COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tenofovir disoproxil Accordpharma 245 mg film-coated tablets

(tenofovir disoproxil fumarate)

NL/H/4119/001/DC

Date: 7 March 2019

This module reflects the scientific discussion for the approval of Tenofovir disoproxil Accordpharma 245 mg film-coated tablets. The procedure was finalised at 1 October 2018. 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 Tenofovir disoproxil Accordpharma 245 mg film-coated tablets, from Accord Healthcare Ltd.

The product is indicated for:

Human Immunodeficiency Virus type 1 (HIV-1) infection
Tenofovir disoproxil Accordpharma 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 Accordpharma 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 Accordpharma 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 fumarate 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
The product is 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

The product is 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).

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Czech Republic, Denmark, Greece, Spain, Finland, Hungary, Ireland, Italy, Malta, Norway, Poland, Romania, Sweden, Slovenia, Slovak Republic 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

Tenofovir disoproxil Accordpharma is a white coloured, almond shaped, film-coated tablet, debossed with 'H' on one side and '123' on the other side. Each film-coated tablet contains tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

The film-coated tablets are packed in Aluminium//PVC/Aluminium/OPA (unit dose) blisters.

The excipients are:
Tablet core - cellulose, microcrystalline (E460), lactose monohydrate, pregelatinised starch (maize), croscarmellose sodium (E468) and magnesium stearate (E470b)
Film-coating - hypromellose (E464), lactose monohydrate, titanium dioxide (E171) and triacetin (E 1518)

II.2 Drug Substance

The active substance is tenofovir disoproxil fumarate, an established active substance. The active substance is not described in the European Pharmacopoeia however described in the WHO international Pharmacopoeia (Ph.Int.) and in a pending monograph for the United Stated Pharmacopoeia (USP). Tenofovir disoproxil fumarate is a crystalline powder and is slightly soluble in water. The active substance contains one stereogenic centre which is adequately controlled. The active substance exhibits polymorphism, polymorphic Form-I is consistently manufactured

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 manufacturing process of the active substance consists of five steps. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents. No class I solvents are used in the process.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is identical to the specification of the ASMF-holder. 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, by the drug substance manufacturer, on three full scale batches, and by the drug product manufacturer on two full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches stored at 5°C (60 months), 20°C/60% RH (36 months) and 40°/75% RH (6 months). The proposed retest period of 60 months with the storage condition 'store in a refrigerator (2 to 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 the excipients justified and their functions explained. The main development studies were formulation trials and comparative dissolution studies with the innovator product.

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. This has been justified. 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 manufacturing process by wet granulation process involves sifting, dry mixing, granulation, drying, compression followed by film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for a third full scaled batch will be performed post authorisation.

Control of excipients
The excipients comply with their corresponding Ph.Eur. monographs. 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 description, identity, water, average weight, disintegration time, dissolution, uniformity of dosage units, related compounds, assay, microbiological examination and identification of colorant. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Except for water content, assay and related compounds and assay, the release and shelf-life limits are identical. This is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for two full scaled batches stored at 25°C/60% RH (18 months), 30°C/65% RH (12 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 a Alu-Alu blister pack. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. As significant change in specified impurity is observed under accelerated conditions. During long term stability studies only a minor increase in the specified impurity is observed while the assay value remains stable. The proposed shelf-life, for the product packaged in blisters, of 24 months with the storage condition “store below 30°C” is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the excipients used in this formulation are of animal origin except lactose 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 Accordpharma 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 Accordpharma 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 fumarate 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tenofovir disoproxil Accordpharma 245 mg film-coated tablets (Accord Healthcare Ltd., UK) is compared with the pharmacokinetic profile of the reference product Viread 245 mg, film-coated tablets (Gilead Sciences Ireland UC, Ireland).

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.

Bioequivalence study

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 18-44 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 start of intake of a high fat, high caloric breakfast (consisting of toast, chana chat, vegetable cutlets and milk). There were 2 dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 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.

The design of the study is acceptable. 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.

Results

All 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 tenofovir disoproxil under fed conditions.

Treatment N=34	**AUC_{0-72h}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	3796 ± 988	4076 ± 1070	351 ± 109	2.0 (1.0 - 3.5)	19 ± 3
Reference	3673 ± 856	3925 ± 952	357 ± 100	2.25 (0.75 – 3.5)	19 ± 3
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	--	0.97 (0.92 – 1.03)	--	--
CV (%)	9.6	--	14.4	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 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 Tenofovir disoproxil Accordpharma 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 Tenofovir disoproxil Accordpharma.

Table 2. 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 HBV mono-infected and HIV/HBV co-infected patients - Interaction with didanosine - Pancreatitis
Important potential risks	- Development of resistant during long term exposure in HBV infected patients
Missing information	- Safety in children (including long-term safety) - Safety in elderly patients - Safety in pregnancy - Safety in lactation - Safety in black HBV infected patients - Safety in patients with renal impairment - Safety in patients with decompensated liver diseases and CPT score >9 (including long term safety) - Safety in liver transplant recipients

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

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 Viread. 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

Tenofovir disoproxil Accordpharma 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 Tenofovir disoproxil Accordpharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 October 2018.

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