

## **Public Assessment Report**

### **Scientific discussion**

**Tenofoviridisoproxil DOC Generici 245 mg  
film-coated tablets**

**(tenofovir disoproxil succinate)**

**NL/H/3437/001/DC**

**Date: 13 October 2016**

This module reflects the scientific discussion for the approval of Tenofoviridisoproxil DOC Generici 245 mg film-coated tablets. The procedure was finalised on 11 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

ALT	Alanine aminotransferase
ASMF	Active Substance Master File
BP	British Pharmacopoeia
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 Tenofovir disoproxil DOC Generici 245 mg film-coated tablets, from DOC Generici S.r.l.

The product is indicated for:

### *Human Immunodeficiency Virus type 1 (HIV-1) infection*

Tenofovir disoproxil 245 mg film coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults.

In adults, the demonstration of the benefit of tenofovir disoproxil in HIV-1 infection is based on results of one study in treatment-naïve patients, including patients with a high viral load (>100,000 copies/ml) and studies in which tenofovir disoproxil was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (<10,000 copies/ml, with the majority of patients having <5,000 copies/ml).

Tenofovir disoproxil 245 mg film-coated tablets are also indicated for the treatment of HIV-1 infected adolescents, with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to <18 years.

The choice of tenofovir disoproxil to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients.

### *Hepatitis B infection*

Tenofovir disoproxil 245 mg film-coated tablets are indicated for 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

Tenofovir disoproxil 245 mg film-coated tablets are indicated for 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 persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis.

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 Viread 245 mg film-coated tablets which has been registered in the EEA by Gilead Sciences International Limited since 5 February 2002 through centralised procedure EU/1/01/200/001-009. Tenofovir disoproxil DOC Generici contains the phosphate salt of the prodrug tenofovir disoproxil while the originator Viread 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

Tenofovir disoproxil DOC Generici is a light blue, almond-shaped, film-coated tablet. Each film-coated tablet contains 245 mg of tenofovir disoproxil (as succinate).

The product is packed in High Density Polyethylene (HDPE) bottles with a polypropylene (PP) child-resistant cap and an HDPE canister containing silica gel.

The excipients are:

*Tablet core* – anhydrous lactose, microcrystalline cellulose 112 (E460), pregelatinised starch (maize), croscarmellose sodium and magnesium stearate (E470b)

*Film-coating* - indigo carmine aluminium lake (E132), titanium dioxide (E171), poly (vinyl alcohol) (E1203), macrogol 4000 (E1521) and talc (E553b)

### II.2 Drug Substance

The active substance is tenofovir disoproxil succinate, an established active substance. Tenofovir disoproxil succinate is not described in the European Pharmacopoeia (Ph.Eur.). The related fumarate salt is described in the WHO International Pharmacopoeia (Ph.Int.) and in a pending monograph for the United States Pharmacopoeia (USP). Tenofovir disoproxil succinate is a white to off-white crystalline powder which is 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. Five 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 the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

#### Manufacturing process

The 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 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. The MAH applies the specification and analytical methods of the drug substance manufacturer. 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. 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. The choices for the packaging are justified in relation to the innovator. The manufacturing process was selected, optimised and scaled-up to commercial scale. In the reference product Viread, tenofovir disoproxil fumarate is used. The Tenofovir disoproxil DOC Generici 245 mg tablets were developed using an alternative salt, tenofovir disoproxil succinate. 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.

One bioequivalence study was carried out. The manufacture and composition of the bio-batch used in the bioequivalence study is similar to the formulation for marketing. The dissolution profiles in three different media (0.1N HCl; acetate buffer pH 4.5; phosphate buffer pH 6.8) of the reference batch and the test batch in the bioequivalence study were found to be similar (>85% in 15 minutes).

#### Manufacturing process

The tablets are manufactured by compressing dry compacted granules of drug substance and excipients, followed by film coating. It is considered to be a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data have been presented for three pilot scaled batches. Process validation on full commercial scale will be performed post authorisation.

#### Control of excipients

The pharmacopoeial excipients all comply with the Ph.Eur. The colourant indigo carmine aluminium lake complies with Commission Regulation EU 231/2012 on food additives. 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 and dimensions, identity of drug substance and colourants, assay, related substances, 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. The limits at release and shelf-life are acceptable in view of the available batch analysis and stability data. The specification is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from at least 3 pilot scale 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 5 pilot scale batches and 1 smaller batch stored at 25°C/60% RH (12-18 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. A slight increase mainly in one of the specified impurities was observed. No clear trends or changes were seen in any of the other tested parameters. It was adequately demonstrated that the packed and the unpacked product is photo stable. The claimed shelf-life of 30 months with storage condition 'This medicinal product does not require any special storage conditions' 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 anhydrous lactose 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 Tenofovir disoproxil DOC Generici 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 Tenofovir disoproxil 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 Viread 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**

Tenofovir disoproxil succinate is a well-known active substance 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 Tenofovir disoproxil DOC Generici 245 mg film-coated tablets (DOC Generici S.r.l., Italy) is 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*

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 bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 20-64 years. Each subject received a single dose (245 mg) of one of the 2 tenofovir disoproxil 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. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected taken pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. 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 (nasopharyngitis) prior to check in for Period II. 35 subjects completed the study and were eligible for pharmacokinetic analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t<sub>max</sub> (median, range)) of tenofovir under fed conditions.**

Treatment N=35	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	2899 ± 666	3111 ± 696	289 ± 83	2.33 (0.67 – 4.0)	17.1 ± 2.9
<b>Reference</b>	2981 ± 622	3190 ± 641	265 ± 72	2.0 (0.67 – 5.0)	17.4 ± 3.2
<b>*Ratio (90% CI)</b>	0.97 (0.94 – 1.00)	--	1.09 (1.02 - 1.15)	--	--
<b>CV (%)</b>	8.1	--	14.7	--	--
<b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life <b>CV</b> coefficient of variation					

*\*In-transformed values*

**Conclusion on bioequivalence study**

The 90% confidence intervals calculated for AUC<sub>0-t</sub> and C<sub>max</sub> are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Tenofovir disoproxil DOC Generici 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 Tenofoviridisoproxil DOC Generici.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> <li>- Renal toxicity</li> <li>- Bone events due to proximal renal tubulopathy/loss of bone mineral density</li> <li>- Post treatment hepatic flares in HBV mono-infected and HIV/HBV co-infected patients</li> <li>- Interaction with didanosine</li> <li>- Pancreatitis</li> <li>- Lactic acidosis and severe hepatomegaly with steatosis</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>- Development of resistant during long term exposure in HBV infected patients</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>- Safety in children (including long-term safety)</li> <li>- Safety in elderly patients</li> <li>- Safety in pregnancy</li> <li>- Safety in lactation</li> <li>- Safety in black HBV infected patients</li> <li>- Safety in patients with renal impairment</li> <li>- Safety in patients with decompensated liver diseases and CPT score &gt;9 (including long term safety)</li> <li>- Safety in liver transplant recipients</li> </ul>

Additional risk minimisation measures are required relating to renal toxicity. These have been laid down in line with the reference product. It concerns the following additional risk minimisation measures:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

The educational material should be submitted to the national competent authority for assessment prior to the actual launch of this tenofovir-containing product onto the market.

### 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 Tenofoviridisoproxil DOC Generici 123 mg, 163 mg and 204 mg film-coated tablets. Hence successful user testing was carried out on the combined PL for these lower strengths. 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**

Tenofoviridisoproxil DOC Generici 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 Tenofoviridisoproxil DOC Generici with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 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