13 October 2016
EMA/798405/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tenofovir disoproxil Mylan

International non-proprietary name: tenofovir disoproxil

Procedure No. EMEA/H/C/004049/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AE	Adverse events
ANOVA	Analysis of variance
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
Clr	Renal clearance
Cmax	Maximum concentration
CMS	Concerned Member State
CoA	Certificate of Analysis
CRP	C -reactive protein
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of variation
DMF	*N*,*N*-dimethylformamide
DNA	Deoxyribonucleic Acid
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EDTA	Ethylene diamine tetra acetic acid
EMA	European Medicines Agency
EP	European Pharmacopoeia
EU	European Union
FPM	Finished Product Manufacturer
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
H	Hour
Hb	Hemoglobin
HCV	Hepatitis C virus

HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HIV-1	human immunodeficiency virus Type 1,
HIV-2	human immunodeficiency virus Type 2,
HPLC	High performance liquid chromatography
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IPC	In-process control
IR	Infrared
IU	International Units
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
LDPE	Low Density Polyethylene
LOA	Letter of Access
LoD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
MA	marketing autorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MS	Mass Spectrometry
NA	Not applicable
NC	Non-clinical
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NS	Not significant
OOS	Out of Specifications
P	Probability p value
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetics
p.o.	Per os
PP	Polypropylene
ppm	parts per million
PVC	Poly vinyl chloride
PXRD	Powder x-ray diffraction
QOS	Quality Overall Summary
R or B	Reference product

RH	Relative Humidity
RP	Restricted Part (or Closed Part) of an ASMF
rpm	Revolutions per minute
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard deviation
SmPC	summary of product characteristics.
SOP	Standard operation procedure
T or A	Test product
t1/2	Elimination half-life
t0	Time of drug administration
TGA	Thermo-Gravimetric Analysis
Tlast	Time of last measurable concentration
TLC	Thin layer chromatography
tmax	Time to reach the maximal concentration
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
UPLC	ultra-high performance liquid chromatography
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
V	Volume
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 29 July 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Tenofovir disoproxil Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication.

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 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 (see section 5.1).
- evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1).
- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

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 (see sections 4.4, 4.8 and 5.1).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Viread 245 mg film-coated tablets instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Viread 245 mg film-coated tablets
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 05-02-2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/01/200/001-2

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Viread 245 mg film-coated tablets
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 05-02-2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/01/200/001-2

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Viread 245 mg film-coated tablets
- Marketing authorisation holder: Gilead Sciences International Limited

- Date of authorisation: 05-02-2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/01/200/001-2
- Bioavailability study number(s): TE-14-024

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Romaldas Mačiulaitis

- The application was received by the EMA on 29 July 2015.
- The procedure started on 20 August 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 November 2015.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 20 November 2015.
- During the meeting on 3 December 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 17 December 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 December 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 March 2016.
- The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product:
  - GCP inspections at the analytical laboratory and the sponsor site in India (inspection dates: 11/02/2016 to 16/02/2016). The outcome of the inspection carried out was issued on 11 April 2016
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 May 2016.
- During the PRAC meeting on 13 May 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 26 May 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 June 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses on the 8 July 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a list of outstanding issues to be

addressed in writing and/or in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 13 September 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses on the 29 September 2016.
- During the meeting on 13 October 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Tenofovir disoproxil Mylan.

2. Scientific discussion

2.1. Introduction

The generic medicinal products serve public health need and the applicant developed one version of generic medicinal product against reference medicinal product Viread (MAH Gilead Sciences International Limited). Viread was authorised in the Union on the basis of a complete dossier is as film-coated tablet containing 245 mg of Tenofovir disoproxil. Tenofovir disoproxil maleate Mylan is identical in terms of qualitative and quantitative composition of the active substances (Tenofovir disoproxil) and is therefore expected to perform identically in vivo within the clinical setting.

The application for Tenofovir disoproxil maleate Mylan 245 mg film-coated tablets was submitted by Mylan SAS, France via the centralised procedure as Generic of a Centrally Authorised Medicinal Product of Regulation (EC) No 726/2004 and according Article 10(1) generic application of Directive 2001/83/EC. The chosen reference medicinal product authorised in the Union on the basis of a complete dossier is Viread (MAH Gilead Sciences International Limited, UK) film-coated tablet containing 245 mg of Tenofovir disoproxil fumarate. Marketing authorisation number: EU/1/01/200/001-002. Date of authorisation 05-02-2002.

The Applicant seek Centralised marketing authorisation (MA) approval for Tenofovir disoproxil maleate Mylan for the treatment of HIV-infected adults of 18 years of age and older and for the treatment of chronic hepatitis B in adults

Quality data showed that both medicinal products are based on same active moieties and are composed by different salts in case of tenofovir (maleate in case of applied product vs fumarate in case of reference product). Based on the data provided, there is no need to generate additional data. A number of quality issues related to the active substance have been clarified and the drug product manufacturer's active substances specifications are considered acceptable.

Non-clinical data presented (i) original studies (repeat dose toxicity study, genotoxicity screen and a single species general toxicity study in support of the Tenofovir disoproxil dimer, mixed dimer, and mono POC dimer impurities) as well as (ii) overviews on pharmacology, pharmacokinetics and toxicology overview were provided. These data justified the no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

A clinical dataset consisted of two parts – clinical overview (bibliographic data on clinical pharmacology, efficacy and safety of tenofovir) and the comparative bioequivalence study in fed condition. These data could justify why

there is no need to generate additional clinical pharmacology, pharmacokinetics, efficacy, and safety data. The positive benefit risk assessment can be concluded.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 245 mg tenofovir disoproxil (as maleate) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, lactose monohydrate, low substituted hydroxypropylcellulose, colloidal anhydrous silica and magnesium stearate.

Film-coating: hypromellose, lactose monohydrate, titanium dioxide (E171), triacetin and Indigo Carmine Aluminium Lake (E132).

The product is available in high density polyethylene (HDPE) bottles with polypropylene (PP) child resistant closures with wads containing aluminium induction sealing liner and silica gel desiccant as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of tenofovir disoproxil (as maleate) is *bis*({[propan-2-yloxy)carbonyl]oxy}methyl) ({[2*R*)-1-(6-amino-9*H*purin-9-yl)propan-2-yl]oxy}methyl)phosphonate(2*Z*)-but-2-enedioate, corresponding to the molecular formula $C_{19}H_{30}N_5O_{10}P{\cdot}C_4H_4O_4$. It has a relative molecular mass of 635.51 g/mol and the following structure (**Figure 1**):

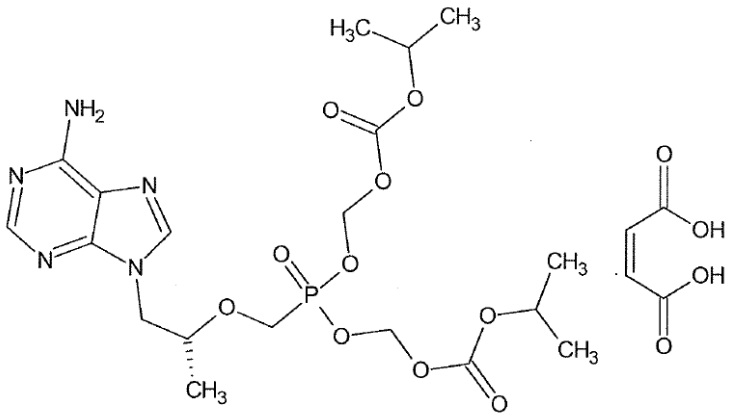

Figure 1. Structure of tenofovir disoproxil maleate

The structure of the active substance was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis and XRD.

Tenofovir disoproxil maleate is a white to off-white, non-hygroscopic, crystalline powder, freely soluble in DMF and soluble in aqueous solutions (pH 1.2-8.0) and methanol. Its pKa is 3.5 and its partition coefficient is 0.67.

Tenofovir disoproxil maleate exhibits stereoisomerism due to the presence of one chiral centre at C-11 (the C-2 position of the propyl side-chain). Two isomers are possible due to this asymmetric carbon. The *R*-isomer is commercially produced. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation.

Tenofovir disoproxil maleate exhibits polymorphism and different forms are reported in the literature (form I and form II). The PXRD method distinguishes the polymorphic forms and PXRD data confirmed that Form I is consistently produced and that it is stable upon storage. Three tenofovir disoproxil maleate batches were undergone compaction followed by milling. The milled tenofovir disoproxil maleate batches were analysed by PXRD. The XRD pattern comparison demonstrated that compaction followed by milling operations does not affect polymorphism.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance was provided in the restricted part of the ASMF and considered satisfactory.

Tenofovir disoproxil maleate is synthesized in three main steps (Stages I, II and III) using commercially available well defined starting materials with acceptable specifications. Two manufacturing sites carry out stages I and II. Stage III only takes place at the second site. The synthesis was described in sufficient detail.

The synthetic process encompasses the stereoselective formation of the desired tenofovir disoproxil maleate *R*-enantiomer from a commercially available optically active starting material. The process has been shown able to consistently produce tenofovir disoproxil maleate that meets the required quality standards.

The critical process parameters have been presented and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities is in accordance with the relevant EU guidance. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packed in double polyethylene bags which are in turn packed in triple laminated aluminium packs, heat sealed, and placed in HDPE containers which comply with the Ph. Eur. and relevant EC regulations 2015/174.

Specification

The active substance specification includes tests for description (visual), solubility (visual), identification (IR, HPLC), clarity of solution (visual), water content (KF), sulfated ash (in house), heavy metals (Ph. Eur.), *S*-isomer content (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), chloromethyl isopropyl carbonate (GC), 9-propenyl adenine (LC-MS), impurities (sum of diethyl(hydroxymethyl)phosphonate and tosyl

phosphonate) (LC-MS), formaldehyde content (UPLC), total genotoxic impurities (LC-MS, UPLC) and particle size (laser diffraction particle).

Skip testing for 9-propenyl adenine, limit of impurities (sum of diethyl(hydroxymethyl)phosphonate and tosyl phosponate), formaldehyde and total genotoxic impurities in the active substance specification has been adequately justified as they are consistently below 30% of the TTC as per ICH M7 option 1.

Omission of tests for polymorphism and microbiological quality in the active substance specification has been justified. Regarding polymorphism, it was demonstrated the same polymorphic form was consistently produced in the process and was stable upon storage. The absence of microbiological control was also considered acceptable as tenofovir disoproxil maleate is recrystallised from isopropyl alcohol which does not allow microbial growth, which was confirmed by testing representative production scale batches for microbiological quality.

All the proposed specification limits are considered justified and in line with the relevant ICH guidelines. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three consecutive production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under intermediate conditions (30 ºC / 75% RH), according to the ICH guidelines were provided. Stability studies under accelerated conditions (40 ºC / 75% RH) were conducted.

The following parameters were tested*:* description, identification (IR, HPLC), water content (KF), *S*-isomer content (HPLC) and assay (HPLC). The analytical methods used were the same as for release and were stability indicating.

A significant increase in impurities was observed under accelerated conditions and the batches did not meet the specifications. Therefore, additional stability studies were conducted under intermediate conditions. Under these conditions, a slight increase in the level of the monoester impurity was observed but no other degradation was noted. All other measured parameters remained well within their specification limits.

Results from forced degradation studies were also provided. Tenofovir disoproxil maleate was exposed to aqueous acid, aqueous base, oxidant, heat and UV. Solid samples were exposed to white fluorescent light (according to ICH Q1B), UV at 365 nm and heat at 60 ºC.

Significant degradation of tenofovir disoproxil maleate was observed in solution under alkaline, acid and oxidative conditions and when exposed to heat or UV light. No significant degradation was observed in solid state when samples were exposed to heat or white fluorescent light but slight degradation was observed on exposure to UV light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 12 months in the proposed container and the storage precaution “store below 25 ºC.”

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Tenofovir Disoproxil Mylan finished product is a round, bioconvex light blue film coated tablet. The aim of development was to produce an immediate release solid dosage form bioequivalent with the reference product, Viread. The excipients chosen are the same as those in the reference product except that pregelatinised starch and croscarmellose sodium are substituted with low substituted hydroxypropylcellulose as disintegrant and colloidal anhydrous silica as a glidant.

Tenofovir Disoproxil Mylan uses a different salt of the active substance (maleate rather than fumarate). The active substance exhibits pH-independent solubility across the physiological pH range and is a BCS class III compound. It is non-hygroscopic with poor flow properties but susceptible to hydrolysis and thus, a dry granulation method was selected. Compatibility with excipients was investigated with binary mixtures and some degradation was seen on storage. However, similar degradation was seen with the control active substance study and the long term stability studies show the chosen formulation to afford adequate stability. Levels of excipients and manufacturing parameters were selected based on the dissolution performance of the resultant tablets, as well as flow properties of powders and manufacturability aspects.

Dissolution profiles of the biobatch, manufactured on pilot scale, and a second production scale batch of Tenofovir Disoproxil Mylan were compared with Viread over the physiological pH range. All tablets dissolved (>85%) within 15 minutes in all cases and profiles can thus be considered as similar.

Since the finished product is absorbed from the gastrointestinal tract and aqueous solubility is not linked to pH, an acidic pH medium was selected for dissolution testing. Other parameters were optimised to ensure sink conditions whilst maintaining discriminatory power. Batches manufactured with too little disintegrant or tablets which had been over-compressed or over-lubricated dissolved much slower than tablets manufactured using the commercial process and formula, thus demonstrating the discriminatory nature of the method.

In section 4.2 of the SmPC, it is stated that in exceptional circumstances for patients with difficulty swallowing, the finished product can be administered following disintegration of the tablet in 100 ml of water, orange juice, or grape juice. Data was provided showing comparative disintegration times of Tenofovir Disoproxil and Viread in water and demonstrating that disintegration occurs for both products within 6 minutes. Since tenofovir disoproxil maleate (BCS III) is highly soluble in water, it was considered that a clinical study to investigate relative bioequivalence was not necessary as membrane permeability rather than dissolution is likely to be the rate limiting step for absorption.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging is a HDPE bottle with PP child resistant closure with a wad containing aluminium induction sealing liner and silica gel desiccant. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: mixing of intra-granular materials followed by compaction; milling and blending with extra-granular excipients; compression to form tablets; film coating; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on the lowest proposed production scale (200,000 tablets). Validation will be carried out as per the presented protocol on the proposed 625,000 and 1,400,000 tablet scales before commercialisation. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are used to control critical steps in the process (uniformity of powder blend, core tablet properties, coating of tablets, and integrity of primary packaging). They are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identity (HPLC and TLC), colour identification (colour test and UV), dissolution (UV), uniformity of dosage units (Ph. Eur.), impurities (HPLC), assay (HPLC), water content (KF) and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided from four batches produced on the smallest of the proposed commercial scales confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from four batches of finished product manufactured on the smallest of the proposed commercial scales batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH), up to 12 months under intermediate conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches of Tenofovir Disoproxil Mylan are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, dissolution, assay, impurities, water content and microbiological quality. The analytical procedures used are stability indicating. There were no significant trends in dissolution and microbiological quality under any conditions. Water content remained fairly steady under accelerated and intermediate conditions but dropped under long term conditions. Impurities increased and assay decreased over time under all conditions with more degradation at higher temperatures and humidities. Assay results were out of specification in 3 out of 4 batches under accelerated conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant trends were observed and the finished product is not considered to be photosensitive.

An in-use stability study is also in progress. Bottles were opened every day for 2 minutes over a 30 day period. Completed studies used batches stored for 0 and 5 months before instigating the protocol. The study will be repeated on bottles stored for 23 and 35 months as per the Note for Guidance on In-use stability testing of human medicinal products (CPMP/QWP/2934/99).

Based on available stability data, the proposed shelf-life of 24 months below 25 ^{o}C stored in the original package to protect from light and moisture as stated in the SmPC is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products. The magnesium stearate is of vegetal origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should repeat the in-use stability study on a batch towards the end of its shelf-life.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical data consisted of literature overview and own studies. The non-clinical safety profile of Tenofovir disoproxil fumarate has been studied in mice, rats, guinea pigs, rabbits, dogs, and monkeys (Viread SBOA 2001). Less non-clinical safety data is available for the maleate salt form. However, following oral administration, Tenofovir disoproxil fumarate is rapidly absorbed and converted to Tenofovir. While the

pharmacological profile of Tenofovir disoproxil will be equivalent subsequent to administration of either salt, a brief scientific review and safety assessment was conducted to compare the potential toxicity profiles of the two salt forms.

In addition, the Applicant evaluated and compared the toxicity profiles Tenofovir disoproxil maleate and Tenofovir disoproxil fumarate in a 90-day oral repeated dose toxicity study in rats. Results from this study demonstrate the toxicity profile to be comparable for Tenofovir disoproxil maleate and fumarate, thus the maleate salt is considered to be equivalent and therefore not expected to alter the patient response. These data taken together, as summarized below, demonstrates that maleate exposure (55 mg/tablet; 0.9 mg/kg/day for a 60 kg individual) at the maximum recommended dose of 245 mg/day (Viread SPC 2015) in Applicant's Tenofovir Disoproxil Maleate film coated tablets is safe for use and is not expected to alter the toxicological profile.

Data for bibliographical overview has been obtained from literature searches of the internet as well as the US National Library of Medicine database (MEDLINE/TOXLINE) back to 1965. Tenofovir disoproxil fumarate (CAS# 202138-50-9), Tenofovir disoproxil maleate, Tenofovir (CAS# 147127-20-6), and common synonyms for these were used in the conduction of these searches. These searches were completed June 1, 2015.

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Tenofovir disoproxil Mylan manufactured by MYLAN S.A.S. is considered unlikely to result in any significant increase in the combined sales volumes for all Tenofovir disoproxil containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

Non clinical data for this application consisted of data from literature. There are some differences in the active substance entity in Reference product Viread. Viread contains Tenofovir disoproxil fumarate, while Tenofovir disoproxil maleate is contained in the generic product. Based on literature data, the applicant stated that Tenofovir disoproxil maleate will be rapidly absorbed and converted to Tenofovir as is established for Tenofovir disoproxil fumarate. The applicant provided a GLP compliant 90-day oral repeated dose toxicity study in rats where toxicity profile Tenofovir disoproxil maleate and Tenofovir disoproxil fumarate was evaluated. On the basis of the results, it can be said, that both the maleate and fumarate salt formulations of Tenofovir disoproxil were well tolerated at doses up to and including 300 mg/kg/day findings limited to slight salivation at 300 mg/kg/day. Furthermore, the amount of maleate at the NOAEL delivered daily for 90 days is approximately 53-fold the estimated maximum exposure (on a body surface area basis) to the maximum anticipated maleate exposure in Applicant's Tenofovir disoproxil maleate film coated tablets. The CHMP considered this as acceptable.

Concerning ERA the Applicant state that Tenofovir disoproxil Mylan 245 mg film-coated tablet correspond to the Reference product Viread 245 mg film-coated tablets as such impact to the environment is expected to be similar and not increased. Thus, the ERA is expected to be similar and not increased.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Tenofovir disoproxil Mylan and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and therefore additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing tenofovir disoproxil to support the marketing authorisation application the applicant conducted a bioequivalence study with open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose design under fed conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

GCP inspections at the analytical laboratory and the sponsor site in India (inspection dates: 11/02/2016 to 16/02/2016) were conducted following request by CHMP. The outcome of the inspection carried out was issued on 11 April 2016.

Exemption

One strength was applied; therefore an exemption is not applicable.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study TE-14-024.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of patients	Duration of Treatment	Study status; Type of Report
BA	Not Applicable								
BE	Project No. TE-14-024	Clinical Study Report & PK Report and Adverse Event Listing 5.3.1.2 CRFs and Individual Subject Listings 5.3.7 Literature References 5.4	To assess the single dose bioequivalence of Tenofovir disoproxil film coated tablets 245 mg (Test) with that of Viread® (Tenofovir disoproxil) film coated Tablets 245 mg in healthy adult male human subjects, under fed conditions. To monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Tenofovir disoproxil film coated tablets 245 mg under fed conditions.	An open-label, randomized, two-period, two-treatment, two-sequence, crossover, oral bioequivalence study in 36 healthy, adult, male, human subjects.	**Test Product:** Tenofovir Disoproxil Film coated tablets 245 mg Dosage Regimen: 245 mg **Route of administration:** Oral **Reference Product:** Viread® (Tenofovir disoproxil) 245 mg film-coated tablets Dosage Regimen: 245 mg **Route of administration:** Oral	No. of subjects dosed Period I: 36 Period II: 36 Completed-36 Subjects considered for pharmacokinetic and statistical analysis-36	healthy adult human subjects	Single dose	Complete Study Report

The administrative structure of the study is as follows:

Sponsor: Mylan Laboratories Limited, Clinical Research Centre, Saradhi Chambers, Plot No.4-A, Beside Poulomi Hospital, Rukminipuri, Dr. A.S. Rao Nagar, Hyderabad 500062, India

Clinical Research Centre: Erciyes University, Medical School, Hakan Çetinsaya GCP Centre, 38039 Melikgazi, Kayseri-Turkey. Principal Investigator: Assist. Prof. Dr. Zafer Sezer

Analytical Facility: Mylan Laboratories Limited, Clinical Research Centre, Saradhi Chambers, Plot No.4-A, Beside Poulomi Hospital, Rukminipuri, Dr. A.S. Rao Nagar, Hyderabad 500062, India

Bioanalytical Investigator: Mr. Amarnath Jaiswal

Pharmacokinetic and Statistical Facility: Parmacokinetics/Drug Metabolism Mylan Pharmaceuticals Inc., 3711 Collins Ferry Road, Morgantown, WV 26505, USA. Name of the group leader or investigator is not provided.

The study protocol (TE-14-024, protocol version 1.0, dated 26.09.2014) and the informed consent documents in Turkish and in English (version no. 02, dated 17.11.2014) were approved by Erclyes University Bioavaibility-Bioequivalence Trial Ethical Committee on 01.10.2014 and by Turkey Drug and Medical Device Agency, Ministry of Health on 04.12.2014. The Ethics Committee approval letter and the list of Ethics Committee members are enclosed.

The clinical part of the study was conducted between 10.12.2014 and 29.12.2014. The dosing dates were following: 12.12.2014 for Period I, and 24.12.2014 for Period II.

The final clinical study report is signed and dated 10.03.2015.

2.4.2. Pharmacokinetics

Study TE-14-024 Title: An open label, balanced, randomised, two treatment, two sequence, two period, cross-over, single dose comparative bioequivalence study of tenofovir disoproxil film-coated tablets 245 mg (test) of Mylan and Viread (tenofovir disoproxil) in healthy adults under fed conditions

Methods

Study design

This was an open-label, balanced, randomized, single dose, two treatment, two sequence, two period crossover, fed oral bioequivalence study to assess the single dose bioequivalence of Tenofovir disoproxil (as maleate [TDM]) film coated Tablets 245 mg with that of Viread® (Tenofovir disoproxil [as fumarate]) film coated tablets 245 mg in 36 healthy adult male human subjects, under fed conditions. Also it was anticipated to monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of TDM film coated Tablets 245 mg under fed conditions

Study consisted of two periods (Period I and Period II) separated by at least 10 days washout period. In the study, washout period lasted 12 days. After the washout period, in Period II, the subjects have been administered by the other drug that they have not been administered in the Period I. Subjects were housed in the clinical facility from at least 12 hours prior to investigational product administration until after the 72 hours post dose in both the study periods. Blood samples were collected before dosing and up to 72 hours after each dosing period.

The Applicant explained that the elimination half-life range was ~12 to 18 hours for tenofovir in literature. The last sampling time was evaluated as 5 times of t½ which was found as ~60 to 90 hours for tenofovir. The period of 72 hours sampling in this study was judged to be sufficient by the Applicant to characterise the concentration-time curve.

The Applicant noted that the wash-out period was evaluated as 10 times of t½ which was found as ~120 to 180 hours (5-7.5 days) for tenofovir. Therefore, the two treatment periods were separated by a wash-out period of at least 10 days between two periods to minimize the carry-over effect.

The treatments (one tablet containing and 245 mg Tenofovir disoproxil (as Maleate) for test product and 245 mg Tenofovir disoproxil (as Fumarate) for reference product) were given to each subject by oral route with 240 mL of water, in the morning to overnight fasted subjects for at least 10 hours prior to start of high fat high calorie non-vegetarian breakfast approximately 800-1000 kilo calories till at least 4 hours post dose. Subjects were instructed to complete breakfast within 30 minutes.

A total of 23 (6 ml) blood samples for PK analysis were collected during each period. Blood samples were drawn pre-dose (no earlier than 2 hours prior to dosing) and at 0.167,0.333,0.500,0.667,0.833, 1.000, 1.250, 1.500, 1.750,2.000,2.500,3.000, 4.000, 5.000, 6.000, 8.000, 10.000, 12.000, 24.000, 36.000, 48.000 and 72.000 hours post dose in K2 EDTA tubes. Blood samples were cooled in an ice bath or other chilling device .until centrifugation. Blood samples were centrifugated under refrigeration at 3S00rpm at 4°C for 10 min within 30 minutes after the last blood sample collection of respective time point. Plasma was extracted, divided in duplicates (primary (l.5 mL) and secondary (rest of the volume) aliquots) and stored in in a freezer within 60 minutes of blood sample collection at -70°C ± 20°C at the clinical facility until shipment to analytical facility (Mylan Laboratories Limited, India). The samples have been stored at -70°C ± 15°C at the analytical facility (Mylan Laboratories Limited, India) until analysed.

Blinding

This was an open-labelled clinical study. But, bioanalytical analyst was blinded towards the treatments (Test or Reference) administered to subjects.

Safety was evaluated through assessment of physical examination, vital signs and laboratory evaluation, physical examination and monitoring for adverse events throughout the course of the study.

There was no change or deviation in the conduct of the study. None of the randomised subjects dropped out the study. The following protocol deviation was reported: PROC GLM procedure was used instead of PROC MIXED and Pharmacokinetic parameters were computed in SAS instead of WinNonlin. According the Applicant, this may not affect the outcome of the study.

In conclusion, this was an open-label, balanced, randomized, single dose, two treatment, two sequence, two period crossover fed oral bioequivalence study. The basis of the bioequivalence study under fed conditions is justified and the study design is acceptable. The total caloric content of meal is acceptable (approximately 800-1000 kcal), the description of composition of meal with regard to protein, carbohydrate and fat content is lacking. Randomization was conducted properly. This was an open-labelled clinical study. Bioanalytical analyst was blinded towards the treatments (Test or Reference) administered to subjects. The wash-out period was long enough. The sampling period was long enough, no pre-dose levels were detected. The AUC ratio was higher than 80% in all subjects. The sampling scheme was adequate to estimate the pharmacokinetic parameters. Tmax was not observed in any subject in the first sample time point. The scope of study does not interfere with statistical considerations and recommendations for bioequivalence trial. The design of study was based on the fact that the crossover increases the statistical test power. The design of study is considered as adequate for given conditions. Protocol deviations were minor and did not affect the overall outcome of the study.

Test and reference products

Table 2. Test and reference product information

Product Characteristics	Reference product	Test Product
Name	Viread® (Tenofovir disoproxil)	Tenofovir disoproxil maleate
Strength	245 mg	245 mg
Dosage form	Film-coated tablets	Film-coated tablets
Manufacturer	Gilead Sciences International Limited, United Kingdom	Mylan Laboratories Limited, Pithampur, India
Batch number /Lot number	13VR034D	2006496
Batch size (Biobatch)	-	200,000
Measured content(s) (% of label claim)	98.3% w/w	100.2% w/w
Commercial Batch Size	-	1,400,000
Manufacturing date	-	May 2014
Expiry date	March 2018	-
Location of Certificate of Analysis	5312-compar-ba-bestud-rep, Appendix-16.1.6	5312-compar-ba-bestud-rep, Appendix-16.1.6
Member state where the reference product is purchased from	Germany (MAH – UK)	-
This product was used in the following trials	Study no.: TE-14-024	Study no.: TE-14-024

The Marketing Authorisation Holder for Viread 245 mg film-coated tablets is Gilead Sciences International Limited, United Kingdom. The date of authorisation in the EU for Viread® 245 mg film-coated tablets is 05/02/2002. The certificates of analysis of the biobatches were provided. Thus, the required data are given and the reference product is correct

Tenofovir disoproxil Mylan 245 mg manufactured by MYLAN S.A.S. (Batch No: 2006496; exp. date May 2014) has been compared to Viread 245 mg manufactured by Gilead Sciences International Limited (Batch No: 13VR034D, exp. date March 2018).

Population studied

A total of 44 subjects were screened and enrolled to this study; of them, 36 were randomised to the study. Study included healthy, adult, Caucasian, non-smoking, human male subjects, between 18 and 53 years of age with a 163.8 – 187.4 cm of height. All 36 subjects completed all periods of the study and were considered for pharmacokinetic and statistical analysis. Concomitant therapies: In the study it was prohibited (1) to use of any medication, including over-the-counter products for 14 days prior to the initial dose of study medication and (2) to use of any vitamins or herbal products within 7 days prior to the initial dose of the study medication. If necessary for the treatment of ordinary pain (e.g. headache), some analgesics which have no drug interaction with study drugs could be given by investigator. Compliance: The subjects' mouths were checked after dosing. Compliance was also ensured from the presence of drug in the plasma.

The population is chosen according to guidelines. Although males and females s were planned to be included into

the study, however, only males are included. This is acceptable the homogeneity of studied population is even higher in this case. The inclusion and exclusion criteria are acceptable. Baseline characteristics or deviations at baseline: criterion physical examination with no clinically significant findings is indicated as inclusion criterion. The Applicant states that all subjects, included in the study, were healthy and all physical examinations were considered as normal.

Analytical methods

The bioanalytical method documented in a pre-study validation report VR-126-00. An ultra performance liquid chromatographic method using tandem mass spectrometry detection for determination of Tenofovir in human plasma validated in bioanalytical laboratory of CRC Mylan Laboratories Ltd.

Table 3. Summary of the validation results (analyte: tenofovir)

Analytical Validation Report Location(s)	VR-126-00 Mod-5314, Bioanalytical Report, Attachment-5	
This analytical method was used in the following studies	TE-14-024	
Short description of the method	LC-MS/MS, Solid phase extraction technique	
Biological matrix	K_3 EDTA Human Plasma (blank matrix)	
Analyte Location of product certificate	Tenofovir, VR-126-00 Mod-5314, Bioanalytical Report, Attachment-5, Apendix2C	
Internal standard (IS) Location of product certificate	Tenofovir D6, VR-126-00 Mod-5314, Bioanalytical Report, Attachment-5, Apendix2C	
Calibration concentrations (Units)	5.012, 10.023, 20.046, 50.116, 120.278, 240.556, 400.926, 501.157, 601.389 ng/mL	
Lower limit of quantification (Units)	5.012 ng/mL , 98.32%, 1.26%	
QC concentrations (Units)	LLOQQC- 5.025 ng/mL, Low- 15.074 ng/mL, M1QC- 100.492 ng/mL, M2QC- 221.083 ng/mL, HQC- 462.264 ng/mL	
Between-run accuracy	88.70% to 102.58%	
Between-run precision	3.45% to 5.62%	
Within-run accuracy (P& A-1)	91.22% to 103.42%	
Within-run precision (P& A-1)	1.77% to 2.85%	
Within-run accuracy (P& A-2)	88.36% to 101.30%	
Within-run precision (P& A-2)	1.74% to 4.78%	
Within-run accuracy (P& A-3)	91.36% to 102.83%	
Within-run precision (P& A-3)	1.66% to 4.85%	
Within-run accuracy (P& A-4)	83.86% to 102.76%	
Within-run precision (P& A-4)	4.73% to 7.54%	
Matrix Factor (MF) (all QC) IS normalized MF (all QC) C.V.% of IS normalized MF (all QC) % of QCs with 85% and 115% n.v. % matrix lots with mean 80% or120% n.v	LQC 1.003 1.002 0.52 NA NA	HQC 1.004 1.002 0.73 NA NA
	Mod-5314, Appendix-16.5, Bioanalytical Report, Attachment-6, Supplement-04-00	

Due to method transferred from API 4000 (CRC/BU I71) to API 5500 (eRe/BU220) and to facilitate study sample analysis for the determination of Tenofovir only in human plasma for bioequivalence and bioavailability study of Tenofovir, partial validation have been performed, validation report submitted (VR·126-00, Supplement-04-00).

The applicant provided bioanalytical report on an open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, comparative oral bioequivalence study of tenofovir disoproxil film coated tablets 245 mg (test) of Mylan Laboratories Limited, India and Viread (tenofovir

disoproxil) film coated tablets 245 mg of Gilead Sciences Intl Ltd, United Kingdom in healthy adult human subjects, under fed conditions (study No. TE-14-024).

Table 4. Summary of the bioanalytical report

Title of Study	*"An open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, comparative oral bioequivalence study of Tenofovir Disoproxil Film Coated Tablets 245 mg (test) of Mylan Laboratories Limited, India and Viread® (Tenofovir Disoproxil) Film Coated Tablets 245 mg of Gilead Sciences Intl Ltd Cambridge CB21 6GT, United Kingdom in healthy adult human subjects, under fed conditions."*
Study No	TE-14-024
Bioanalytical Method Title	Determination of Emtricitabine, Rilpivirine and Tenofovir in Human Plasma using Ultra Performance Liquid Chromatography Method with Tandem Mass Spectrometry
Method No	AMP-126-01 (Refer: Attachment-2)
Calibration curve range for study	4.961 to 595.274 ng/mL
Validation Report No	VR-126-00 (Attachment-5)
Calibration curve range for Validation	5.012 to 601.389 ng/mL for Tenofovir
Partial validation Report No	Supplement-04-00 – For the determination of Tenofovir only. Supplement-05-00 – Anticoagulant Effect & Whole blood stability
Calibration curve range for Partial Validation	Supplement-04-00 – 4.997 to 599.627 ng/mL Supplement-05-00 – 4.961 to 595.274 ng/mL
Instrument(s) used for Validation	CRC/BL/171 & CRC/BL/169
Instrument(s) used for Partial Validation	Supplement-04-00 – CRC/BL/220 Supplement-05-00 – CRC/BL/171 & CRC/BL/220
Instrument(s) used for Biostudy	CRC/BL/220
Date of Dosing (Period-I)	12th December 2014
Clinical site	Erciyes University School of Medicine, Turkey
Study Samples received date from clinical site	02nd January 2015
Storage condition at clinical site	-70°C ±15°C
Samples condition during Transit	Frozen and intact
Deviations any during Transit	No
Storage condition at bioanalytical site until sample analysis	-70±15 °C
Total number of samples received	1656
Number of Subjects completed the study	36
Date of analysis started	20th January 2015
Date of analysis completed	04th February 2015
PK and statistical analysis	Mylan Laboratories Limited, India

Summary of the bioanalytical method results

Table 5. Calibration curve standard concentrations and quality control sample data

Tenofovir			
Parameter	**Results**		**Table No.**
Total Number of Analytical runs	Twenty One (21) acceptable analytical runs		3
Correlation Coefficient (r)	≥ 0.9979		
Calibration Curve	Accuracy (% Nom)	Precision (% CV)	4
	94.13% to 103.84%	1.25% to 2.53%	
Quality control	Accuracy (% Nom)	Precision (% CV)	5
	91.82% to 100.97%	2.58% to 3.38%	
DQC (½ dilution)	Accuracy (% Nom)	Precision (% CV)	NA
	NA	NA	
• There were no rejected analytical runs.			

Table 6. Sample Analysis and Repeats

Total No. of samples from repeated analytical runs	Nil
No. of discrete samples repeated (%)	8 (0.48%)
Note: The reasons for repeats and their results are reported in Table 2A.	

Table 7. Long term stability details

Long Term Stability required	55 Days
Long Term Stability Proven	118 days (Addendum-01-00)

Table 8. Incurred samples reanalysis

Incurred sample reanalysis: Performed on 10% for first 1000 samples + 5% on rest of the samples of the total samples analysed during the study.

Analytes	**Tenofovir**
Total Number of incurred samples analyzed	136
Total Number of samples considered for Incurred samples Reanalysis Calculation	136
Total Number of samples met acceptance criteria	134
Total % of samples within the acceptance range	98.53%

Pharmacokinetic variables

Single-dose pharmacokinetic parameters for Tenofovir were calculated using non-compartmental techniques. The maximum concentration (C_{max},) and the time at which it occurred relative to the administered dose (T_{max}) was determined from the observed plasma concentration-time profile over the sampling time interval. The elimination rate constant (Kel) was determined by linear regression of the terminal linear phase of the log plasma concentration-time profile. Area under the plasma concentration-time curve (AUCt) was the sum of the

linear trapezoidal estimation of the areas from the time of dosing to the time of the last quantifiable concentration. The elimination half-life (t1/2) was calculated as t1/2 = 0.693/Kel.

Primary parameters (AUC0-t, Cmax), and secondary parameters (AUC0-∞, Tmax, AUCratio, Kel and t1/2) were calculated using WinNonlin® professional software (Version: 5.3 or higher; Pharsight Corporation, USA).

Standards for bioequivalence: The 90% confidence intervals of the relative mean (Geometric mean) AUC0-t and Cmax of the test to reference formulation for Ln-transformed data should be within 80% to 125% for Tenofovir to establish bioequivalence.

Thus, the PK variables are adequate. Standard methods were used.

Statistical methods

Unless otherwise stated, analyses were performed on pharmacokinetic data of subjects using SAS® statistical software, and all hypothesis tests were conducted with alpha of 0.05 and beta 0.90. Data were summarized using adequate descriptive statistics. Majority of analyses used the parametric tests.

Descriptive statistics: mean, standard deviation, coefficient of variance, median, maximum and minimum for all pharmacokinetic parameters will be calculated. Consistent with Schuirmann's two one-sided tests procedure for bioequivalence, ANOVA was performed on log-transformed data. Analysis of variance: log-transformed data of AUC0-∞, AUC0-t and Cmax was to be evaluated statistically using the PROC MIXED from SAS® for difference due to treatment, period and sequence as a fixed effects and subject within sequence as a random effect. The period, treatment and sequence effects were to be tested at 5% level of significance using the mean square error as the error. Non-parametric analysis of Tmax was also performed on untransformed data of Tenofovir using the Wilcoxon signed-rank test.

The primary parameters were AUC0-t, Cmax, and secondary parameters were AUC0-∞, Tmax, AUC ratio, Kel and $t_{1/2}$, calculated using WinNonlin® software.

The 90% confidence intervals of the relative mean (Geometric mean) AUC0-t and Cmax of the test to reference formulation for log-transformed data should be within 80% to 125% for Tenofovir to establish bioequivalence.

The log-transformations were specified in the protocol and conducted properly as analyses.

Determination of sample size

Based on the literature and in-house studies data the highest intra-subject CV was found to be around 23%. Hence, considering the variability of 23% a minimum of 32 subjects are required to detect a clinically significant difference of 20% between the formulations at 5% level of significance with a power of 90% for a two way crossover design. In total, 36 subjects were planned and randomized for the study with additional 8 subjects screened only. There were no dropouts in this study. The recruitment of study sample was conducted based on pre-defined inclusion and exclusion criteria. The required sample size was calculated.

Results

A summary of the pharmacokinetic data for Tenofovir is presented in Table 10-11 and in Figure 12.

Table 9. Summary of Pharmacokinetic Data for Tenofovir

		Test			Reference		
Variable	N	Mean	Std Dev	Coeff of Variation	Mean	Std Dev	Coeff of Variation
*T_{max} (hr)	36	1.250 (0.667-4.000)	0.700	49.991	1.250 (0.667-3.000)	0.573	39.337
C_{max} (ng/mL)	36	341.918	80.742	23.614	326.205	69.990	21.456
AUC_{0-t} (ng. hr/mL)	36	2819.040	565.561	20.062	2799.744	563.979	20.144
AUC0-inf (ng. hr/mL)	36	3021.675	568.412	18.811	3008.516	585.791	19.471
Lambda_z (z or K_{el}) (1/hr)	36	0.0387	0.0054	13.8309	0.0379	0.0065	17.2434
HL_Lambda_z ($t_{½}$) (hr)	36	18.232	2.479	13.595	18.795	3.044	16.196

*Median values (range) reported for T_{max}

Table 10. Summary of Geometric mean, Ratio, 90% Confidence intervals, Intra-subject CV (%) and power for Tenofovir

Tenofovir (n=35)						
Parameters (Units)	***Geometric Mean**		**Intra Subject CV %**	**90% Confidence Limits (%)**	**Power%**	**Ratio (A / B)%**
	Test product (A)	**Referen ce product (B)**				
LnC_{max} (ng/mL)	318.943	331.947	14.84	**90.59-101.90**	>99.00	96.08
$LnAUC_{0-t}$ (ng. hr/mL)	2744.09	2762.24	6.72	**96.72-102.04**	>99.00	99.34
LnAUC0-inf (ng. hr/mL)	2953.20	2968.73	6.27	97.02-101.99	>99.00	99.48

Note: *Geometric means values are taken from the appendix 16.2.6 Individual Efficacy Response Data

Table 11. Linear and Semi-Log mean plots for tenofovir

Tenofovir	
Linear Scale	Semi-Log Scale

periods; (2) analytical error, as the plasma samples of each subject of both the periods are analysed all together and in a sequence in which the blood samples were collected; (3) period effect, as in each period both the products were dosed (Test and Reference). The Applicant stated that “It can simply be ignored because the decision of equivalence is based on the 90% confidence interval is within the equivalence boundaries.”

The Applicant concluded that for the log transformed data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits for AUC0-t and Cmax. Based on these results, Tenofovir disoproxil Maleate film coated Tablets 245 mg of Mylan Laboratories Limited, India and Viread (Tenofovir disoproxil) film coated Tablets 245 mg of Gilead Sciences Intl Ltd, Cambridge CB21 6GT, Verenigd Koninkrijk, Royaume-Uni, Vereinigtes Konigreich, are bioequivalent under fed conditions.

Thus, the AUC ratio is above 80% for all subjects and treatments. No subject had detectable pre-dose plasma levels and no subject reached Cmax at the first sampling time point. The test to reference ratio of geometric means and the corresponding 90% confidence interval for the Cmax and AUC0-t were all within the acceptance range of 80.00 to 125.00%. The bioequivalence has been shown appropriately under fed conditions.

Safety data

Neither death nor serious adverse event occurred during the study. Total 3 adverse events occurred in study, out of them 2 adverse events were moderate and 1 adverse events was mild in nature:
For Test Product: Subject 24 had musculoskeletal pain in Period I. 500 mg paracetamol tablet was given to this subject. For Reference Product: Subject 26 had myalgia in Period I. Subject 28 had pain in extremity in Period I.
The Applicant explained that the adverse events that occurred in the study are possibly related to the study product. These adverse events considered as the most common adverse events mentioned in the literatures. All physical examinations and all laboratory parameters were considered as normal by the investigator. Blood pressures, heart rate and ECG results were judged as normal (except Subject 01, 02, 03, 05, 16, 19, 25, 28, 30 and 36 for pre-study, Subject 02, 03, 06, 07, 08, 09, 11, 12, 13, 14, 15, 19, 20, 23, 25, 28, 32, 33 and 36 for post-study for only ECG) by the investigator. The Applicant summarised that overall tolerability of the products found to be good. It is agreed that the medicines were generally safe and well tolerated by the subjects in the study.

Conclusions

Based on the presented bioequivalence study Tenofovir disoproxil Mylan is considered bioequivalent with Viread.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate. To support the application, the applicant has submitted one bioequivalence study. Statement of GCP compliance and compliance with applicable principles of GLP is provided.

Upon review of the study results a number of issues were raised (uncertainties in data management, including peri-database lock procedures, misreported “normal values”, questionable “null” values at the end of sampling periods, statistical analyses pre-specifications, account for possible dropouts, back-transformation, uncertain precision in data calculation and missing information on the database lock). All these issues were clarified and the CHMP considered the responses acceptable. In addition, an EU GCP inspection has been conducted and concluded that the clinical trial data was acceptable and could be used for the evaluation.

The study was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single dose, comparative oral bioequivalence study of Tenofovir disoproxil 245 mg film-coated tablets (manufactured by Mylan Laboratories Limited, Pithampur, India) and Viread 245 mg film-coated tablets of Gilead Sciences International Limited, United Kingdom in healthy adult male volunteers, under fed conditions.

Study consisted of two periods (Period I and Period II). After 12 days of washout period, in Period II, the subjects have been administered by the other drug that they have not been administered in the Period I. After 10 hours of overnight fasting, patients were given high-fat high-calorie non vegetarian breakfast ~ 800-1000 kcal till 4 hours post dose. Subjects were housed in the clinical facility from at least 12 hours prior to investigational product administration until after the 72 hours post dose in both the study periods. Blood samples were collected before dosing and up to 72 hours after each dosing period. A validated LC/MS/MS method by solid phase extraction was used to detect tenofovir concentrations in plasma in human Ks EDTA plasma matrix. The pharmacokinetic and statistical methods applied were adequate. The test to reference ratio of geometric mean and corresponding 90% CI for the Cmax and AUC0-t were reported as falling within acceptable range of 80.00 to 125%. The bioequivalence is presented under the fed condition. Both the test and the reference medicine were generally safe and well tolerated by the subjects included in the study.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Tenofovir disoproxil Mylan and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	Renal toxicity Bone events due to proximal renal tubulopathy/loss of bone mineral density

Summary of safety concerns	
	Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients Interaction with didanosine Pancreatitis
Important potential risks	Development of resistance 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 patients with renal impairment Safety in black HBV infected patients Safety in liver transplant recipients infected with HBV Safety in patients with decompensated liver disease and CPT score > 9 (including long-term safety)

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to TDF during pregnancy	Missing information: Safety in pregnancy	Mylan is planning to participate in Antiretroviral Pregnancy Registry following product approval. Company will initiate communication with registry organisers	Not applicable

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Renal toxicity (MedDRA PT: Nephropathy toxic)	Sections 4.2, 4.4, 4.5 and 4.8 of SPC contain transparent warnings on this risk Sections 2 and 4 of PL advise patients on this risk	Educational brochure for physicians
Important identified risks: Bone events due to proximal renal tubulopathy/loss of bone mineral density (MedDRA PTs: Bone abnormalities; Proximal renal tubulopathy; Loss of bone mineral density)	Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk Sections 2 and 4 of PL advise patients on this risk	Educational brochure for physicians
Important identified risks: Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients (MedDRA PT: Hepatitis B)	Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk Section 3 of PL advises patients on this risk	None proposed
Important identified risks: Interaction with didanosine (MedDRA PT: Drug interaction)	Sections 4.4, 4.5 and 4.8 of SPC contain transparent warnings on this risk Section 2 of PL advises patients on this risk	None proposed
Important identified risks: Pancreatitis (MedDRA PT: Pancreatitis)	Sections 4.4, 4.5 and 4.8 of SPC contain transparent warnings on this risk Sections 2 and 4 of PL advise patients on this risk	None proposed
Important potential risks: Development of resistance during long-term exposure in HBV infected patients (MedDRA PT: Drug resistance)	Sections 4.1 and 5.1 of SPC contain transparent warnings on this risk Sections 3 of PL advises patients on this risk	None proposed
Missing information: Safety in children (including long-term safety)	Sections 4.2, 4.4 and 5.2 of SPC contain transparent warnings on this risk Section 2 of PL advises patients on this risk	Educational brochure for physicians
Missing information: Safety in elderly patients	Sections 4.2, 4.4 and 5.2 of SPC contain transparent warnings on this risk Section 2 of PL advises patients on this	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	risk	
Missing information: Safety in pregnancy	Section 4.6 of SPC contains transparent warnings on this risk Section 2 of PL advises patients on this risk	None proposed
Missing information: Safety in lactation	Section 4.6 of SPC contains transparent warnings on this risk Section 2 of PL advises patients on this risk	None proposed
Missing information: Safety in patients with renal impairment	Sections 4.2, 4.4 and 5.2 of SPC contain transparent warnings on this risk Section 2 of PL advises patients on this risk	Educational brochure for physicians
Missing information: Safety in black HBV infected patients	Sections 4.4 and 4.8 of SPC contain warnings on chronic heptatitis, no safety information specifically to black HBV infected patients is known on this risk Section 2 of PL advises patients on chronic hepatitis again not specifically to black HBV infected patients	None proposed
Missing information: Safety in liver transplant recipients infected with HBV	Section 4.4 of SPC contains transparent warnings on this risk Section 2 of PL advises patients on this risk	None proposed
Missing information: Safety in patients with decompensated liver disease and CPT score > 9 (including long-term safety)	Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk Section 2 of PL advises patients on this risk	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.0 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any

subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

In line with the reference product, the SmPCs/PILs state in section 4.2 that for administration, the tablets may be disintegrated and mixed with at least 100 ml of water, orange juice, or grape juice prior to administration in patients with difficulties swallowing tablets whole. The applicant has provided data as requested by the CHMP in support of the alternative method of administration. Although the BE was demonstrated with tablets taken whole, the data provided support the applicability of specific administration recommendation in the reference product (Viread) SmPC to Tenofovir Disoproxil Mylan.

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

3. Benefit-risk balance

This application concerns a generic version of tenofovir disoproxil film-coated tablets. The reference product Viread is indicated for treatment of HIV infection and treatment of chronic hepatitis B. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, balanced, randomized, single dose, two treatment, two sequence, two period crossover, bioequivalence study under fed conditions in healthy subjects. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period was adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of tenofovir disoproxil met the protocol-defined criteria for bioequivalence when compared with the Viread. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tenofovir disoproxil Mylan is favourable in the following indication:

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 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 (see section 5.1).

- evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1).

- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

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 (see sections 4.4, 4.8 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Tenofovir disoproxil Mylan in adults and/or paediatric patients are provided with a physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- 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 HIV and HBV renal educational brochures should contain the following key messages:

• That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil-containing products such as Tenofovir disoproxil Mylan

• That Tenofovir disoproxil Mylan 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 Tenofovir disoproxil Mylan in adult patients with creatinine clearance of 30-49 ml/min
- That Tenofovir disoproxil Mylan is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min). If no alternative treatment is available, prolonged dose intervals may be used
- That use of Tenofovir disoproxil Mylan should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Tenofovir disoproxil Mylan 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 Tenofovir disoproxil Mylan therapy
- The importance of regular monitoring of renal function during Tenofovir disoproxil Mylan 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 re-evaluated 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 Tenofovir disoproxil Mylan therapy. Interrupting treatment with Tenofovir disoproxil Mylan should also be considered in case of progressive decline of renal function when no other cause has been identified.
- Instructions on the use of the creatinine clearance slide ruler

The HIV and HBV paediatric educational brochures should contain the following key messages:

- That a multidisciplinary approach is recommended for the management of paediatric patients
- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil-containing products such as Tenofovir disoproxil Mylan
- That Tenofovir disoproxil Mylan is not recommended for use in paediatric patients with renal impairment
- That use of Tenofovir disoproxil Mylan should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Tenofovir disoproxil Mylan 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 Tenofovir disoproxil Mylan therapy
- The importance of regular monitoring of renal function during Tenofovir disoproxil Mylan therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil, renal function should be re-evaluated within one week. If renal abnormalities are detected or suspected then consultation with a nephrologist should be obtained to consider interruption of Tenofovir disoproxil Mylan treatment. Interrupting treatment with Tenofovir disoproxil Mylan should also be considered in case of progressive decline of renal function when no other cause has been identified.

- That Tenofovir disoproxil Mylan may cause a reduction in BMD and the effects of Tenofovir disoproxil Mylan associated changes in BMD on long term bone health and future fracture risk are currently unknown in paediatric patients
- That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained