15 September 2016
EMA/650230/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emtricitabine / Tenofovir disoproxil Zentiva

International non-proprietary name: emtricitabine / tenofovir disoproxil

Procedure No. EMEA/H/C/004137/0000

Note

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

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List of abbreviations

3TC	lamivudine
ABC	abacavir
ADV	adefovir dipivoxii
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
ART	active antiretroviral therapy
AS	active substance
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC0-24	area under the plasma concentration-time curve from zero to 24 hours
AUC0-t concentration	area under the plasma concentration-time curve from zero to the last measurable
AUC0-∞	area under the plasma concentration-time curve from zero to infinity
AZT	zidovudine
bis[POC]PMPA	Tenofovir disoproxil fumarate
BCS	Biophamaceutics Classification system
BMD	bone mineral density
CBV	carbovir
CDC	Centers for Disease Control and Prevention
CG	Cockroft-Gault
CHB	chronic hepatitis B
CI	confidence interval
CL	clearance
Cmax	maximum plasma concentration
CoAs	Certificate of Analysis
CQA	critical quality attributes
CrCl	creatinine clearance
CYP	cytochrome P450
DART	Development of AntiRetroviral Therapy in Africa
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EFV	efavirenz

eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	end-stage renal disease
FDA U.S.	Food and Drug Administration
FTC	emtricitabine
GC	gas chromatography
GCP	good clinical practise
GFR	glomerular filtration rate
h	hour
HAART	highly active antiretroviral therapy
HBeAg	hepatitis B e antigen
HBV	hepatitis B virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
ICH	International Conference on Harmonisation
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
(FT-)IR	(Fourier transfom) Infrared
iPrEx	iniciativa Profilaxis Pre-Exposicion
IQR	interquartile range
ITT	the intent-to-treat
KF	Karl Fischer method
LAM	lamivudine
LC/MS/MS	liquid chromatography-tandem mass spectrometry
LDL	low-density lipoprotein
LDPE	Low density polyethylene
LPV	lopinavir
MDRD	Modification of Diet in Renal Disease
MS	mass spectrometry
(^{1}H / ^{13}C) NMR	(proton/ carbon) Nuclear magnetic resonance
NNRTI	nonnucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor

PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PMPA	9-(2-phosphonomethoxypropyl)adenine
p.o.	peroral
PVA	polyvinyl alcohol
r	ritonavir
RH	relative humidity
RNA	ribonucleic acid
SmPC	summary of product characteristics
t1/2 β	terminal elimination half-life
TDF	Tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
Tenofovir DF	Tenofovir disoproxil fumarate
TFV-DP	Tenofovir diphosphate
TLC	Thin layer chromatography
Tmax	time to maximum plasma concentration
UV	ultra violet
vs.	versus
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva k.s. submitted on 7 October 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Emtricitabine / Tenofovir disoproxil Zentiva, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 December 2014.

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:

Emtricitabine/Tenofovir disoproxil Zentiva 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-naïve patients (see section 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 Truvada, 200mg/245mg, 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 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(s): 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(s): 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): ETI-P4-464

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: Alar Irs

- The application was received by the EMA on 7 October 2015.
- The procedure started on 29 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 January 2016 The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 January 2016
- During the meeting on 8-11 February 2016 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 11 February 2016
- During the meeting on 22-25 February 2016, 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 February 2016
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 April 2016.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 May 2016
- During the PRAC meeting on 6-9 June 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP. The PRAC assessment Overview and Advice was sent to the applicant on 09 June 2016
- During the CHMP meeting on 20-23 June 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 14 August 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to List of Outstanding Issues on 31 August 2016
- During the meeting on 12-15 September 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 Zentiva.

2. Scientific discussion

2.1. Introduction

On June 5, 1981, the Morbidity and Mortality Weekly Report, published by the Centers for Disease Control and Prevention (CDC), described Pneumocystis carinii (now P. jiroveci) pneumonia in 5 homosexual men in Los Angeles, California, USA, documenting for the first time what became known as acquired immunodeficiency syndrome (AIDS). These reports were sentinels for what became one of history's worst pandemics, with >60 million infections, 30 million deaths, and no end in sight.

In 1983, HIV was discovered, an accomplishment for which French scientists received the Nobel Prize for Medicine in 2008. In 1985, a serologic test for HIV became commercially available. HIV type 1, group M (HIV-1), the predominant cause of the AIDS epidemic, evolved from a virus that crossed the species barrier from chimpanzees to humans. The earliest retrospective diagnosis of HIV-1 infection was made from a serum specimen collected in 1959 in Kinshasa, capital of what is now the Democratic Republic of Congo. Two additional but rare groups of HIV-1 (N and O) cause related zoonotic infections that are essentially restricted to central Africa. HIV-2, a second type of HIV rarely found outside western Africa, originated in sooty mangabeys. Although the epidemic appears to have begun in central Africa, HIV prevalence is now highest in southern Africa; the Republic of South Africa alone is home to about one sixth of the world's HIV-infected persons. The reasons for this geographic distribution are not entirely clear, but biological factors, such as lack of male circumcision and rates of other genital (especially ulcerative) infections that facilitate HIV transmission, and social factors (some of which may have been influenced by the end of apartheid), such as frequent partner change and concurrent sexual partnerships, migration, and commercial sex, likely play a role.

Tenofovir disoproxil is a first in class of nucleotide reverse transcriptase inhibitors (NRTI). Scientific advances resulted in the development of lifesaving, albeit not curative, treatment for HIV. Beginning with the approval of azidothymidine or zidovudine in 1987, the development of antiretroviral drugs and the design of simple and standardized approaches for therapy in the developing world constituted a public health triumph. By the end of 2009, >5 million persons in low- and middle-income countries were accessing ART, unimaginable just a few years before and made possible through the use of generic drugs,

price reductions for brand-name drugs, and efforts of international donors through initiatives such as the President's Emergency Plan for AIDS Relief and the Global Fund.

The current treatment guidelines recommend two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a protease inhibitor (preferably boosted with ritonavir), a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase strand transfer inhibitor, or a CCR5 antagonist for initial antiretroviral therapy in treatment-naive, HIV-infected adults and adolescents include. The combination of tenofovir and FTC (or lamivudine) is the preferred dual-NRTI option in treatment-naive, HIV-infected adults and adolescents, particularly for patients co-infected with both HIV and hepatitis B virus as these agents are active against both viruses [EACS 2014; Panel on Antiretroviral Guidelines for Adults and Adolescents 2015].

The combination of tenofovir and FTC (or lamivudine) is the preferred dual-NRTI option in treatment-naive, HIV-infected adults and Emtricitabine/Tenofovir Disoproxil (Phosphate) 200/245 mg Film Coated tablet has been submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended.

The proposed indication was : Emtricitabine/Tenofovir disoproxil Zentiva 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-naïve patients.

The aim of the pharmaceutical development work was to develop a stable formulation of Emtricitabine/Tenofovir disoproxil containing 200/245 mg of drug substances, which would be pharmaceutically equivalent to the innovator product Truvada 200mg/245mg Film-Coated Tablets.

The recommended dose of Emtricitabine/Tenofovir disoproxil Zentiva is one tablet, taken orally, once daily.

2.2. Quality aspects

2.2.1. Introduction

Emtricitabine/Tenofovir disoproxil Zentiva is presented as film coated tablet containing a fixed-dose combination of 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 291.5 mg of tenofovir disoproxil phosphate or 136 mg tenofovir) as the active substances.

Other ingredients of the tablet core are microcrystalline cellulose, croscarmellose sodium, talc, hydrophobic colloidal silica and magnesium stearate. The film coating is composed of polyvinyl alcohol, titanium dioxide, macrogol, talc and indigo carmine aluminum lake (E132).

The product is available in high density polyethylene (HDPE) bottles with polypropylene child-resistant caps, induction heat sealing (with aluminium foil) and silica gel desiccants (in the HDPE container), as described in section 6.5 of the SmPC.

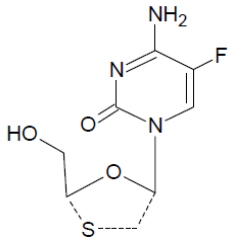
2.2.2. Active substance

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 247.25 g/mol and the following structure:

Figure 1. Structure of emtricitabine.



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

Emtricitabine appears as a white to off-white non-hygroscopic crystalline powder, sparingly soluble in water and in methanol. Its pKa was found to be 4.73 and the partition coefficient log P -0.40. 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.

Emtricitabine exhibits polymorphism. The same crystalline form-I is consistently manufactured, which is characterised and controlled by XRD method during the manufacture and at release.

Manufacture, characterisation and process controls

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

Emtricitabine is synthesized in four main chemical steps followed by purification drying, milling, sifting and packing. The starting material is well-defined with acceptable specifications. The first two steps of the synthesis leading to the key intermediate are performed by two manufacturers using slightly different solvents in the chemical reactions.

One manufacturer of the above is responsible for the production of the final active substance from the key intermediate. The starting materials were re-defined during the procedure in order to ensure that the incorporation of structural elements and stereochemistry is documented in the dossier and is carried out under GMP requirements, resulting in the addition of a second manufacturer. The key intermediate, solvents and reagents are described and are controlled by appropriate specifications. A satisfactory brief description of the micronisation step has also been provided.

Adequate in-process controls are applied during the synthesis. 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 including genotoxic impurities were well discussed with regards to their origin and characterised.

Emtricitabine is packed in two layers of LDPE bags placed in an HDPE drum. The polythene bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended. The specification of the LDPE bag as well as CoAs were presented.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), solubility (visual), identity (IR, HPLC), polymorphism (XRD), specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), heavy metals, chloride content (potentiometry), related substances (TLC, HPLC), enatiomeric purity (HPLC), assay (HPLC) and residual solvents (GC).

The potential impurities and possible genotoxic impurities which are possible from the re-defined starting material are controlled in the final AS by validated test methods and the results from three commercial scale emtricitabine batches are summarised. As the results are either below detection limit or not detected, it has been demonstrated that the impurities are generally adequately controlled during manufacturing of the AS. Based on the data provided, the fate and carry-over of above impurities has been sufficiently demonstrated.

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 from three 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 four production scale batches of active substance from the proposed manufacturers stored in the intended commercial packaging for up to 60 months under long term conditions (25 °C ± 2 °C / 60 %RH ± 5% RH) was provided. Three of the above batches were stored for up to 6 months under accelerated conditions (40 °C ± 2 °C /75 %RH ± 5% RH) according to the ICH guidelines. Samples were tested for the parameters included in the release specification. The analytical methods used were the same as for release and were stability indicating.

No significant changes to any of the measured parameters were observed under either storage condition and all remained within specification. Based on the presented data a change of polymorphic form during the proposed retest period is considered highly unlikely.

Photostability testing following the ICH guideline Q1B was performed on one commercial scale batch. The results showed that the AS is not sensitive to light.

Stress testing (thermal, light, hydrolysis, acidic, basic, oxidative and reductive conditions) was also performed on one commercial scale batch. Samples were tested for description, identification, specific optical rotation, loss on drying, assay and related substances. The degradation pathways and the stability indicating power of the assay and related substance methods have been demonstrated.

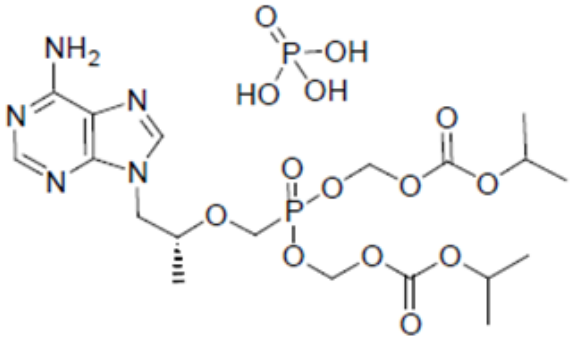
The stability results justify the proposed retest period of 60 months in the proposed container.

Tenofovir disoproxil

General information

The chemical name of tenofovir disoproxil phosphate is 9-((*R*)-2-*bis*(((isopropoxycarbonyl)oxy) methoxy)phosphinyl)-methoxy)propyl)adenine phosphate corresponding to the molecular formula $C_{19}H_{30}N_5O_{10}P.H_3PO_4$ and has a relative molecular mass of 617.44 g/mol. It has the structure shown in figure 3:

Figure 2. Structure of tenofovir disoproxil phosphate.



The active substance is a white to off-white crystalline powder, slightly hygroscopic and slightly soluble in aqueous media across the physiological pH range. A single polymorphic form has been observed which is routinely produced by the manufacturing process. There is one chiral centre which originates in one of the starting materials and is controlled in the active substance by chiral HPLC.

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.

Tenofovir disoproxil phosphate is synthesized in five main steps using well-defined starting materials with acceptable specifications. One manufacturer is responsible for the production of an intermediate which is then converted to the active substance by a second manufacturer. The starting materials were re-defined during the procedure in order to ensure that enough of the process is documented in the dossier and carried out under GMP, resulting in addition of the second manufacturer. The single chiral centre is controlled in one of the starting materials and carries through unaltered to the active substance.

Adequate in-process controls are applied during the synthesis. Potential and actual impurities were well discussed with regards to their origin and characterised. A thorough assessment of potential mutagenic impurities was carried out and adequate controls have been put in place. 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.

The active substance is packaged in double LDPE bags inside a drum. The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification re-produced in table 2 includes tests for appearance, identity (IR), assay (HPLC), phosphoric acid assay (HPLC), impurities (HPLC), enantiomeric purity (chiral HPLC), residual solvents (GC), water content (KF), heavy metals (ICP-AES), and microbiological purity (Ph. Eur.). The mono-POC PMPA impurity present at higher than the qualification threshold according to ICH Q3A is a known metabolite and thus qualified. Other impurities are adequately controlled by the specifications. There are no controls for polymorphic form as only one crystalline form is known.

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 from three 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 three production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 12 months under long term conditions (5±3 °C) and for up to 6 months under accelerated conditions (25 °C / 60% RH) according to the ICH guidelines were provided. Samples were tested for appearance, impurities, enantiomeric purity, water content and assay. The analytical methods used were the same as for release and were stability indicating. No significant changes to any of the measured parameters were observed under either storage condition and all remained within specification.

Photostability testing following the ICH guideline Q1B and stress testing (high temperature, elevated humidity, acidic, basic and oxidising aqueous media) was performed on one batch. The active substance is not photosensitive but is sensitive to heat and extremely sensitive to heat and moisture. It degrades, mainly via hydrolysis, under all the aqueous conditions.

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 24 months at 5±3 °C in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as blue, oval biconvex film coated immediate release tablets, intended for oral administration.
The aim of the pharmaceutical development work was to develop a stable formulation containing 200 mg of emtricitabine and 245 mg of tenofovir disoproxil which would be bioequivalent to the innovator product Truvada 200mg / 245mg film-coated tablets.

At the beginning of development, dry granulation was favoured over wet granulation since this technique requires relatively low amounts of excipients and consequently more advantageous in terms of reduction of the size of the tablet. It was also favoured because it avoids exposure of the active substances to heat and moisture, important since tenofovir disoproxil is susceptible to hydrolysis in the presence of moisture. Roller compaction was used as dry granulation method for the manufacturing process. Different manufacturing parameters were tested in combination with different excipients and ratios throughout the development of the manufacturing process. The manufacturing process follows a conventional approach for solid dosage forms, employing widely used, non-specialised manufacturing equipment. As a result of

the selected process, the qualitative composition of the generic product is different from the reference product. The selected final composition was superior to the others based on the physical properties of the tablets, and the flow and compression properties of the final blends. All the excipients used in the finished product are of pharmacopoeial quality and are commonly used for this type of medicinal product. Based on the presented information, emtricitabine and tenofovir disoproxil phosphate do not show any incompatibility either with the excipients used in the formulation or with each other, which was also confirmed during the formal stability studies.

The coating material was selected as Opadry II Blue 85F30675 which is a polyvinyl alcohol (PVA) based solid preparation for tablet coating. Dissolution profile studies were performed with core and film coated tablets. It was proven that the coating materials have no effect on the dissolution behaviour of the samples. A number of different formulations were investigated in this study.

The reference medicinal product contains tenofovir disoproxil as a fumarate salt, however, the phosphate salt of tenofovir disoproxil is used in the Zentiva generic formulation. Based on literature information, emtricitabine is a class I (high solubility, high permeability) substance and tenofovir disoproxil phosphate is a class III (high solubility, low permeability) substance according to the Biophamaceutics Classification system (BCS). The impurity profiles of Emtricitabine/Tenofovir disoproxil (phosphate) Zentiva 200/245 mg film-coated tablets and Truvada 200 mg/245 mg film-coated tablets were determined using an HPLC method. The impurity profiles can be considered essentially similar based on the submitted results.

The bioequivalence of the generic to the reference was demonstrated by bioequivalence study ETI-P4-464. Comparison of dissolution profiles of four batches of the test product (including the two biobatches) and four batches of the reference showed that release of both substances was more than 85 % within 15 minutes in all tested media.

For the QC dissolution method, sink conditions were obtained in all media that were investigated for both substances. However, a coning effect was observed visually and the release of the two ASs was incomplete with the initially was selected paddle conditions. It was therefore decided to switch to apparatus 1 (basket) and set the rotational speed at 75 rpm. Obtained results were satisfactory after executing the dissolution tests in four different media under these conditions. Since the dissolution profiles in all media are similar, the release medium was selected as 0.1N HCl.

The primary packaging of Emtricitabine/Tenofovir Disoproxil 200/245 mg film coated tablets was selected as HDPE bottles with child resistant polypropylene (PP) screw caps with induction heat sealing (with aluminium foil). 3 grams of silica gel (in a HDPE canister) is added to each bottle as desiccant to reduce adventitious headspace moisture. The provided stability results indicate that the proposed packaging materials are suitable for the storage of the finished product. The primary packaging material complies with EU-Regulations No.10/2011 and No.1935/2004/EC.

Manufacture of the product and process controls

The manufacturing process can be considered as a standard process which comprises the following main steps: a) preparation of the blend ready for compression (sieving, mixing, dry granulation (roller compaction) / milling, blending, lubricating (final blending); b) compression of tablets; c) coating of tablets; d) packaging.

Based on the submitted risk assessment study to demonstrate control and understanding of the manufacturing procedure, no critical steps in the manufacturing process of the finished product have been identified. The proposed IPCs have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

The batch sizes intended for commercial use have been clearly stated. The process has been validated on three batches at the minimum commercial batch size and the validation report was presented. The process will be further validated on the first 3 production scale batches of each proposed batch size.

In conclusion, it is considered that the manufacturing process is sufficiently robust to provide assurance that film-coated tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification of emtricitabine and tenofovir disoproxil (HPLC, TLC), identification of colourant (chemical), identification of phosphate (HPLC), disintegration (Ph. Eur.), water content (Ph. Eur.), average weight (Ph. Eur.), uniformity of dosage units (mass variation, Ph. Eur. and content uniformity, Ph. Eur.), dissolution (HPLC), assay of emtricitabine and tenofovir disoproxil (HPLC), related substances (HPLC) and microbial purity (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data three commercial scale batches were presented. All batches are representative of the commercial formula and process. All batches meet the commercial specification limits.

Stability of the product

Stability data from three commercial scale batches stored under long term conditions for up to 18 months (25 °C / 60% RH), for up to 18 months under intermediate conditions (30 °C / 65% RH and 30 °C / 75% RH) and for up to six months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, average tablet weight, water content, dissolution, assay, related substances and microbial purity. The methods used were the same as for release testing and are stability indicating. There is no significant change in any of characteristic of Emtricitabine/Tenofovir Disoproxil Zentiva 200/245 mg film coated tablets as tested at any time point. No trends were observed.

One commercial scale batch of the finished product was subjected to in-use stability testing. Based on the presented results, a shelf life after first opening is not warranted. However, once opened the product should be stored below 30 °C. An in-use study will be performed on a second batch at the end of the long term stability period, too.

A photostability study was carried out on one commercial scale batch of finished product according to ICH Q1B Guideline. Light exposure did not result in any significant change. Additional storage restrictions are not considered necessary.

Forced degradation / stress studies were carried out on one commercial scale batch of finished product in order to demonstrate the stability indicating nature of the assay and related substances methods. Samples of tenofovir and emtricitabine drug substances and the drug product were tested after exposure to acid, basic, oxidative conditions, elevated temperature and exposed to UV light. The results of degradation studies together with mass balance calculations demonstrate that that the assay and related substances methods are stability indicating.

Based on the provided stability data, the proposed shelf life of 24 months stored in the original package in order to protect from moisture, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No materials of human or animal origin are used in the manufacture of the finished product.

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.

2.2.6. Recommendation(s) 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 with a batch of finished product towards the end of its shelf life.

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical data have been provided. 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 reference medicinal product contains tenofovir disoproxil as a fumarate salt, however, a phosphate salt is used in the generic formulation. Fumarate is a Class 1 product; however it is not considered a Generally Recognized As Safe (GRAS) substance. Phosphate is also a Class 1 product, but is additionally considered a GRAS substance. This has been discussed and was considered acceptable.

2.3.2. Ecotoxicity / environmental risk assessment

No full Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Emtricitabine/Tenofovir disoproxil tablets manufactured by Zentiva is considered unlikely to result in any significant increase in the combined sales volumes for all Emtricitabine/Tenofovir disoproxil containing products and the exposure of the environment to the active substances. Thus, the environmental risk is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The pharmacology, pharmacokinetics and toxicology data as well known for tenofovir disoproxil and thus new non-clinical data are not required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed in the non-clinical overview.

2.3.4. Conclusion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The pharmacology, pharmacokinetics and toxicology data as well known for tenofovir disoproxil and thus new non-clinical data are not required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing emtricitabine/tenofovir disoproxil phosphate. To support the marketing authorisation application the applicant conducted one bioequivalence study with two-period, two-sequence, two-way cross-over, open label, randomized design under fed conditions. This study was the pivotal study for the assessment.

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.

Exemption

Not applicable.

Clinical studies

To support the application, the applicant has submitted ETI-P4-464 bioequivalence study.

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
BE	ETI-P4-464 *Sponsor Project Number EMTEDL07235*	Vol. 1, Section 5.3.1.2, p. 2	Evaluate and compare the bioavailability and therefore to assess the bioequivalence of two different formulations of emtricitabine/tenofovir after a single oral dose administration under fed conditions. Determine the safety and tolerability of the Test product compared to the Reference formulation in healthy volunteers	Crossover; Fed State	Two film-coated tablet formulations; 200 mg emtricitabine / 245 mg tenofovir single dose; oral	36	Healthy Subjects	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Study ETI-P4-464 - ZENTIVA study code: EMTEDL07235 : Study Title: Single Dose Crossover Comparative Bioavailability Study of Emtricitabine/Tenofovir 200 mg/245 mg Tablets in Healthy Male and Female Volunteers / Fed State.

Methods

Study design

The study was a randomised, laboratory-blinded, two-treatment, two-sequence, two-period, crossover, single dose bioequivalence study conducted under fed conditions with a wash out period of 14 calendar days between two administrations. One tablet containing 200 mg/245 mg of Emtricitabine/Tenofovir disoproxil phosphate was administered in each period.

The choice of BE study strength 200 mg/245 mg is derived from the single clinical dosage combination for adults recommended by innovator.

Test and reference products

Test drug: Emtricitabine/Tenofovir disoproxil (phosphate) 200 mg/245 mg film coated tablets by Zentiva k.s., Czech Republic; manufacturer Zentiva Sağlik Ürünleri, Turkey; batch No. P01062014, batch size: 100, 000 tablets, manufacturing date: 26/06/2014, expiry date: 09/11/2014

Reference drug: Truvada 200 mg/245 mg film-coated tablet by Gilead Sciences Limited UC, Ireland; batch No. 12TRS107D from German market, expiry date: 08/2016

Population studied

36 healthy volunteers (aged 18 – 79 years, BMI 20.93 – 29.94, 18 male and 18 female subjects) were included in the study. Non-smokers, ex-(stopped smoking for at least 6 months before) or light smokers (<10 cigarettes per day) were allowed in this study.

36 subjects completed both study phases and were included in the pharmacokinetic and statistical

analysis. No major protocol deviations were reported. Inclusion and exclusion criteria were presented and were acceptable for a BE study and for the product under investigation.

The population chosen as well as the sample size was found to be adequate and according to guidelines.

Analytical methods

In each study period, 21 blood samples were collected. The first blood sample was collected prior to drug administration while the others were collected up to 72 hours after drug administration. Blood samples were collected in pre-cooled K2 EDTA Vacutainers. As soon as possible following blood collection, samples were centrifuged at a temperature of 4°C nominal and at approximately 1500 *g* for 10 minutes. The plasma obtained was separated into duplicate polypropylene culture tubes, when feasible. The tubes were labelled with a code number that did not reveal formulation identity. The samples were frozen in an upright position and retained in the clinic's freezers at a temperature of -20°C nominal until sent on dry ice to the laboratory for assay. The time from blood sample collection to plasma aliquot storage should have been within 90 minutes.

Plasma concentrations of Emtricitabine and Tenofovir were determined using a validated reversed phase HPLC-MS/MS methods.

The subject sample analysis was performed between 2014/11/03 and 2014/11/19, including re-assays and incurred samples. For emtricitabine, the lower limit of quantitation and upper limit of quantitation were 10.0 ng/ml and 4000.0 ng/ml, respectively. For tenofovir, the lower limit of quantitation and upper limit of quantitation were 2.50 ng/ml and 800.00 ng/ml, respectively.

The concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using least squares regression analysis employing a weighted ($1/x^2$) linear ($y=mx+b$) for Emtricitabine and for Tenofovir.

Pre-study validation and bio-analytical report are presented. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested. Composition of analytical runs has been described.

The maximum study sample storage period from first blood draw (13/10/2014) to last sample analysis (19/11/2014) was 36 days for Emtricitabine and Tenofovir disoproxil.

The long-term stability of Emtricitabine in human plasma covers 37 days at -20°C nominal. The long-term stability of Tenofovir in human plasma covers 60 days at -20°C nominal.

Pre- and within study validation for the determination of Emtricitabine/Tenofovir in human plasma is sufficient.

Pharmacokinetic variables

Primary variables: C_{max} and AUC_{0-72}.
Pharmacokinetic parameters C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $AUC_{0-72/\infty}$, λ_z and T_{half} were determined.

Statistical methods

The pharmacokinetic and statistical analyses were generated using Phoenix® WinNonlin®, version 6.3, Phoenix® ConnectTM version 1.3.1 and SAS® version 9 software.

The ratio of geometric LS means with corresponding 90% confidence interval calculated from the

exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-72} were all to be within the 80.00 to 125.00% bioequivalence range.

The pharmacokinetic parameters calculated are appropriate for a single dose study. Standard bioequivalence criteria are proposed for C_{max} and AUC_{0-72}.

Results

Table 2. Pharmacokinetic parameters for Emtricitabine (non-transformed values)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**SD**	**arithmetic**	**SD**
$AUC_{(0-72h)}$	**11087.3**	**±2492.9**	**11260.8**	**±2340.1**
$AUC_{(0-\infty)}$	**11382.1**	**±2617.2**	**11444.9**	**±2387.5**
C_{max}	**1836.6**	**±365.6**	**2027.5**	**±454.9**
T_{max}*	**1.68 (0.67 – 5.00)**		**1.67 (1.00 – 9.00)**	

<AUC0-t	area under the plasma concentration-time curve from time zero to t hours>
<AUC0-72h	area under the plasma concentration-time curve from time zero to 72 hours>
AUC0-∞	area under the plasma concentration-time curve from time zero to infinity
Cmax	maximum plasma concentration
Tmax	time for maximum concentration (* median, range)

Table 3. Statistical analysis for Emtricitabine (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0-72h)}$	**98.42%**	96.28% - 100.61%	5.5
C_{max}	**90.83%**	85.21% - 96.82%	16.1

* estimated from the Residual Mean Squares

Table 4. Pharmacokinetic parameters for Tenofovir disoproxil (non-transformed values)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**SD**	**arithmetic**	**SD**
$AUC_{(0-72h)}$	**3019.58**	**±884.75**	**3117.30**	**±841.42**
$AUC_{(0-\infty)}$	**3188.80**	**±944.28**	**3298.15**	**±906.81**
C_{max}	**301.20**	**±91.77**	**315.92**	**±86.38**
T_{max}*	**1.33 (0.67 – 5.00)**		**1.67 (1.00 – 9.00)**	

Pharmacokinetic	Test	Reference
<AUC0-t	area under the plasma concentration-time curve from time zero to t hours>	
<AUC0-72h	area under the plasma concentration-time curve from time zero to 72 hours>	
AUC0-∞	area under the plasma concentration-time curve from time zero to infinity	
Cmax	maximum plasma concentration	
Tmax	time for maximum concentration (* median, range)	

Table 5. Statistical analysis for Tenofovir disoproxil (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$	**96.60%**	93.61% - 99.68%	7.9
C_{max}	**94.67%**	87.10% - 102.89%	21.1
* estimated from the Residual Mean Squares			

The 90% confidence intervals for ln-transformed pharmacokinetic variables Cmax and AUC0-72 were within the conventional bioequivalence range of 80% to 125%.

For Emtricitabine, ANOVA revealed significant period effect for AUC0-t and significant sequence effect for Cmax, which are considered acceptable. Any subjects did not reach Cmax at the first sampling time point indicating that sampling time schedule was adequate. None of the subjects had measurable pre-dose plasma concentrations of Emtricitabine or Tenofovir.

The %AUCextrap values were not applicable because sampling scheme reached out to 72 hours.

The pharmacokinetic variables for Emtricitabine and Tenofovir are comparable between test and reference product.

Safety data

Although the incidence of drug-related AEs was slightly higher for subjects dosed with the Test formulation (Test 28% vs. Reference 19%), in general, both formulations were well tolerated in the study. The most frequent AEs reported were headache and somnolence, which are known as very common AEs of Emtricitabine/Tenofovir combination.

2.4.3. Pharmacokinetic conclusion

Based on the presented bioequivalence study Emtricitabine/Tenofovir disoproxil 200 mg/245 mg film-coated tablet by Zentiva k.s., Czech Republic, is considered bioequivalent with Truvada 200 mg/245 mg film-coated tablet by Gilead Sciences Ireland UC, Ireland.

2.4.4. Pharmacodynamics

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

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 clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate. To support this application the MAA submitted the bioequivalence study.

The 90% confidence intervals for ln-transformed pharmacokinetic variables Cmax and AUC0-72 were within the conventional bioequivalence range of 80% to 125%. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **).

Treatments were well tolerated by the subjects enrolled in the study. The adverse events mentioned above are all included in the SmPC.

2.4.7. Conclusions on clinical aspects

Based on the presented bioequivalence study Emtricitabine/Tenofovir disoproxil 200 mg/245 mg film-coated tablet by Zentiva k.s., Czech Republic, is considered bioequivalent with Truvada 200 mg/245 mg film-coated tablet.

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 • Post-treatment hepatic flares in HIV-1/HBV co-infected patients • Interaction with didanosine • Pancreatitis
Important potential risks	-
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

CHMP agrees that the safety concerns listed by the applicant are in line with the originator.

Pharmacovigilance plan

The Applicant committed to update the pharmacovigilance plan relating to monitoring of pregnancy outcomes/ safety in pregnancy within 2 months after Commission decision.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal toxicity	This item is appropriately communicated through proposed labelling: SmPC Sections 4.2 - Posology and method of administration 4.4 - Special warnings and precautions for use 4.5 – Interaction with other medicinal products and other forms of interaction 4.8 - Undesirable effects Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	**Educational brochure for physicians**
Bone events due to proximal renal tubulopathy/loss of bone mineral density	This item is appropriately communicated through proposed labelling: SmPC Sections 4.2 – Posology and method of administration 4.4 - Special warnings and precautions for use 4.8 - Undesirable effects Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	None proposed.
Post-treatment hepatic flares in HIV-1/HBV co-infected patients	This item is appropriately communicated through proposed labelling: SmPC Sections 4.2 – Posology and method of administration 4.4 – Special warnings and precautions for use 4.8 - Undesirable effects Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	None proposed.
Interaction with didanosine	This item is appropriately communicated through proposed labelling: SmPC Sections 4.4 – Special warnings and precautions for use 4.5 – Interaction with other medicinal products and other	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	forms of interaction 4.8 - Undesirable effects Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	
Pancreatitis	This item is appropriately communicated through proposed labelling: SmPC Sections 4.4 – Special warnings and precautions for use 4.5 – Interaction with other medicinal products and other forms of interaction 4.8 – Undesirable effects Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	None proposed.
Safety in children (including long-term safety)	This item is appropriately communicated through proposed labelling: SmPC Sections 4.2 – Posology and method of administration 4.8 – Undesirable effects 5.1 – Pharmacodynamic properties Paediatric population 5.2 – Pharmacokinetic properties Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	None proposed.
Safety in elderly patients	This item is appropriately communicated through proposed labelling: SmPC Sections 4.2 – Posology and method of admnistration 4.4 – Special warnings and precautions for use Elderly 4.8 – Undesirable effects 5.2 – Pharmacokinetic properties Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	None proposed.
Safety in pregnancy	This item is appropriately communicated through proposed	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	labelling: SmPC Sections 4.6 – Fertility, pregnancy and lactation 5.3 – Preclinical safety data Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	
Safety in lactation	This item is appropriately communicated through proposed labelling: SmPC Sections 4.6 – Fertility, pregnancy and lactation Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	None proposed.
Safety in patients with renal impairment	This item is appropriately communicated through proposed labelling: SmPC Sections Proposed text in SmPC: 4.2 – Posology and method of administration 4.4 – Special warnings and precautions for use 4.8 – Undesirable effects 5.2 – Pharmacokinetic properties Prescription only medicine. Therapy should be initiated by a physician experienced in the management of HIV infection.	**Educational brochure for physicians**

The applicant's proposal for routine risk minimisation measures is considered sufficient to address most of safety concerns. Additional risk minimisation measures are need to address the safety in patients with renal impairment.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 could be acceptable if the applicant implements the changes to the RMP with the following details:

The Applicant committed to update the RMP with an updated pharmacovigilance plan relating to monitoring of pregnancy outcomes/ safety in pregnancy within 2 months after Commission decision.

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 that as method of administration the tablets may be disintegrated and mixed with water or food prior to administration in patients with difficulties swallowing tablets whole. The Applicant has submitted additional investigation results demonstrating that dissolution and disintegration of both test and reference products are taking place within 15 minutes, dissolution test of crushed tablets are unaffected (>85% dissolved in 15 min in the physiological pH range) and therefore are not expected to translate into any differences in pharmacokinetic parameters. Although the BE was demonstrated with tablets taken whole, the additional disintegration and dissolution data using crushed tablets support the applicability of specific administration recommendation in originator SmPC to the generic Emtricitabine/Tenofovir disoproxil Zentiva product.

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 a [design summary]. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. [Comment on appropriateness of parallel design, studies in fed status, investigation of metabolites, etc] 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 Emtricitabine/Tenofovir disoproxil (phosphate) met the protocol-defined criteria for bioequivalence when compared with Truvada. 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 Zentiva is favourable in the following indication:

Emtricitabine / Tenofovir disoproxil Zentiva 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).

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