CBG MEB

Public Assessment Report

Scientific discussion

Emtricitabine/Tenofovirdisoproxil Accord 200/245 mg film-coated tablets

(emtricitabine/tenofovir disoproxil)

NL/H/3715/001/DC

Date: 1 September 2017

This module reflects the scientific discussion for the approval of Emtricitabine/Tenofovirdisoproxil Accord 200/245 mg film-coated tablets. The procedure was finalised on 23 March 2017. 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 Accord 200/245 mg film-coated tablets, from Accord Healthcare Ltd.

The product is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults and in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

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, Denmark, Spain, Finland, Ireland, Italy, Norway, Poland, Portugal, Romania, Sweden 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 Accord is a blue coloured, capsule shaped film-coated tablet, debossed with 'H' on one side and 'E29' on the other side. Each tablet contains 200 mg of emtricitabine and 245 mg tenofovir disoproxil (equivalent to 136 mg of tenofovir).

The tablets are packed in OPA-Al-PVC/Al blisters and high density polyethylene 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 (PH 101 and PH 102), pregelatinised maize starch, croscarmellose sodium and magnesium stearate.
Film-coating - hypromellose 15 m.Pas, lactose monohydrate, titanium dioxide (E171), triacetin 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, sparingly 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 contains two chiral centres in its structure. The opposite enantiomer is controlled as part of the drug substance specification

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 six stages, a chlorination and condensation step, a reduction step, desertification step and purification step and a drying, milling sifting and packaging step. The starting materials are acceptable. 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 drug substance specification for emtricitabine as applied by the drug product manufacturer has been established in-house, based on the specification of the drug substance supplier, with additional requirements for microbiological quality and 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 three batches.

Stability of drug substance
Stability data on emtricitabine have been provided for five pilot scale batches and two full scaled batch stored at 25°C/60% RH (9- 48 months) and 40°C/75% RH (6 months, four batches only). No clear up- or downward trends are observed, under both long term and accelerated conditions. The proposed retest period of 60 months without any special storage requirements is justified.

Tenofovir disoproxil
The second active substance is tenofovir disoproxil, an established active substance not described in the Ph.Eur. Tenofovir disoproxil is a white to off-white powder and soluble in water (pH dependant) and sparingly soluble in methanol and ethanol. The active substance is consistently manufactured with the same polymorph form.

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

Manufacturing process
The active substance is manufactured in a three step synthesis. No class 1 solvents or heavy metal catalysts are used in the synthesis of tenofovir disoproxil. 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 has been established in-house and is identical to the specification of the ASMF-holder, with additional requirements for particle size distribution and microbial examination. The specification is acceptable in view of the route of synthesis and various European guidelines. Batch analytical data demonstrating compliance with the currently proposed active substance specification have been provided.

Stability of drug substance
Stability data on tenofovir disoproxil have been provided for three commercial scale batches stored at 2-8°C (18 months), 25°C/60% RH (18 months), 30°C/75% RH (18 months) and 40°C/75% RH (6 months). No trends or changes were seen in any of the tested parameters at all four storage conditions. Based on the stability data provided the claimed re-test period of 24 months without special storage conditions can be granted.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the reference product, optimization of the formulation and manufacturing process and performance of comparative *in vitro* dissolution studies complementary to the *in vivo* bioequivalence study. The choices of the packaging and manufacturing process are justified. The drug product batch that was used in the bioequivalence study versus the reference product was manufactured according to the

finalised composition and manufacturing process. The pharmaceutical development has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are sifting, blending and lubrication, compaction, prelubrication and lubrication, compressing and coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scaled 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 film-coating material, the excipients comply with their respective Ph.Eur. monographs. The film-coating material is controlled according to an in-house specification. 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 appearance, identity, average mass, water content, dissolution, uniformity of dosage units, related substances, assay and microbiological quality. Except for water content and related substances the release and shelf-life requirements are identical. All 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 the proposed production site have been provided on two pilot scaled batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided on two pilot scaled batches stored at 25°C/60% RH (12 months), 30°C/65% RH (12 months) and 40°C/75% RH (3-6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. At all storage conditions an increase in impurities was seen, which was more pronounced at accelerated storage conditions. Out-of-specification results for impurities were observed for the product packed in Al-Al blisters after 3 months storage at accelerated conditions. Photostability studies showed that the product is not sensitive to light.
Based on these results, the proposed shelf-life of 2 years is justified with the following storage requirements: “Store in the original package in order to protect from moisture. Keep the bottle tightly closed. This medicinal product does not require any special temperature storage conditions.” for the bottle pack and “Store below 30°C. Store in the original package in order to protect from moisture. ” for the blister pack.
Stability data has been provided demonstrating that the product remains stable for 30 days in-use following first opening of the container, when stored at 25°C/60% RH. The stability results did not clearly differ from the formal long-term stability studies. Therefore, no separate in-use shelf life for the bottle pack is needed.

Specific measures for the prevention of the transmission of animal spongiform encephalo-pathies
The only component of animal origin used in the drug product is lactose monohydrate. It has been confirmed that the lactose is produced from milk sourced from healthy cows in the same condition as milk collected for human consumption. The lactose has been prepared without the use of other ruminant material than calf rennet to the description as published in Public Statement EMEA/CPMP/571/02.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Emtricitabine/Tenofovirdisoproxil Accord 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 Accord 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 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 a 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 Accord 200/245 mg film-coated tablets (Accord Healthcare Ltd, the United Kingdom) 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 50 healthy male subjects, aged 18-43 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 slices of bread with cheese, 1 cutlet, 35 mg walnuts, 20 ml green chutney and 20 ml tomato chutney. There were 2 dosing periods, separated by a washout period of 12 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, 3.33, 3.67, 4.00, 4.50, 5, 6, 8, 10,12, 16, 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) and one subject withdrew consent. Therefore, a total of 48 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=48	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	10.9 ± 2.3	11.2 ± 2.3	1.82 ± 0.40	2.5 (0.75 – 5.0)	7.1 ± 2.4
Reference	10.9 ± 2.3	11.3 ± 2.3	1.88 ± 0.41	2.0 (0.75 – 5.0)	7.6 ± 3.1
***Ratio (90% CI)**	1.00 (0.97 – 1.02)	1.00 (0.98 – 1.02)	0.97 (0.93 – 1.01)	--	--

$AUC_{0-\infty}$ 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
**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tenofovir under fed conditions.

Treatment N=48	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3.47 ± 0.88	3.73 ± 0.97	0.395 ± 0.12	2.0 (0.75 – 4.0)	19 ± 3.2
Reference	3.39 ± 0.81	3.66 ± 0.89	0.384 ± 0.10	2.0 (0.75 – 5.0)	19 ± 3.5
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	1.02 (0.98 – 1.05)	1.02 (0.97 – 1.08)	--	--

$AUC_{0-\infty}$ 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
**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Emtricitabine/Tenofovirdisoproxil Accord 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 Accord.

- 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 Accord 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 Accord to Reduce the Risk of getting Human Immunodeficiency Virus (HIV) Infection'
- PrEP reminder card.

<u>HIV renal educational brochure</u>

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-containing products such as Emtricitabine/Tenofovirdisoproxil Accord
- That Emtricitabine/Tenofovirdisoproxil Accord 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 Accord should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Emtricitabine/Tenofovirdisoproxil Accord 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 Accord therapy
- The importance of regular monitoring of renal function during Emtricitabine/Tenofovirdisoproxil Accord 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.

<u>PrEP educational brochure for prescribers:</u>

- Reminder of the key safety information regarding the use of Emtricitabine/Tenofovirdisoproxil Accord 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 Accord 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 Accord
- Provides information on the possible side effects
- Provides information on how to store Emtricitabine/Tenofovirdisoproxil Accord.

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

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 Truvada 200 mg/245 mg film-coated tablets. For the design, lay-out and style of writing reference was made to the PL of Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Emtricitabine/Tenofovirdisoproxil Accord 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 Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 March 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse