13 October 2016
EMA/CHMP/636453/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emtricitabine/Tenofovir disoproxil Mylan

International non-proprietary name: emtricitabine / tenofovir disoproxil

Procedure No. EMEA/H/C/004050/0000

Note

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

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List of abbreviations

AE	Adverse events
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active substance
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
C_{max}	Maximum concentration
CPP	Critical process parameter
CQA	Critical Quality Attribute
CV	Coefficient of variation
EC	European Commission
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra acetic acid
EMA	European Medicines Agency
EU	European Union
FPM	Finished Product Manufacturer
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus Type 1,

HPLC High performance liquid chromatography

Hr Hour

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IPC In-process control

IR Infrared

IU International Units

KF Karl Fischer titration

LDPE Low density polyethylene

LOD Loss on drying

LoD Limit of Detection

LOQ Limit of Quantitation

LoQ List of Questions

LT Less than

MA Marketing Authorisation

MAH Marketing Authorisation holder

MS Mass Spectrometry

ND Not detected

NLT Not less than

NMR Nuclear Magnetic Resonance

NMT Not more than

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

PVC Poly vinyl chloride

QOS Quality Overall Summary

QC Quality Control

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
$t_{1/2}$	Elimination half-life
t_0	Time of drug administration
TGA	Thermo-Gravimetric Analysis
t_{last}	Time of last measurable concentration
t_{max}	Time to reach the maximal concentration
TLC	Thin layer chromatography
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
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 7 July 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Emtricitabine/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 in the Union on the basis of a complete dossier in accordance with Article 8(3).

The applicant applied for the following indication:

Emtricitabine/Tenofovir disoproxil Mylan is a fixed dose combination of emtricitabine and tenofovir disoproxil. It is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults aged 18 years and over.

The demonstration of the benefit of the combination emtricitabine and tenofovir disoproxil in antiretroviral therapy is based solely on studies performed in treatment-naabine and tenofovir disoproxil

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 Truvada 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: Truvada, 200mg/245mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 21-02-2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: : EU/1/04/305/001-002

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

- Product name, strength, pharmaceutical form: Truvada, 200mg/245mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 21-02-2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/305/001-002

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: Truvada, 200mg/245mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 21-02-2005
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/04/305/001-002
- Bioavailability study number(s): TEEM – 14-021

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 7 July 2015.
- The procedure started on 23 July 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 October 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 22 October 2015.
- During the meeting on 6 November 2015 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 12 November 2015.
- During the meeting on 19 November 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 25 November 2016.
- 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 Quality/Safety/Efficacy assessment of the product:
  - GCP inspections at the clinical facility in Turkey (inspection dates: 07/12/2015 to10/12/2015),

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 an oral explanation and/or in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 21 June 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 July 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a second list outstanding issues to be addressed by the applicant in writing and/or during an oral explanation before the CHMP.
- The applicant submitted the responses to the CHMP consolidated second List of Outstanding Issues on 14 September 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 28 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 Emtricitabine/Tenofovir disoproxil Mylan.

2. Scientific discussion

2.1. Introduction

The application for Emtricitabine/Tenofovir disoproxil maleate Mylan was submitted by MYLAN S.A.S, 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. Emtricitabine and Tenofovir disoproxil (as maleate) 200 mg/245 mg film-coated tablets are immediate release solid oral dosage form and are generic version of the already approved reference product Truvada (MAH Gilead Sciences International Limited) film-coated tablet containing 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate). Marketing authorisation number: EU/1/04/305/001-002. Date of authorisation 2005-02-21.

The quality data showed that both medicinal products are based on same active moieties and are composed by the same active substance in case of emtricitabine and 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 consisted of (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) and (ii) overviews on pharmacology, pharmacokinetics and toxicology. These data

justified the no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The clinical dataset consisted of two parts – clinical overview (bibliographic data on clinical pharmacology, efficacy and safety of both emtricitabine and tenofovir, including their fixed combination) 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 a fixed combination of two active substances (emtricitabine and tenofovir disoproxil maleate) presented as film-coated tablets containing 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil maleate).

Other ingredients are:

Tablet core: cellulose, microcrystalline; hydroxypropyl cellulose, low-substituted; iron oxide red (E172); silica, colloidal anhydrous; lactose monohydrate; magnesium stearate.

Film-coating: lactose monohydrate; hypromellose; titanium dioxide (E171); triacetin; brilliant blue FCF Aluminium lake (E133); iron oxide yellow (E172).

The product is available in either HDPE bottles with white opaque polypropylene screw caps or white opaque polypropylene child resistant closure with wad containing aluminium induction sealing liner and desiccant, or cold form blisters laminated with embedded desiccant layer on one side and hard tampered aluminium foil as described in section 6.5 of the SmPC.

2.2.2. Active substance

Emtricitabine

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1*H*)-pyrimidinone corresponding to the molecular formula $C_8H_{10}FN_3O_3S$. It has a relative molecular mass of 247.24 g/mol and the following structure (**Figure 1**):

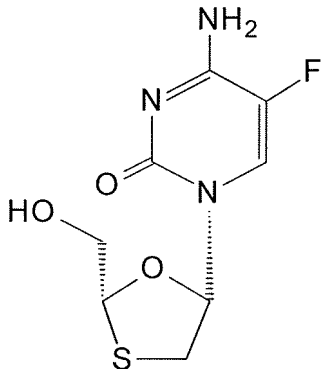


Figure 1. Structure of emtricitabine

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.

Emtricitabine appears as a white to off-white crystalline powder, freely soluble in methanol and water and soluble in ethanol. Its pKa is 4.90 and the partition coefficient Log P is -0.43. It has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. There are four possible isomers due to these asymmetric carbons in the molecule and the isomer 2*R*,5*S* is commercially produced. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation.

Various polymorphs of emtricitabine exist (Form I, Form II, Form III and amorphous form). XRD data confirms that the manufacturer produces Form I consistently and that it remains stable upon storage. Polymorph identification test by XRD is included in the active substance specification.

Manufacture, characterisation and process controls

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

Four manufacturing sites are involved in the synthesis of the active substance and two of these manufacturing sites only manufacture the intermediate (2*R,*5*S*)-5-(4-amino-5-fluoro-2-oxo-2H-pyrimidin-1-yl)-[1,3]-oxathiolane-2-carboxylic acid, 2*S*-isopropyl-5*R*-menthyl-1*R*-cyclohexyl ester (FCE).

Emtricitabine is synthesized in six main steps using well defined starting materials with acceptable specifications. The synthetic route was described in sufficient detail.

The synthetic process encompasses the stereoselective formation of an intermediate and thus the formation of the desired emtricitabine enantiomer. The manufacturing process of emtricitabine at both manufacturing sites was validated on three individual batches for accuracy and repeatability.

The critical process parameters were presented and justified. 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 are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packed in polyethylene bags (LDPE) inside HDPE drums which comply with the European Pharmacopeia and relevant EU regulations.

Specification

Emtricitabine specification includes tests and limits for description (visual), solubility (Eur. Ph.), identification (IR, HPLC, PXRD), melting range (Ph. Eur.), specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), content of emtricitabine enantiomer (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), content of triethylamine (GC), formaldehyde content (UPLC), bulk density, apparent density and tapped density (in-house) and particle size (laser diffraction particle).

Skip testing for formaldehyde in the active substance specification has been adequately justified. Omission for testing microbiological quality in the active substance specification has been justified based

on the use of isopropyl alcohol for the crystallisation of emtricitabine, which is not favourable for the microbial growth, and results from production scale batches which were tested for microbiological quality.

The set limits in the active substance specification are sufficiently justified and the acceptance criteria of the related substances are in accordance with ICH guidelines. The limits for residual solvents are in accordance with the ICH Q3C guideline except for triethylamine for which the acceptance criteria is adequately justified toxicologically.

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

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

Stability

Stability data on six production scale batches (from both proposed manufacturers) and three pilot scale batches (from one of the manufacturers) of active substance stored in the intended commercial package for up to 60 months under long term conditions at 25 ºC / 60% RH, for up to 36 months under intermediate conditions at 30 ºC / 65% RH or for up to 24 months at alternative conditions 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines, was provided.

The following parameters were tested: description, identification (IR, HPLC), melting range, specific optical rotation, loss on drying, limit of emtricitabine enantiomer, related substances and assay. The analytical methods used were the same as for release and were stability indicating.

Results on forced degradation studies (stress studies and solid state stability studies) were also provided as part of the related substances method validation of. Exposure to acid hydrolysis, basic hydrolysis, oxidation, heat degradation and UV as well as white fluorescence light, UV at 365 nm and heat at 105 ºC in solid state was measured.

All tested parameters were within the specifications. The degradation of emtricitabine is significantly increased upon exposure to acid, base and heat. The major degradants formed were *S*-oxide and desamino. Emtricitabine solutions were found to be stable under UV exposure. No degradation was observed in solid state indicating that emtricitabine is stable upon exposure to white fluorescent light, UV light and heat at 105 ºC.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed packaging and the storage precaution "Store below 30 ºC".

Tenofovir disoproxil

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 4**):

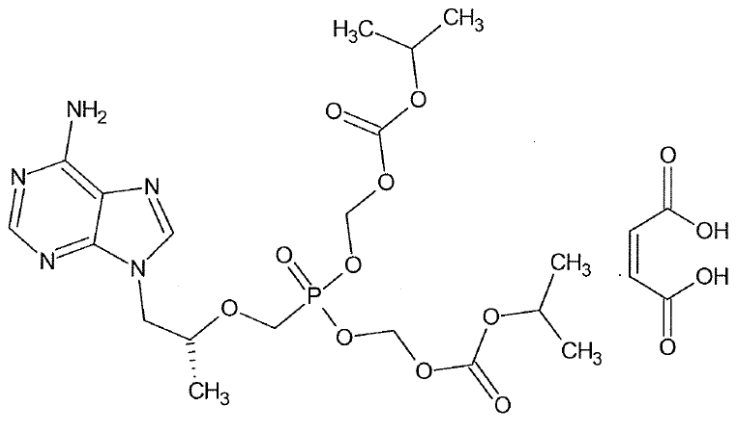


Figure 2. Structure of tenofovir disoproxil maleate

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 for testing polymorphism and microbioloical 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

The finished product is presented as light green, capsule shaped, biconvex film-coated immediate release tablets debossed with 'M' on one side of the tablet and 'ETD' on the other side. The dimensions of the tablets are 19.8 mm ± 0.3 mm x 9.00 mm ± 0.3 mm. The composition of the film coated tablets is was presented.

The aim of the pharmaceutical development studies was to develop a generic product of Truvada 200/245 mg (Emtricitabine/Tenofovir disoproxil) film-coated tablets. Composition comparison demonstrates that the finished product uses a different salt of the active substance tenofovir disoproxil (maleate rather than fumarate) and the reference product has different type of disintegrant and additionally contains pre-gelatinized starch.

All excipients are conventional pharmaceutical ingredients and their quality is compliant with Ph. Eur/NF standards. The Opadry green coating material is proprietary material supplied to an agreed specification and the individual components used in its manufacturing comply with the Ph. Eur. and EU regulation 231/2012. 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 binary mixture of emtricitabine with tenofovir disoproxil maleate was prepared to study the compatibility of both active substances and with various excipients. The samples were evaluated for any change in appearance and related substances after 4 weeks at 40 ºC / 75% RH. Although there was no change in the appearance of the binary mixtures, significant increase in level of related substances was observed in binary mixture of emtricitabine with tenofovir disoproxil maleate and in binary mixtures of tenofovir disoproxil maleate with excipients. However, accelerated stability data of the prototype formulation was found to be satisfactory and it was concluded that emtricitabine and tenofovir disoproxil maleate are compatible with all excipients to use in the product development.

Both active substances were analysed for particle size distribution, bulk density, tapped density, compressibility index and Hausner ratio. Results indicated that emtricitabine has "very, very poor" flow properties and tenofovir disoproxil maleate has "very poor to very, very poor" flow properties. Solubility studies were also conducted and the results indicated that emtricitabine is freely soluble within the pH range studied (pH 1.2-8.0 in different buffers) and tenofovir disoproxil maleate has pH independent solubility. The effect of different particle size on dissolution for emtricitabine and tenofovir disoproxil maleate was evaluated and data confirmed that there is no significant effect of particle size on dissolution profile in the particle size range studied.

The prototype product development was carried out by dry granulation technique since, as stated in scientific literature, emtricitabine and tenofovir disoproxil maleate degrade in high moisture/ temperature conditions. The following parameters were considered for the optimisation of the manufacturing process for emtricitabine and tenofovir disoproxil: roller compaction process, milling process, number of compaction cycles, granules to fines ratio, blending time at various stages and tablet hardness.

Monolayer tablets were manufactured by taking trials with different lubricants (magnesium stearate and sodium stearyl fumarate), and based on total impurity results and API-excipient compatibility study (under accelerated stability conditions), it was decided to evaluate the bilayer tablet strategy. The same lubricants were tested with the bilayer tablet strategy and the formulation with magnesium stearate was selected for further development as the level of total impurities was found to be slightly high (under accelerated stability conditions) when manufactured with sodium stearyl fumarate.

Comparative dissolution profiles of the finished product and the reference product were generated in different dissolution media (0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phospate buffer). More than 85% of the emtricitabine and tenofovir disoproxil maleate are released within 15 minutes in pH 1.2, pH 4.5 and pH 6.8 except for tenofovir disoproxil maleate at pH 1.2. At this pH the data showed that the release of tenofovir from reference product was found to be faster as compared to the finished product. However, after 30 min, more than 85% of the drug is released and hence, both products can be considered as rapid dissolving. The change in salt of tenofovir disoproxil, qualitative composition and manufacturing process may have contributed in this difference, however, no effect on *in-vivo* performance was observed as the finished product was found to be bioequivalent with the reference product. Comparative impurity profiles were also studied and both the finished product and the reference product exhibited similar impurity profile.

It has been shown that there is no difference in the unit composition of the batches used in the bioequivalence study and the proposed for commercial supply.

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 Emtricitabine/Tenofovir Disoproxil and Truvada in water and demonstrating that disintegration occurs for both products within 8 minutes. Since both emtricitabine (BCS I) and tenofovir disoproxil maleate (BCS III) are 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.

Paddle apparatus was selected for dissolution testing. Dissolution profile data in different media on the reference product was generated. Both, emtricitabine and tenofovir disoproxil maleate showed complete release within 10 minutes. Based on the pharmacokinetic of the active ingredients and the fact that the target product is an immediate release tablet, dissolution in the stomach and absorption in the upper small intestine is expected, hence, the use of a dissolution medium with low pH was selected (0.1N HCl). Paddle speed of 50 rpm and 900mL volume of dissolution medium were selected as it is generally recommended for tablet dosage form. Based on the solubility of both active substances and their unit doses, it was concluded that sink condition will be maintained in the selected dissolution method. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is either HDPE bottles with white opaque polypropylene screw caps or white opaque polypropylene child resistant closure with wad containing aluminium induction sealing liner and desiccant, or cold form blisters laminated with embedded desiccant layer on one side and hard tampered aluminium foil on the other. The materials comply with Ph. Eur. and EC requirements. The choice of the

container closure systems have been validated by stability data and are adequate for the intended use of the product.

The bulk shipment packs, which are proposed for storage and transportation of the finished product to the European repackaging site, comprises low density polyethylene (LDPE) bags that are placed in outer triple laminated bags along with desiccant bags in between the LDPE bag and the outer bag and sealed. These bags are placed in suitable tertiary packs. The materials comply with Ph. Eur. and EC requirements.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: (1) preparation of tenofovir disoproxil maleate layer (dispensing, sifting, precompaction blending, compaction, mixing and sifting, sifting of extragranular materials, final blending); (2) preparation of emtricitabine layer (dispensing, sifting, precompation blending, compaction, milling and sifting, sifting of extragranular materials, final blending); (3) tablet compression; (4) film-coating; and (5) packaging. The manufacturing process is considered adequate for immediate release film-coated tablets, containing poorly compatible components. One manufacturing site is responsible for the manufacture of the bulk finished product. Flow diagrams depicting the manufacturing process steps with associated in-process controls (IPCs) were provided.

The critical steps include (1) blending, (2) compression, (3) film-coating and (4) packaging. The proposed in-process controls are adequate for this pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies carried out at the lowest proposed production scale batches (150,000 units). The Applicant commits to perform process validation studies on the first three production scale batches (700,000 units) of the finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and include description (visual), identification (HPLC, TLC, maleic acid (HPLC)), color identification (in house, chemical method), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), limit of monoester impurity of tenofovir disoproxil maleate (HPLC), assay (HPLC), water (KF) and microbiological tests (Ph. Eur.).

The limits for related substances are based on the limits in the active substances, nature of the impurity, identification and qualification threshold limits recommended in ICH guidelines and toxicological data.

Skip testing for color identification and microbiological tests has been justified and is considered acceptable based on ICH guidelines.

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.

Certificates of analysis for four production scale batches (150,000 units) of finished product were provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of four production scale batches (150,000 units) of finished product in the container closure system proposed for marketing and stored under long term conditions for up to 18 months at 25 ºC / 60% RH (cold blisters or HDPE bottles), for up to 12 months under intermediate conditions at 30 ºC / 65% RH (cold blisters) and for up to 6 months under accelerated conditions at 40 ºC / 75% RH (HDPE bottles) according to the ICH guidelines were provided. Additionally, stability data of four production scale batches (150,000 units) of finished product in simulated bulk shipment pack stored under long term conditions for up to 12 months at 25 ºC / 60% RH, and for up to 12 months under intermediate conditions at 30 ºC / 65% RH according to the ICH guidelines were also provided. The batches of medicinal product are identical to those proposed for marketing and were packed in both primary packaging proposed for marketing and representative bulk shipment packaging.

Samples were tested for description, assay, water content, dissolution, microbiological limits, limit of monoester impurity of tenofovir disoproxil maleate and related substances. The analytical procedures used are stability indicating.

The data presented indicates that the product complies with the proposed finished product shelf life specifications during accelerated and long term stability studies in HDPE bottle pack. However, the product did not comply with the proposed shelf life specifications during accelerated stability studies performed on cold form blister pack and simulated bulk pack and an extensive discussion on the possible causes has been presented. It was justified that the non-compliance may be due to the susceptibility to hydrolysis of both active substances in aqueous solutions and to degrade in high moisture/temperature conditions with a possibility of incompatibility between the two active substances and associated degradation products and the packaging used. Therefore stability studies were performed under the intermediate conditions and the results comply with the proposed finished product shelf life specification.

In-use stability data for two production scale batches (150,000 units) of the finished product up to 90 days in HDPE bottle pack at 25 ºC / 60% RH were provided. The design of in-use stability study and the tests performed at each time point was provided covering the duration of the shelf life. The tests performed at each time station were description, assay, related substances, dissolution, water content and microbiological test. The data demonstrated no tendency for a change of tested parameters.

Results on forced degradation studies were also provided as part of the related substances and assay method validation. Exposure to acid hydrolysis, basic hydrolysis, oxidation, heat degradation and UV as well as to heat, humidity, white light and UV in solid state was measured.

Based on available stability data, the proposed shelf-life of 24 months and the storage conditions ("Do not store above 25 ºC") as stated in the SmPC (section 6.3) are acceptable for both proposed packaging. The in-use shelf life of 90 days after first opening the container is also considered acceptable.

The proposed holding time of 12 months and the storage conditions ("Do not store above 25 ºC") for tablets in bulk shipment pack are also considered 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.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The medicinal product is a fixed combination containing two active substances, emtricitabine and tenofovir disoproxil maleate. 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

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical part of the dossier consisted of literature overview and some 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, Truvada SBOA 2012). Less non-clinical safety data is available for the maleate salt form. Following oral administration, Tenofovir disoproxil fumarate is rapidly absorbed and converted to Tenofovir. While the pharmacological profile of Tenofovir disoproxil is expected to be equivalent after administration of any of the salts, a brief scientific review and safety assessment was conducted to compare the potential toxicity profiles of the two salt forms.

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 200/300 mg/day (Truvada SmPC 2015) in Applicant's Emtricitabine/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. Emtricitabine (CAS# 143491-57-0), 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 23, 2015.

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 Emtricitabine/Tenofovir disoproxil Mylan manufactured by MYLAN S.A.S., France is considered unlikely to result in any significant increase in the combined sales volumes for all emtricitabine and tenofovir disoproxil maleate containing products and the exposure of the environment to the active substances. Emtricitabine and Tenofovir disoproxil Mylan 200/300 mg film-coated tablet contain identical amount of Emtricitabine and Tenofovir disoproxil drug substances and has been formulated with a range of commonly used excipients to be pharmaceutically equivalent to Truvada 200 mg/245 mg (Emtricitabine/Tenofovir disoproxil) film-coated tablets and as such is not considered to pose any greater environmental risk to that from the reference product. 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 Truvada. Truvada 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. Of note, no non-clinical primary pharmacology or safety studies have been conducted with the Tenofovir disoproxil maleate or/and the Emtricitabine/Tenofovir disoproxil maleate combination. However, the applicant provided GLP compliant 90-day oral repeated dose toxicity study in rats where toxicity profile Tenofovir disoproxil maleate and Tenofovir disoproxil fumarate was evaluated. The results showed 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 Emtricitabine/Tenofovir disoproxil maleate film coated tablets. The CHMP considered this as acceptable.

Concerning ERA the Applicant stated that Emtricitabine and Tenofovir disoproxil Mylan 200/300 mg film-coated tablet correspond to the Reference product Truvada 200 mg/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 Emtricitabine/Tenofovir disoproxil Mylan and justifications along with a 90-day oral repeated dose toxicity study to show 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, which 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 Emtricitabine/Tenofovir disoproxil. To support the marketing authorisation application the applicant conducted one bioequivalence study with an open-label, balanced, randomized, single dose, two treatment, two sequence, two period crossover

bioequivalence study design under fed conditions. This study was the pivotal study for the assessment.

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 clinical facility in Turkey (inspection dates: 07/12/2015 to10/12/2015), the analytical laboratory and the sponsor site in India (inspection dates: 11/02/2016 to 16/02/2016) were conducted following the request of the CHMP. The outcome of the inspection carried out was issued on 11 April 2016

Exemption

Not applicable as the application applies to only one strength.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study, TEEM-14-021.

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. TEEM-14-021	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 oral bioequivalence of Emtricitabine/ Tenofovir disoproxil Maleate film coated Tablets 200/300 mg of Mylan Laboratories Limited, India and Truvada® (Emtricitabine/ Tenofovir disoproxil) film coated Tablets 200/245 mg from Gilead Sciences Intl Ltd, Cambridge CB21 6GT, Verenigd Koninkrijk, Royaume-Uni, Vereinigtes Konigreich in healthy adult human subjects, under fed conditions. To monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Emtricitabine/ Tenofovir disoproxil maleate tablets 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:** Emtricitabine/Tenofovir disoproxil Maleate film coated Tablets 200/300 mg Dosage Regimen: 200 mg/300 mg **Route of administration:** Oral **Reference Product:** Truvada® (Emtricitabine/ Tenofovir disoproxil) film coated Tablets 200/245 mg Dosage Regimen: 200 mg/245 mg **Route of administration:** Oral	No. of subjects dosed Period I: 36 Period II: 35, Completed-35, Subjects considered for pharmacokinetic and statistical analysis-35	healthy adult human subjects	Single dose	Complete Study Report

2.4.2. Pharmacokinetics

Study TEEM-14-021 Title: *An open-label, balanced, randomised, two treatment, two sequence, two period, cross-over single dose, comparative oral bioequivalence study of emtricitabine disoproxil maleate*

film-coated tablets 200/300 mg Mylan and Truvada 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 bioequivalence study under fed conditions to assess the single dose bioequivalence of Emtricitabine/Tenofovir disoproxil Maleate film coated Tablets 200/300 mg with that of Truvada (Emtricitabine/Tenofovir disoproxil) film coated tablets 200/245 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 Emtricitabine/Tenofovir disoproxil Maleate film coated Tablets 200/300 mg under fed conditions

Study consisted of two periods (Period I and Period II). After 10 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. 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 and ~10 hours for emtricitabine in literature. The last sampling time was evaluated as 5 times of t½ which was found as ~60 to 90 hours for tenofovir and ~50 hours for emtricitabine. 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 and ~100 hours (~4 days) for emtricitabine. Therefore, the two treatment periods were separated by a wash-out period of 10 days between two periods to minimize the carry-over effect.

The treatments (one tablet containing 200 mg Emtricitabine and 300 mg Tenofovir disoproxil Maleate for test product and 200 mg Emtricitabine 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. 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. The following protocol deviations were reported: ***(1)*** One subject (subject 09) dropped-out in Period 1; ***(2)*** 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. The dosing dates were 10 days apart - on 09.12.2014 for Period I and 19.12.2014 for Period II.

Thus, the study design is acceptable however a number of clarifications were requested during the evaluation.

Test and reference products

The Marketing Authorisation Holder for Truvada 200 mg/245 mg film-coated tablets is Gilead Sciences International Limited, United Kingdom.

The date of authorisation in the EU for Truvada 200 mg/245 mg film-coated tablets is 21st February 2005.

The certificates of analysis of the biobatches are provided in Table 6.

Bioequivalence trial information

Table 2. Test and reference product information

Product Characteristics	Reference product	Test Product
Name	Truvada (Emtricitabine/Tenofovir disoproxil) film coated tablets	Emtricitabine and Tenofovir disoproxil maleate film-coated Tablets
Strength	200 mg /245 mg	200 mg /300 mg
Dosage form	Film-coated tablets	Film-coated tablets
Manufacturer	Gilead Sciences International Limited, United Kingdom	Mylan Laboratories Limited, India.
Batch number / Lot Number	12TRS141D	8023739*
Batch size (Biobatch)	-	150, 000
Measured content(s) (% of label claim)	Emtricitabine: 100.8 % Tenofovir: 100.3 %	Emtricitabine: 100.7 % Tenofovir: 100.8 %
Proposed additional commercial batch size	-	700,000 tablets
Expiry date (Retest date)	November 2016	April 2016
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.6	5312-compar-ba-be-stud-rep, Appendix-16.1.6
Member State where the reference product is purchased from:	UK	-
This product was used in the following trials:	Study no.: TEEM-14-021	Study no.: TEEM-14-021

* Emtricitabine and Tenofovir disoproxil maleate 200 mg/300 mg film-coated tablets from the Batch No. 2006426 were re-packed into Batch No. 8023739 and used in bioequivalence study.

Emtricitabine/Tenofovir disoproxil Mylan 200/245mg manufactured by MYLAN S.A.S - SAINT PRIEST (batch No. 8023739*; exp. date April 2016) has been compared to Truvada 200/245 mg manufactured by Gilead Sciences International Limited, (Batch No: 12TRS141D, exp. date November 2016).

Population studied

A total of 46 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 19 and 55 years

of age with a 161.5 – 184.7 cm of height. Study was open for both male and female volunteers but only males were available for the study.

Out of 36 subjects, 35 subjects completed all periods of the study and were considered for pharmacokinetic and statistical analysis. Subject 09 dropped out in Period I after dosing.

The population is according to the guideline. Although both genders were planned to be included into the study, the males were included. This is acceptable as for BE exercise the homogeneity of studied population is even higher. The inclusion and exclusion criteria were considered acceptable.

Analytical methods

The bioanalytical method documented in a pre-study validation report VR-126-00.

The plasma samples of subjects were analysed using LC/MS/MS method over a concentration range of 25.196 to 3999.407 ng/ml for emtricitabine and 5.002 to 600.185 ng/ml for tenofovir. The analytical method was developed and validated over a concentration range of 25.202 to 4000.254 ng/ml for emtricitabine and 5.012 to 601.389 ng/ml for tenofovir and later it was partially validated over a concentration range of 25.224 to 4003.776 ng/ml for emtricitabine and 4.961 to 595.274 ng/ml for Tenofovir as a part of anticoagulant effect and whole blood stability at Bio analytical laboratory of CRC, Mylan Laboratories Ltd.

Table 3. Summary of the validation results (Analyte: emtricitabine)

Analytical Validation Report Location(s)	VR-126-00 Mod-5314, Bioanalytical Report
This analytical method was used in the following studies:	TEEM-14-021
Short description of the method	LC/MS/MS; Solid Phase extraction technique
Biological matrix	K_3 EDTA Plasma
Analyte Location of product certificate	Emtricitabin e, VR-126-00; Mod-5314, Bioanalytical Report
Internal standard (IS) Location of product certificate	Emtricitabine-15ND 2, VR-126-00; Mod-5314, Bioanalytical Report 2C.
Calibration concentrations (Units)	25.202, 50.403, 100.806, 300.019, 800.051, 1600.101, 2400.152, 3200.203 and 4000.254 ng/mL
Lower limit of quantification (Units)	25.202 ng/mL, 98.61%, 0.86%
QC concentrations (Units)	LLOQQC- 25.242 ng/mL, Low- 75.725 ng/mL, M1QC- 600.992 ng/mL, M2QC- 1502.481 ng/mL, High- 3004.961 ng/mL
Between-run accuracy	96.24% to 98.54%
Between-run precision	3.18% to 4.94%
Within-run accuracy (P& A-1)	96.02% to 99.87%
Within-run precision (P& A-1)	2.15% to 2.85%

Within-run accuracy (P& A-2)	93.36% to 100.06%	
Within-run precision (P& A-2)	1.90% to 8.88%	
Within-run accuracy (P& A-3)	96.07% to 98.80%	
Within-run precision (P& A-3)	1.01% to 3.11%	
Within-run accuracy (P& A-4)	95.94% to 101.79%	
Within-run precision (P& A-4)	2.07% to 6.00%	
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% or>120% n.v	LQC 1.021 1.006 2.10 NA NA	HQC 1.010 0.995 1.70 NA NA
Long term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 50 days in Diluent 1(stock solution) & 12 days in Diluent 2 (working solution) for analyte at 2-8°C Analyte: LQC: -0.88% (Diluent-1), -2.95% (Diluent-2) HQC: -1.23% (Diluent-1), 0.45% (Diluent-2) Confirmed up to 46 days in Diluent 1(stock solution) & 12 days in Diluent 3 (working solution) for ISTD at 2-8°C ISTD: -1.06% (Diluent-1), -1.77% (Diluent-3)	
Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 21 hrs 13 min LQC -2.34% & HQC	
Long term stability in biological matrix (Observed change %) Location	Confirmed up to 118 days at -70±15°C LQC: -0.64% & HQC -1.23% Confirmed up to 118 days at -20±5°C LQC: -1.66% & HQC -1.09% Mod-5314, Bioanalytical Report, Attachment-5 (VR-126-00 – Addendum-01-00)	
Autosampler storage stability (Observed change %)	Confirmed up to 106 hrs 10 min at 10°C LQC -11.40% & HQC 6.88%	
Post-preparative stability (Observed change %)	Refrigerator Stability in Matrix Confirmed up to 20 hrs 01 min at 2-8°C LQC -2.68% & HQC -1.91% Dry Extract Stability Confirmed up to 20 hrs 32 min at 2-8°C LQC 0.05% & HQC 0.73%	
Freeze and thaw stability (Observed change %)	-20±5 °C, 6 cycles, LQC 1.30% & HQC -2.42% -70±15 °C, 6 cycles, LQC -0.40% & HQC 2.37%	

Dilution integrity	Concentration diluted 1/2-fold Accuracy - 98.00%, Precision 1.82% Concentration diluted 1/4-fold Accuracy - 100.02%, Precision 3.33%
Partial validation Location(s)	Supplement-05-00 - Partially validated for Anticoagulant Effect & Whole blood stability. Mod-5, App-16.5, Bioanalytical Report, Attachment-6
Cross validation(s) Location(s)	Not applicable

Table 4. 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:	TEEM-14-021
Short description of the method	LC/MS/MS; Solid Phase extraction technique
Biological matrix	K_3 EDTA Plasma
Analyte Location of product certificate	Tenofovir, VR-126-00; Mod-5314, Bioanalytical Report, Attachment-5, Appendix-2C.
Internal standard (IS) Location of product certificate	Tenofovir-D6, VR-126-00; Mod-5314, Bioanalytical Report, Attachment-5, Appendix-2C.
Calibration concentrations (Units)	5.012, 10.023, 20.046, 50.116, 120.278, 240.556, 400.926, 501.157 and 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, High- 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% or>120% n.v	LQC 1.00 9 0.995 2.58 NA NA	HQC 1.00 1 0.987 2.62 NA NA
Long term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 48 days in Diluent 2 (stock solution) & 12 days in Diluent 2 (working solution) for analyte at 2-8°C Analyte: LQC: -0.45% (Diluent-2), -3.16% (Diluent-2) HQC: 1.50% (Diluent-2), -0.23% (Diluent-2) Confirmed up to 50 days in Diluent 2 (stock solution) & 12 days in Diluent 3 (working solution) for ISTD at 2-8°C ISTD: 0.49% (Diluent-2), -1.75% (Diluent-3)	
Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 21 hrs 13 min LQC -1.05% & HQC	
Long term stability in biological matrix (Observed change %) Location	Confirmed up to 118 days at -70±15°C LQC: -0.02% & HQC -2.69% Confirmed up to 118 days at -20±5°C LQC: -2.63% & HQC -1.88% Mod-5314, Bioanalytical Report, Attachment-5 (VR-126-00 – Addendum-01-00)	
Autosampler storage stability (Observed change, %)	Confirmed up to 106 hrs 10 min at 10°C LQC 0.15% & HQC -2.20%	
Post-preparative stability (Observed change %)	Refrigerator Stability in Matrix Confirmed up to 20 hrs 01 min at 2-8°C LQC -0.77% & HQC -1.90% Dry Extract Stability Confirmed up to 20 hrs 32 min at 2-8°C LQC 1.08% & HQC 0.47%	
Freeze and thaw stability (Observed change %)	-20±5 °C, 6 cycles, LQC -2.79% & HQC -7.02% -70±15 °C, 6 cycles, LQC -3.30% & HQC -3.41%	
Dilution integrity	Concentration diluted 1/2-fold Accuracy - 99.99%, Precision 1.18% Concentration diluted 1/4-fold Accuracy - 90.36%, Precision 3.30%	

Partial validation Location(s)	Supplement-05-00 - Partially validated for Anticoagulant Effect & Whole blood stability. Mod-5, App-16.5, Bioanalytical Report, Attachment-6
Cross validation(s) Location(s)	Not applicable

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

Emtricitabine			
Parameter	**Results**		**Table** No.
Total Number of Analytical runs	Twenty One (21) acceptable analytical runs		3A
Correlation Coefficient (r)	> 0.9934		
Calibration Curve	Accuracy(% Nom)	Precision (% CV)	4A
	91 .45% to 107.44%	2.70% to 4.99%	
Quality control	Accuracy(% Nom)	Precision (% CV)	*SA*
	97.37% to 105.24%	3.93% to 6.29%	
DQC *(Yz* dilution)	Accuracy(% Nom)	Precision (% CV)	Nil
	Nil	Nil	
There were no rejected analytical runs.			

Tenofovir			
Parameter	**Results**		**Table** No.
Total Number of Analytical runs	Twenty One (21) acceptable analytical runs		3B
Correlation Coefficient (r)	> 0.9958		
Calibration Curve	Accuracy(% Nom)	Precision (% CV)	4B
	94.22% to 103.74%	2.50% to 5.76%	
Quality control	Accuracy(% Nom)	Precision (% CV)	5B
	93.95% to 103.51%	4.50% to 7.32%	
DQC *(Yz* dilution)	Accuracy(% Nom)	Precision (% CV)	Nil
	Nil	Nil	
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 (%)		30 (1.86%)
Code A	Discrete Repeats identified for Emtricitabine under bad chromatography were repeated as the analyte peak was integrated with adjacent peak (Mainly samples were BLQ or between LOQ & LQC concentration level), after reanalysis similar peak shape for some of samples at lower concentration shown. Hence these samples were reintegrated for proper quantification and data were reported. The reasons and acceptance of initial/repeated values can be found in Table 2A (Page No.: 29-30).	
Note: The reasons for repeats and their results were reported in Table 2A respectively.		

Table 7. Long term stability details

Long stability details	
Long stability required	70 days
Long stability proved	118 days (Addendum 01-00)

Table 8. Incurred sample reanalysis

Incurred sample reanalysis: 10% of the first 1000 samples plus 5% of the rest of the samples of the total samples analysed in the study.

Analytes	**Emtricitabine**	**Tenofovir**
Total Number of incurred samples analyzed	136	136
Total Number of samples considered for Incurred samples Reanalysis Calculation	136	136
Total Number of samples met acceptance criteria	132	136
Total %of samples within the acceptance range	97.06%	100.00%.

The Applicant provided the bioanalytical report of the bioequivalence study including representative number of chromatograms and other raw data. Main characteristics of the method used (selectivity, lower limit of quantitation, calibration curve performance, accuracy, precision, stability) were validated before study, validation criteria are met, validation reports included.

Pharmacokinetic variables

Single-dose pharmacokinetic parameters for Tenofovir and Emtricitabine 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 (AUC_t) 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 (AUC_{0-t}, C_{max}), and secondary parameters ($AUC_{0-\infty}$, T_{max}, AUC_{ratio}, 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) AUC_{0-t} and C_{max} of the test to reference formulation for Ln-transformed data should be within 80% to 125% for Tenofovir and Emtricitabine to establish bioequivalence.

The PK variables are adequate. Standard methods were used.

Statistical methods

Pre-specification of the analysis: Unless otherwise stated, analyses were performed using SAS software, and all hypothesis tests were conducted with alpha of 0.05 and beta 0.90, which is considered as adequate. Data were summarized using adequate descriptive statistics (mean, SD, variance, median, min-max). Majority of analyses are using parametric tests. The treatment of missing PK values and points is reported as approached adequately.

Results

Pharmacokinetic data for Tenofovir and Emtricitabine are shown in Table 14 and data comparisons in Table 15, and in Figure 11.

Table 9. Summary of Pharmacokinetic Data for Tenofovir and Emtricitabine

Tenofovir

		Test			Reference		
Variable	**N**	**Mean**	**Std Dev**	**Coeff of Variation**	**Mean**	**Std Dev**	**Coeff of Variation**
***T_{max} (hr)**	35	1.000 (0.833-5.000)	0.856	60.601	1.250 (0.500-3.017)	0.702	48.625
C_{max} (ng/mL)	35	273.699	64.272	23.483	278.381	65.472	23.519
AUC_{0-t} (ng. hr/mL)	35	2127.577	458.338	21.543	2168.022	457.27	21.092
AUC0-inf (ng. hr/mL)	35	2371.626	447.028	18.849	2380.279	458.857	19.277
Lambda_z (z or K_{el}) (1/hr)	35	0.0390	0.0052	13.3952	0.0388	0.0070	17.9279
HL_Lambda_z ($t_{½}$) (hr)	35	18.078	2.331	12.892	18.418	3.312	17.983

Emtricitabine

		Test			Reference		
Variable	**N**	**Mean**	**Std Dev**	**Coeff of Variation**	**Mean**	**Std Dev**	**Coeff of Variation**
***Tmax (hr)**	35	1.000 (0.667-5.000)	0.887	64.375	1.500 (0.833-5.000)	0.869	53.724
Cmax (ng/mL)	35	2163.369	486.127	22.471	2210.310	471.838	21.347
AUC0-t (ng. hr/mL)	35	9760.029	1742.657	17.855	9606.822	1571.052	16.354
AUC0-inf (ng. hr/mL)	35	10145.221	1773.928	17.485	9961.360	1611.519	16.178

Lambda_z (z or Kel) (1/hr)	35	0.1035	0.0232	22.4376	0.1161	0.0306	26.3858
HL_Lambda_z (t½) (hr)	35	7.290	3.258	44.688	6.339	1.628	25.690

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

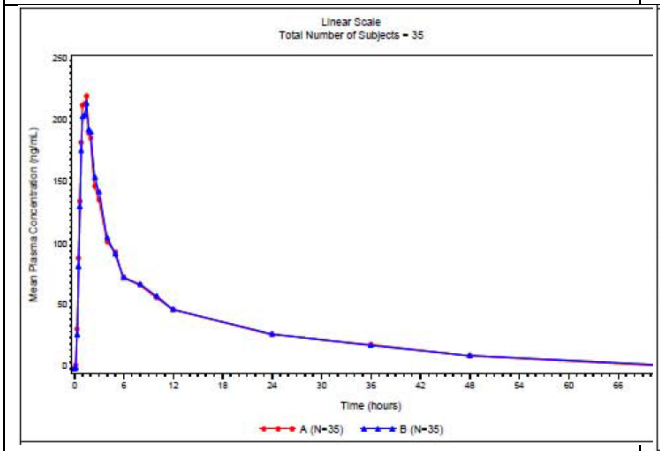
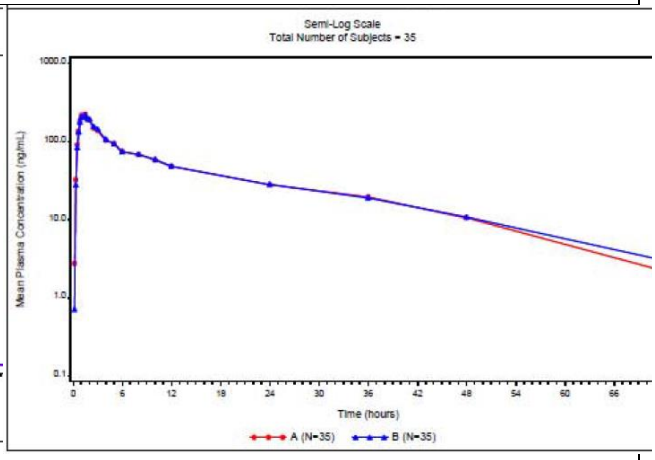
Table 10. Summary of Geometric mean, Ratio, 90% Confidence intervals, Intra-subject CV (%) and power for Tenofovir and Emtricitabine

Tenofovir (n=35)						
Parameters (Units)	***Geometric Mean**		**Intra Subject CV %**	**90% Confidence Limits (%)**	**Power%**	**Ratio (A/B)%**
	Test product (A)	**Reference product (B)**				
LnC_{max} (ng/mL)	266.270	270.646	15.28	**92.52- 104.62**	>99.00	98.38
$LnAUC_{0-t}$ (ng. hr/mL)	2079.73	2118.62	8.03	**95.03- 101.40**	>99.00	98.16
LnAUC0-inf (ng. hr/mL)	2330.29	2332.72	7.98	96.72- 103.17	>99.00	99.90
Emtricitabine (n=35)						
Parameters (Units)	***Geometric Mean**		**Intra Subject CV %**	**90% Confidence Limits (%)**	**Power%**	**Ratio (A / B)%**
	Test product (A)	**Reference product (B)**				
LnC_{max} (ng/mL)	2110.78	2161.53	10.68	**93.53- 101.95**	>99.00	97.65
$LnAUC_{0-t}$ (ng. hr/mL)	9623.30	9487.65	6.15	**98.94- 103.98**	>99.00	101.43
LnAUC0-inf (ng. hr/mL)	10009.28	9840.57	6.30	99.16- 104.34	>99.00	101.71
LnAUC0-inf (ng. hr/mL)	10009.28	9840.57	6.30	99.16- 104.34	>99.00	101.71

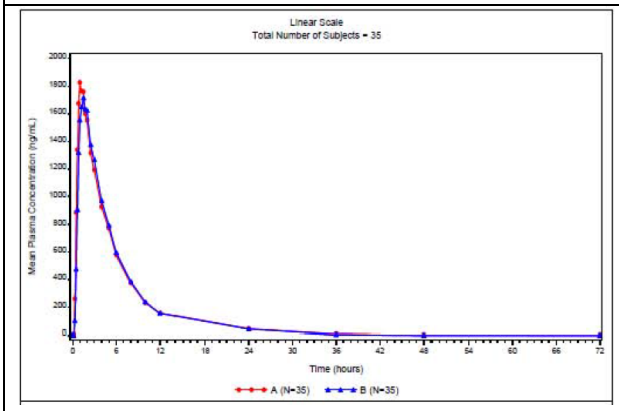
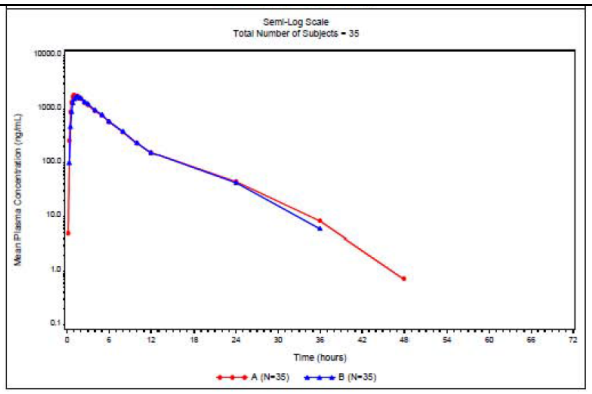
Note: *Geometric means values are taken from Individual Efficacy Response Data

Figure 3. Linear and Semi-Log mean plots for tenofovir and emtricitabine

Tenofovir

Linear Scale	Semi-Log Scale
	

Emtricitabine

Linear Scale	Semi-Log Scale
	

Treatment A: Emtricitabine/Tenofovir Disoproxil Maleate Film Coated Tablets, Lot#: 8023739, Dose: 1 x 200/300 mg, Mylan Laboratories Limited
Treatment B: Truvada (Emtricitabine/Tenofovir Disoproxil) Film Coated Tablets, Lot#: 12TRS141D, Dose: 1 x 200/245 mg, Gilead Sciences International Ltd.

The AUC ratios were higher than 80% in all subjects except in two patients in test arm (in Patients #07 and #08 that were 79.25% and 77.40%, respectively). No subjects had detected pre-dose plasma levels and no subject reached C_{max} at the first sampling time point. The test to reference ratio of geometric mean and corresponding 90% CI for the C_{max} and AUC_{0-t} fall within acceptable range of 80.00 to 125%. The bioequivalence criteria were met under fed conditions.

Safety data

Neither death nor serious adverse events occurred during the study. A total 6 adverse events occurred in the study of which 4 of them were of moderate intensity while 2 adverse events were of mild intensity:

For Test Product: Subject 8 experienced nausea in Period I. Subject 29 experienced pain in extremity in Period I.

For Reference Product: Subject 12 experienced nausea in Period I. Subject 30 experienced headache in washout period. Subject 31 experienced constipation in Period I. Subject 34 experienced pain in extremity in Period I.

The Applicant explained that the adverse events that occurred in the study are possibly related to the study products. 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 02, 14, 25, 28 and 34 for pre-study, Subject 02, 05, 14 and 29 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 Emtricitabine/Tenofovir disoproxil Mylan is considered bioequivalent with Truvada.

2.4.3. Pharmacodynamics

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

2.4.4. Additional data

In vitro dissolution tests complementary to the bioequivalence study
The *in vitro* dissolution tests were conducted using an USP type II apparatus (paddle), 900 ml volume and a speed of 75 rpm at temperature of 37°C ± 0.5°C. Three different dissolution media were used: 0.1N HCl pH 1.2 (Release media), pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer, and a sampling time of 5, 10, 15, 30, 45 and 60 minutes.

Comparison of 12 tablets of the test formulation (batch no. 2006426) and the reference formulation (batch no. 12TRS141D) used in the bioequivalence study was performed. The dissolution profiles of Emtricitabine from the test and from the reference formulation batches were found to be similar when compared at pH 1.2, 4.5 and 6.8 with more than 85% dissolved in 10 minutes, and can be considered as similar without further mathematical calculations. The dissolution profiles of Tenofovir disoproxil at 0.1 N HCl (Release media) differed between products and the similarity factor (f2 value) obtained was found to be less than 50. The lower similarity factor values were considered of no significance as the test product was found to be bioequivalent to the reference product. The dissolution profiles of Emtricitabine from the test and the reference batches were found to be similar at pH levels and at QC conditions with more than 85% dissolved in 10 minutes. Dissolution profiles for Tenofovir disoproxil at 0.1 N HCl were significantly different, but that was not the case at pH 4.5 and 6.8.

2.4.5. Post marketing experience

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

2.4.6. Discussion on clinical aspects

The overview on clinical pharmacology, efficacy and safety provided was considered adequate. To support this application the MAA a bioequivalence study was submitted and a statement that study complies with

GCP principles was 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 a randomized, open label, two-treatment, two-sequence, two-period, cross-over, single dose, comparative oral bioequivalence study comparing Emtricitabine/Tenofovir disoproxil (as Maleate) with Truvada (Emtricitabine/Tenofovir disoproxil (as fumarate)) in 36 healthy, adult male volunteers under fed conditions. Study consisted of two periods (Period I and Period II). After 10 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 both tenofovir and emtricitabine 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.

2.4.7. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Emtricitabine/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	- Post-treatment hepatic flares in HIV-1/HBV co-infected patients - Renal toxicity (in relation to tenofovir) - Bone events due to proximal renal tubulopathy/loss of bone mineral density (in relation to tenofovir) - Interaction with didanosine (in relation to tenofovir) - Pancreatitis (in relation to tenofovir)

Summary of safety concerns	
Missing information	- Safety in elderly patients - Safety in pregnancy - Safety in lactation - Safety in children (including long-term safety) [in relation to tenofovir] - Safety in patients with renal impairment (in relation to tenofovir)

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:		
Post-treatment hepatic flares in HIV-1/HBV co-infected patients	Section 4.2, 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Sections 2 and 3 of PL advise patients on this safety concern.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal toxicity (in relation to tenofovir)	Section 4.2, 4.4, 4.5 and 4.8 of the SPC contain adequate information on this safety concern. Sections 2 and 4 of PL advise patients on this safety concern.	Educational brochure for physicians
Bone events due to proximal renal tubulopathy/loss of BMD (in relation to tenofovir)	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern. Sections 2 and 4 of PL advise patients on this safety concern	Educational brochure for physicians
Interaction with didanosine (in relation to tenofovir)	Section 4.4, 4.5 and 4.8 of the SPC contain adequate information on this safety concern. Sections 2 of PL advise patients on this safety concern	None
Pancreatitis (in relation to tenofovir)	Section 4.4, 4.5 and 4.8 of the SPC contain adequate information on this safety concern. Sections 2 and 4 of PL advise patients on this safety concern	None
Missing information:		
Safety in elderly patients	Section 4.2, 4.4, 4.8 and 5.2 of the SPC contains information on the lack of experience in elderly patients. Section 2 of PIL addresses this lack of information in elderly patients.	None
Safety in pregnancy	Section 4.6 of the SPC contains information on the lack of experience during pregnancy. Section 2 of PIL addresses this lack of information during pregnancy.	None
Safety in lactation	Section 4.6 of the SPC contains information on the lack of experience during lactation. Section 2 of PIL addresses this lack of information during lactation.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety in children (including long-term safety) [in relation to tenofovir]	Section 4.2, 4.8 and 5.2 of the SPC contains information on the lack of experience in children under the age of 18 years. Section 2 of PIL addresses this lack of information in children under the age of 18 years.	None
Safety in patients with renal impairment (in relation to tenofovir)	Section 4.2, 4.4 and 5.2 of the SPC contains information on the lack of experience in patients with renal impairment. Section 2 of PIL addresses this lack of information in patients with renal impairment.	Educational brochure for physicians

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 with the above content 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 (Truvada) SmPC to Emtricitabine/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 Emtricitabine/Tenofovir disoproxil film-coated tablets. The reference product Truvada is indicated for treatment and prevention of HIV infection. 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. 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 were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of [applied product] met the protocol-defined criteria for bioequivalence when compared with the [reference product]. 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 Emtricitabine/Tenofovir disoproxil Mylan is favourable in the following indication:

Emtricitabine/Tenofovir disoproxil Mylan is indicated in antiretroviral combination therapy for the treatment of HIV 1 infected adults (see section 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 Emtricitabine/Tenofovir disoproxil Mylan in adult 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

The HIV renal educational brochure should contain the following key messages:

- That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Emtricitabine/Tenofovir disoproxil Mylan
- That Emtricitabine/Tenofovir disoproxil Mylan should only be used in patients with impaired renal function if the potential benefits are considered to outweigh the potential risks
- That use of Emtricitabine/Tenofovir disoproxil Mylan should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Emtricitabine/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 Emtricitabine/Tenofovir disoproxil Mylan therapy
- The importance of regular monitoring of renal function during Emtricitabine/Tenofovir disoproxil Mylan therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- Instructions on the use of the creatinine clearance slide ruler