with 38 mm polypropylene (PP) child resistant closure and 3 g desiccant canister
- 100 ml white HPDE heavy wall bottles with 38 mm polypropylene (PP) child resistant closure with 4 g molecular sieve

The excipients are:
Tablet core – mannitol, microcrystalline cellulose (E460), hydroxypropyl cellulose-low substituted (E463), hypromellose (E464) and sodium stearyl fumarate
Film-coating - polyvinyl alcohol, part hydrolysed (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), indigo carmine aluminium lake (E132) and iron oxide yellow (E172)

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 the cis enantiomer, having the 2R, 5S absolute configuration, is produced.

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
Emtricitabine is manufactured in two stages, and a final purification. 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 14 batches.

Stability of drug substance
Stability data on emtricitabine have been provided for 15 batches stored at 25°C/60% RH (up to 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 60 months is acceptable, without the need for special storage conditions, however, the storage condition "Store in a well closed container, do not store above 30°C" could be accepted as well.

Tenofovir disoproxil phosphate
The second active substance is tenofovir disoproxil phosphate, 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 phosphate is a white to off white powder, freely soluble in dimethyl formamide and soluble in methanol and water. The aqueous solubility is pH dependent. Tenofovir disoproxil phosphate has one chiral centre at C-2 position of the propyl side-chain with the R-configuration. Only one polymorph has been reported for tenofovir disoproxil phosphate.

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

Manufacturing process
Tenofovir disoproxil phosphate is manufactured in three stages, consisting of four chemical steps and a final salt formation and purification, from the starting materials. No class 1 solvents or heavy metal catalysts are used in the synthesis of tenofovir disoproxil phosphate. 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
Stability data on tenofovir disoproxil phosphate have been provided for 2 pilot scale batches and 3 full scale batches, stored at 5°C (18 months for the full scale batches and 36 months for the pilot batches) and 25°C/60% RH (6 months). No clear up- or downward trends are observed, except for a slight increase over time in one impurity under accelerated conditions (25°C/60% RH). All stability study results remain within the specifications set. Based on the provided stability data the proposed retest period of 24 months with the storage condition "Store at 2-8°C", when stored in the proposed packaging materials, 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.
A bioequivalence study was carried out. The manufacture and composition of the bio-batch used in the study is identical to the marketed product. The batch size of the used bio-batch is acceptable given the proposed maximum batch size of the commercial batches. Comparative dissolution profiles for the test and reference product have been provided; dissolution at pH ~2 and 4.5 is fast (>85% at 15 min), whereas at pH 6.8 the calculated f2 is <50. However, as bioequivalence has been shown *in vivo*, this is sufficient.
Emtricitabine/Tenofovirdisoproxil Teva tablets were developed using an alternative salt of tenofovir disoproxil, tenofovir disoproxil phosphate, 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 2 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
Except for the coating system, all the excipients comply with the Ph.Eur. or the United States Pharmacopeia National Formulary (USP-NF), and acceptable limits for functionality-related characteristics have been set, if required. The individual components of the coating system comply with official pharmacopoeias, except for the indigo carmine aluminium lake colourant. However the colourant complies with European regulations for use in foodstuffs. 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/appearance, identity, dissolution, uniformity of dosage units, assay, impurities/degradation products, water content, and microbiological quality.
The release and shelf-life requirements/limits are not identical. 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. Furthermore, the limits for the impurities/ degradation products are not identical for mono ester impurity and total impurities. The proposed specification at release and shelf-life are acceptable.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on 2 pilot scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on 2 full scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months), for the blister packs and the bottles, and for the blister packs

also at 30°C/65% RH (12 months). The conditions used in the stability studies are according to the ICH stability guideline.

For the tablets stored in blisters a significant change of a specified impurity is seen under accelerated conditions. The claimed shelf-life of 21 months with storage conditions 'Do not store above 30°C. Store in the original blister to protect from moisture' is justified.
For the tablets stored in bottles only a non-significant change in water content is seen under long term conditions. The claimed shelf life of 2 years can be accepted with storage condition 'Store in the original bottle to protect from moisture. Keep the bottle tightly closed'.
In-use stability data has been provided demonstrating that the product remains stable for 30 days following first opening of the containers (bottles).
The drug product was shown not to be sensitive 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 Emtricitabine/Tenofovirdisoproxil Teva 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 Teva 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 phosphate 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 Teva 200/245 mg, film-coated tablets (Teva Nederland B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Truvada 200 mg/245 mg film-coated tablets (Gilead Sciences International Ltd, Germany).

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 42 healthy (19 male and 23 female) subjects, aged 18-79 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 minutes after the start of intake of a high fat, high caloric breakfast. The meal was comprised of approximately 240 ml of whole milk, 2 large eggs, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with approximately 4.5 g of butter and 2 strips 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, 2.33, 2.67, 3, 3.5, 4, 4.5, 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) prior to dosing for Period II. 41 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=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	11618 ± 3080	11940 ± 3173	2010 ± 597	2.0 (0.98 – 6.0)	16.2 ± 9.0
Reference	11561 ± 3133	11931 ± 3250	2048 ± 604	2.0 (0.75 – 5.0)	16.6 ± 9.1
***Ratio (90% CI)**	1.01 (0.99 – 1.03)	--	0.98 (0.92 – 1.05)	--	--
CV (%)	5.4	--	17.7	--	--

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=41	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	3184 ± 946	3382 ± 1032	320 ± 100	2.0 (0.55 – 6.0)	18.7 ± 2.7
Reference	3224 ± 891	3438 ± 982	326 ± 91	2.0 (0.75 – 5.0)	18.7 ± 4.1
***Ratio (90% CI)**	0.98 (0.95 – 1.01)	--	0.97 (0.90 - 1.04)	--	--
CV (%)	7.8	--	19.1	--	--

$AUC_{0-\infty}$	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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Emtricitabine/Tenofovirdisoproxil Teva 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 Emtricitabine/Tenofovirdisoproxil Teva.

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 • Post-treatment hepatic flares in hepatitis B or C virus co-infected patients • 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. 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.

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 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 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 Teva 200/245 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 Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 April 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