21 July 2016
EMA/532453/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tenofovir disoproxil Zentiva

International non-proprietary name: tenofovir disoproxil

Procedure No. EMEA/H/C/004120/0000

Note

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

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List of abbreviations

AUC0-T	Cumulative area under the plasma concentration time curve calculated from 0 to TLQC using the linear trapezoidal method.
AUC0-∞	Area under the plasma concentration time curve extrapolated to infinity, calculated as AUCT + ĈLQC/λz, where ĈLQC is the estimated concentration at time TLQC.
AUC0-T/∞	Relative percentage of AUCT with respect to AUC∞
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human use
Cmax	Maximum observed plasma concentration
EC	European Commission
EU	European Union
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-AES	Inductively coupled atomic emission spectrometry
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
MAH	Marketing Authorisation holder
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
RT	Retention time
SmPC	Summary of Product Characteristics
Thalf	Terminal elimination half-life, calculated as ln(2)/ λz
TLIN	Time point where log-linear elimination phase begins λz Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration versus time curve
TLQC	Time of last observed quantifiable plasma concentration
Tmax	Time of maximum observed plasma concentration; if it occurs at more than one time point, Tmax is defined as the first time point with this value
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
TLIN	Time point where log-linear elimination phase begins λz Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva k.s. submitted on 4 September 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for 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 20 November 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 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 indications:

HIV-1 infection
Tenofovir disoproxil Zentiva is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults.

In adults, the demonstration of the benefit of tenofovir disoproxil in HIV-1 infection is based on results of one study in treatment-naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which tenofovir disoproxil was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml).

Tenofovir disoproxil Zentiva is also indicated for the treatment of HIV-1 infected adolescents, with NRTI (nucleotide reverse transcriptase inhibitor) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

The choice of Tenofovir disoproxil Zentiva to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Hepatitis B infection
Tenofovir disoproxil Zentiva is indicated for the treatment of chronic hepatitis B in adults with:

- *compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).*
- *evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1).*
- *decompensated liver disease (see sections 4.4, 4.8 and 5.1).*

Tenofovir disoproxil Zentiva is indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with:

- *compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis (see sections 4.4, 4.8 and 5.1).*

The legal basis for this application refers to:

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

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

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Viread, 245 mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 05-02-2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/01/200/001-002

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

- Product name, strength, pharmaceutical form: Viread, 245 mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 05-02-2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/01/200/001-002

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: Viread, 245 mg, film-coated tablet
- Marketing authorisation holder: Gilead Sciences International Limited
- Date of authorisation: 05-02-2002
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/01/200/001
- Bioavailability study numbers: TNI-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: John Joseph Borg

- The application was received by the EMA on 4 September 2015.
- The procedure started on 1 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 December 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 07 January 2016.
- During the meeting on 28 January 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 28 January 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 March 2016.
- The GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 02 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 by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 June 2016.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of outstanding issue to all CHMP members on 06 July 2016.
- During the meeting on 21 July 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Tenofovir disoproxil Zentiva.

2. Scientific discussion

2.1. Introduction

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). Tenofovir tablets (containing 245 mg of tenofovir disoproxil, equivalent to 300 mg tenofovir disoproxil fumarate or 136 mg of tenofovir) was first approved in United States (US) (26 October 2001), European Union (EU) (5 February 2002), and other countries worldwide for the treatment of human immunodeficiency virus type 1 (HIV-1) in combination with other antiretroviral (ARV) medicinal products in infected adults age 18 years and older. Tenofovir was subsequently approved for the treatment of chronic hepatitis B in EU (23 April 2008) and US.

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 different initiatives.

Tenofovir film-coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected children aged 6-12 years, adolescents 12-18 years, and adults.

Tenofovir film-coated tablets are also indicated for the treatment of HIV-1-infected patients, with NRTI resistance or toxicities precluding the use of first line agents.

Tenofovir film-coated tablets are indicated for the treatment of chronic hepatitis B in adolescents

compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and / or fibrosis

Tenofovir film-coated tablets are indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease, with evidence of active viral replication, persistently elevated serum-alanine-aminotransferase (ALT) levels and histological evidence of active inflammation and / or fibrosis;
- decompensated liver disease.

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

The applicant applied for all the indication of the reference product. The pharmaceutical form is film-coated tablet containing 245 mg of tenofovir disoproxil. Tenofovir disoproxil Zentiva tablets should be taken once daily, orally with food.

All of the used excipients of Tenofovir disoproxil phosphate Zentiva are well known regarding the safety and applicability in formulation of pharmaceuticals.

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

Core tablet: Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate

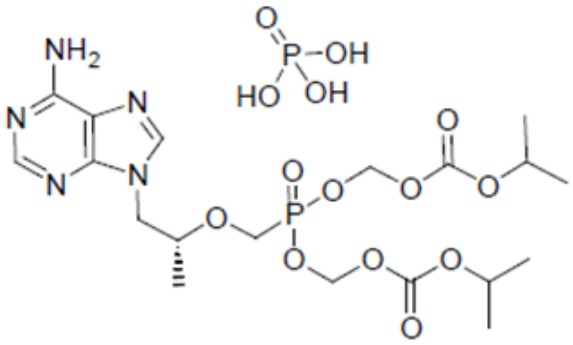
Film coat: Lactose monohydrate, hypromellose, titanium dioxide, triacetin and Indigo Carmine Aluminum Lake

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

2.2.2. Active substance

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 following structure:



The active substance is a white to off-white crystalline powder, slightly hygroscopic and slightly soluble in aqueous media across the physiological pH range. Given the wet granulation process used to manufacture tablets and the rapid dissolution of the active substance from that formulation, particle size is not expected to

affect product performance and is not controlled. 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 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 lack of control for particle size is acceptable given the solubility of the active substance in relevant media and its rapid dissolution profile from the tablets.

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 ºC) and for up to 6

months under accelerated conditions (25 ºC / 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 ^{o}C in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Tenofovir disoproxil Zentiva comes as oblong light blue film coated tablets. The aim was to develop a stable and robust formulation, bioequivalent to the reference product, Viread. A different active substance salt is used (phosphate rather than fumarate) which has been shown to be sufficiently stable. The phosphate salt is slightly less soluble in aqueous media than the fumarate salt but bioequivalence has been demonstrated clinically. The composition of Tenofovir disoproxil Zentiva is based on the composition of the reference product with modifications to excipient content based on the experience of the finished product manufacturer.

Tenofovir disoproxil phosphate is a BCS class III substance which is slightly hygroscopic and susceptible to hydrolysis under acidic and basic aqueous conditions. Nonetheless, given the formulation components, a wet granulation method was investigated and found to afford tablets within the desired specification for hydrolysis impurities. Various parameters for the granulation step were investigated and optimised to ensure adequate dissolution performance and flow parameters.

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

The formulation used for the bioequivalence study is the same as that intended for marketing. Comparative dissolution profiles of Tenofovir Disoproxil and Viread in 0.1 N HCl and pH 4.5 and 6.8 buffer solutions were provided. Rapid dissolution (within 15 minutes) occurred for both products in all media with similar profiles.

In section 4.2 of the SmPC, it is stated that in exceptional circumstances for patients with difficulty swallowing, the finished product can be administered following disintegration of the tablet in 100 ml of water, orange juice, or grape juice. Data was provided showing comparative disintegration times of Tenofovir Disoproxil Zentiva and Viread in all three media and demonstrating that disintegration occurs within 15 minutes in each case. Since tenofovir disoproxil is a BCS class III substance, 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.

Tenofovir disoproxil phosphate is equally soluble across the physiological pH range and all media tested afforded sink conditions. The dissolution conditions were therefore chosen based on data available in the public domain and other parameters optimised. Discriminatory power was investigated by comparing dissolution profiles of

tablets made using different manufacturing parameters. Given the properties of the active substance, the method is considered to be sufficiently discriminatory.

The primary packaging is an HDPE bottle with polypropylene child-resistant cap and induction heat sealing (with aluminium foil). The materials comply with Ph. Eur. and EC requirements. A certificate has been submitted demonstrating compliance with ISO 8317:2015 for child resistance. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: blending of tenofovir disoproxil with intra-granular excipients followed by granulation, drying and milling; blending with extra-granular excipients; compression; film-coating; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three production scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, average weight (Ph. Eur.), water content (KF), disintegration (Ph. Eur.), dissolution (UV spectrophotometry), uniformity of dosage units (Ph. Eur.), identification (active substance: HPLC, UV; phosphate: HPLC; titanium dioxide: colour reaction; Indigo Carmine Aluminium Lake: HPLC), assay (HPLC), impurities (HPLC) and microbiological quality (Ph. Eur.).

Several impurities have limits above the qualification threshold but are also known metabolites. Limits have been set in line with the WHO international monograph, with wider limits at shelf-life given the observed degradation over time. The limits are considered justified.

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

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three production scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), up to 12 months under intermediate conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing and were manufactured from two separate batches of active substance.

Samples were tested for appearance, average tablet weight, dissolution, assay, water content, impurities and microbiological quality. The analytical procedures used are stability indicating. All parameters remained within specification under long term and intermediate conditions although an increase in impurities and decrease in

assay was observed over time. Under accelerated conditions, several impurities and the assay value were out of specification after 6 months.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Some degradation is observed over time, although it has been shown that the container closure system provides adequate protection from light. The batch was also exposed to aqueous acid, base, and oxidant and dry heat and was found to degrade under each set of conditions.

An in-use stability study was also carried out on one batch of finished product over a 60 day period. The film coated tablets were found to be stable. The applicant has committed to repeating the study on a second batch towards the end of its shelf-life.

Based on available stability data, the proposed shelf-life of 15 months with the storage condition “Do not store above 30 ^{o}C. Store in the original package in order to protect from moisture” as stated in the SmPC (section 6.4) is acceptable.

Adventitious agents

It is confirmed that the lactose monohydrate 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

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. Recommendation 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

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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

Pharmacology

Tenofovir disoproxil phosphate is the phosphate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Following oral administration, Tenofovir disoproxil is hydrolyzed enzymatically in the body to the active substance tenofovir-(9-[-(R)-2-{phosphonomethoxy}propyl]adenine) (PMPA) that exhibits anti-HIV activity. Tenofovir diphosphate is, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV 1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300 µmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in in vitro assays.

Data pertaining to HIV

HIV antiviral activity in vitro: The concentration of tenofovir required for 50% inhibition (EC50) of the wild type laboratory strain HIV 1IIIB is 1 6 µmol/l in lymphoid cell lines and 1.1 µmol/l against primary HIV-1 subtype B isolates in PBMCs. Tenofovir is also active against HIV 1 subtypes A, C, D, E, F, G, and O and against HIVBaL in primary monocyte/macrophage cells. Tenofovir shows activity in vitro against HIV 2, with an EC50 of 4.9 µmol/l in MT4 cells.

Resistance: Strains of HIV 1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected in vitro and in some patients (see Clinical efficacy and safety). Tenofovir disoproxil should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation (see section 4.4). In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

No primary pharmacodynamics studies, secondary pharmacodynamics studies, safety pharmacology studies or studies on pharmacodynamic drug interactions were conducted by the applicant.and the Applicant presented literature citations till 2014.

Secondary Pharmacodynamics

Studies investigating the secondary pharmacodynamics of tenofovir disoproxil fumarate or phosphate were not

performed by the Applicant. As this is a generic application, the CHMP considered it as acceptable.

Pharmacokinetics

Reference is made to the SmPC of the Reference product.

Tenofovir disoproxil is a water soluble ester prodrug which is rapidly converted in vivo to tenofovir and formaldehyde.

Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

Absorption

Following oral administration of tenofovir disoproxil to HIV infected patients, tenofovir disoproxil is rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil with a meal to HIV infected patients resulted in mean (%CV) tenofovir Cmax, AUC, and Cmin values of 326 (36.6%) ng/ml, 3,324 (41.2%) ng h/ml and 64.4 (39.4%) ng/ml, respectively. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%. Administration of tenofovir disoproxil with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and Cmax by approximately 14%. Following the first dose of tenofovir disoproxil in fed patients, the median Cmax in serum ranged from 213 to 375 ng/ml. However, administration of tenofovir disoproxil with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution

Following intravenous administration the steady state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

Biotransformation

In vitro studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil at a concentration of 100 µmol/l had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. Based on these data, it is unlikely that clinically significant interactions involving tenofovir disoproxil and medicinal products metabolised by CYP450 would occur.

Elimination

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with

approximately 70 80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4).

Linearity / non-linearity

The pharmacokinetics of tenofovir was independent of tenofovir disoproxil dose over the dose range 75 to 600 mg and was not affected by repeated dosing at any dose level.

The Applicant's product is similar to the branded product Viread (Gilead Sciences Pty Ltd). It is identical in terms of qualitative and quantitative composition of the active substances (Tenofovir disoproxil) and is therefore expected to perform identically in vivo within the clinical setting. Reference is therefore made to the SmPC of the Reference product.

Toxicology

Non-clinical safety pharmacology studies reveal no special hazard for humans. Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5 fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40 fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

Genotoxicity studies revealed positive results in the in vitro mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an in vivo mouse bone marrow micronucleus assay.

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in peri postnatal toxicity studies at maternally toxic doses.

2.3.2. Ecotoxicity / environmental risk assessment

No full Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of tenofovir disoproxil manufactured by Zentiva is considered unlikely to result in any significant increase in the combined sales volumes for all tenofovir disoproxil containing products and the exposure of the environment to the active substance. Thus, the 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 tenofovir disoproxil phosphate to support the marketing authorisation application the applicant conducted one bioequivalence study with a 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. GCP inspections in relation to the conduct of clinical trial with protocol number TNI-P4-464 were requested and conducted at the clinical BA/BE site and the bioanalytical laboratory in Canada. In accordance with the final integrated inspection report, issued on 4 December 2015, the trial is considered to have been conducted at an acceptable level of compliance with GCP and, where applicable, with GLP and the trial data are considered to be acceptable for use in the evaluation procedure.

Exemption

This is a generic application, for only one strength; hence a bio-waiver is not applicable.

Clinical studies

To support the application, the applicant has submitted one 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	TNI-P4-464 (Sponsor Project No TEDIPL07234)	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 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; 245 mg single dose; oral	36	Healthy Subjects	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Study TNI-P4-464, study title: Single Dose Crossover Comparative Bioavailability Study of Tenofovir Disoproxil 245 mg Tablets in Healthy Male and Female volunteers /Fed state

Methods

Study design

This was a randomised, laboratory blinded, two-period, two-treatment, two-sequence, balanced, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Tenofovir disproxil 245 mg film coated tablets (test manufactured by Zentiva k.s.) and Viread 245 mg film coated tablets (MAH: Gilead Sciences Intl. Ltd. Ireland) in 36 healthy, adult male and female human subjects under fed conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

The study centre was Algorithme Pharma Inc. Quebec Canada

Based on the randomised schedule and following an overnight fast of at least 10 hours subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration.

The meal was comprised of approximately 240 mL of whole milk, 2 large eggs, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with approximately 4.5 g of butter and 2 strips of bacon. This meal was composed of 34 g of protein (136 calories), 71 g of carbohydrate (284 calories) and 57.5 g of fat (518 calories) for a total of 938 calories. The relative caloric content for each component corresponds to approximately 15%, 30% and 55% for the protein, the carbohydrate and the fat, respectively.

Thirty minutes after the start of the breakfast, a single dose of the assigned formulation was administered with approximately 240 ml of water at ambient temperature, starting at 08:00, to one subject per minute. Water was allowed ad libitum until 1 hour pre-dose and beginning 1 hour after drug administration.

Subjects fasted for at least 4 hours following drug administration, after which a standardized lunch was served. A supper and a light snack were also served at appropriate times thereafter, but not before 9 hours after dosing.

Subjects were confined to the clinical facility from at least 10 hours prior to dosing of the investigational product until after the 72-hour blood sample collection in each study period. The two periods were separated by a wash-out phase of at least 14 days.

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.

Test and reference products

Tenofovir disoproxil Zentiva 245 mg film-coated tablet manufactured by Zentiva k.s. (batch No. P02092014) has been compared to Viread 245 mg film-coated tablet manufactured by Gilead Sciences (Batch No: 13VR040D).

Table 2. Identity of Investigational Products

Drug Code:	**Test**	**Reference**
Formulation:	Tenofovir Disoproxil 245 mg film-coated tablet	Viread 245 mg film-coated tablet
Manufacturer:	Zentiva, k.s., Turkey	Gilead Sciences Intl. Ltd., Ireland
Marketing Authorization Holder:	N/AP	Gilead Sciences International Limited, Cambridge, CB21 6GT, United Kingdom
Batch No.:	P02092014	13VR040D
Manufacturing Date:	04.09.2014	N/AV
Expiry Date:	18.04.2015	03/2018
Measured Content:	102%	98%

Population studied

36 healthy adult male and female human subjects (11 male and 25 female) were enrolled as per the protocol whilst 35 subjects completed both study periods.

One (3%) subject was withdrawn from the study due to emesis within the restriction period; 35 (97%) subjects completed the study.

Subject 012 (19 years old, female) was withdrawn from the study on 26 October 2014 after dosing of Period 1 due to emesis within the restriction period; this subject experienced a gastrointestinal adverse event (vomiting of moderate intensity) that could have had an impact on her pharmacokinetic profile; she received only the Test.

Table 3. Subject disposition

Category	Overall
Subjects included, N	36
Subjects completing study, N (%)	35 (97)
Subjects who discontinued, N (%)	1 (3)
Subject withdrawn	1 (3)
Subject withdrawn for safety reasons (Investigator's decision)	0
Subject withdrew consent for personal reasons (not related to clinical events)	0
Subject withdrew consent for personal reasons (related to clinical events)	0

For post-dose samples, time deviations that were equal to or greater than 2 minutes were adjusted in the pharmacokinetic analysis to reflect actual sampling times. The other time deviations were considered to have a negligible impact on the assessment of bioequivalence and were not accounted for in the calculation of the pharmacokinetic parameters.

For the sample for which the exact collection time was inconclusive, the scheduled time was used in the statistical analysis without any adjustment.

The protocol deviations reported for the subjects included in the analysis were judged to have no significant impact on the bioequivalence assessment or subject's safety.

Main inclusion criteria:

Male and female volunteers, light-, non- or ex-smokers, of at least 18 years of age with a body mass index greater than or equal to 18.50 and below 30.00 kg/m2 were included in the study. Subjects were in good health as determined by a medical history, complete physical examination (including vital signs), and the usual clinical laboratory tests (general biochemistry, haematology, urinalysis) including negative Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C tests as well as negative urine drug screening of alcohol and drugs of abuse. A 12-lead Electrocardiogram (ECG) was performed and must have been without clinically significant abnormality. For female volunteers, a HCG beta serum pregnancy test must have been negative). Beside enzyme-modifying drugs that were not allowed for 28 days, subjects were instructed not to take any prescription medications used with the intention to treat a condition for 28 days prior to the first dosing and during the study, unless judged differently by the Principal Investigator or designee. Systemic contraceptives and hormone replacement therapy were permitted. Subjects were also instructed not to take any over-the-counter products for the 7 days prior to the first dosing and during the study. They were specifically reminded that this included cold preparations, acetylsalicylic acid, vitamins and natural products used for therapeutic benefits and antacid preparations. If vitamins were used as nutritional supplements in non-therapeutic doses (judged by the Principal Investigator or designee), they may have been accepted, but they must have been stopped at least 48 hours prior to the first dosing and during the study.

Analytical methods

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.

The experimental samples were assayed for tenofovir at the analytical facility of Algorithme Pharma using a validated HPLC method with MS/MS detection. The subject sample analysis was performed from 2014/11/17 to 2014/12/03, including re-assays and incurred samples. The lower limit of quantitation and upper limit of quantitation were 2.50 ng/ml and 800.00 ng/ml, respectively.

Pharmacokinetic variables

Pharmacokinetics parameters: Cmax, Tmax, AUC0-T, AUC0-∞, AUC0-T/∞, λZ and T1/2.

Bioequivalence criteria; The 90% confidence interval of the relative mean AUC t and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

The main absorption and disposition parameters were calculated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate area under the curve. The terminal phase estimation was based on maximizing the coefficient of determination. The pharmacokinetic parameters of this trial were Cmax, Tmax, AUC0-T, AUC0-∞, AUC0-T/∞, λZ and Thalf.

The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the Cmax, AUC0-T and AUC0-∞ was based on ln-transformed data; the Tmax was based on a non-parametric approach.

ANOVA model:

Fixed factors: sequence, period, treatment, subject (nested within sequence)

Criteria for Bioequivalence:

Statistical inference of tenofovir based on a bioequivalence approach using the following standards:

The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters Cmax and AUC0-T were all to be within the 80.00 to 125.00% bioequivalence range.

Safety: Descriptive statistics was performed.

Results

Table 4. Pharmacokinetic parameters for Tenofovir 245mg n=35 (non-transformed values)

Parameter (Units)	Test		Reference	
	Mean	(C.V. %)	Mean	(C.V. %)
C_{max} (ng/mL)	303.82	(23.2)	309.00	(28.8)
ln (C_{max})	5.6894	(4.2)	5.6955	(4.8)
T_{max} (hours)[a]	1.33	(58.9)	1.33	(62.3)
AUC_{0-T} (ng·h/mL)	3099.19	(21.8)	3147.85	(21.9)
ln (AUC_{0-T})	8.0177	(2.6)	8.0335	(2.5)
$AUC_{0-\infty}$ (ng·h/mL)	3310.91	(21.8)	3327.61	(22.0)
ln ($AUC_{0-\infty}$)	8.0830	(2.6)	8.0886	(2.5)
$AUC_{0-T/\infty}$ (%)	93.73	(3.5)	94.65	(1.7)
λ_Z ($hours^{-1}$)	0.0379	(20.0)	0.0382	(12.5)
T_{half} (hours)	19.00	(20.1)	18.40	(12.3)

a median

Table 5. Statistical analysis for Tenofovir 245mg n=35 (ln-transformed values)

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Test	Reference		Lower	Upper
C_{max}	16.6	295.23	297.29	99.31	92.90	106.16
AUC_{0-T}	6.9	3030.46	3081.07	98.36	95.67	101.12

a units are ng/mL for Cmax and ng·h/mL for AUC0-T

Safety data

A total of 36 subjects were randomized in the study, all of which received the Test (Tenofovir Disoproxil) and 35 (97%) of which received the Reference (Viread). A total of 18 adverse events were reported by 11 of the 36 (31%) subjects who participated in this study. Of these events, 11 occurred after administration of the Test and 7 occurred after administration of the Reference. None of the adverse events reported during the study were judged to be both unexpected and drug-related.

The incidence of AEs was similar for subjects dosed with the Test and Reference (22% vs. 14%, respectively). Drug-related AEs were reported with lower incidence (Test 17% and Reference 9%). The AEs were deemed mild (14/18, 78%) and moderate (4/18, 22%) in severity. No severe adverse events were observed during the study.

The AE reported with the highest incidence was vomiting, which was experienced by three (8%) subjects dosed with the Test and one (3%) subject dosed with the Reference. Nausea was experienced by two (6%) subjects dosed with the Test and one (3%) subject dosed with the Reference, and venipuncture site bruise was experienced by two (6%) subjects following administration of only the Reference.

No serious adverse events (SAE) and no deaths were reported for any of the subjects enrolled in this study. No subject was withdrawn by the Investigator for safety reasons. All the abnormal clinical laboratory values were marginally higher or lower than their normal ranges and none were considered clinically significant by the Investigator. Generally, the subjects presented normal findings during physical examinations in both treatment groups and there were no clinically significant abnormalities in vital signs for subjects in this study.

Conclusions

Based on the presented bioequivalence study Tenofovir 245mg film coated tablets of Zentiva k.s. Czech Republicis considered bioequivalent with Viread (Tenofovir) 245mg film coated tablets manufactured by Gilead Sciences Intl. Ltd. Ireland MA holder: Gilead Sciences UK.

2.4.3. Pharmacodynamics

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

2.4.4. Additional data

No additional data is available. Dissolution studies have been presented to support the dosage form and these are assessed in the quality section.

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 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters AUC0-t and Cmax were within 80-125% acceptance range for Tenofovir. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr **).

The two treatments were well tolerated by the subjects (in both periods) 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 Tenofovir 245 mg film coated tablets of Zentiva k.s. Czech Republic is considered bioequivalent with Viread (Tenofovir) 245 mg film coated tablets manufactured by Gilead Sciences Intl. Ltd. Ireland MA holder: Gilead Sciences UK.

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

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Renal toxicity	Sections 4.4, 4.8, 5.1 and 5.3 of SPC contain transparent warnings on this risk Sections 2 and 4 of PL advise patients on this risk.	Educational brochure for physicians

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Bone events due to proximal renal tubulopathy/loss of bone mineral density	Sections 4.4, 4.8, 5.1 and 5.3 of SPC contain transparent warnings on this risk Sections 2 and 4 of PL advise patients on this risk.	N/A
Important identified risks: Post-treatment hepatic flares in HBV monoinfected and HIV/ HBV coinfected patients	Sections 4.2, 4.4 and 4.8 of SPC contain transparent warnings on this risk. Sections 2, 3 and 4 of PL advise patients on this risk.	N/A
Important identified risks: Interaction with didanosine	Sections 4.4, 4. 5 and 4.8 of SPC contain transparent warnings on this risk. Sections 2 of PL advise patients on this risk.	N/A
Important identified risks: Pancreatitis	Sections 4.4, 4.5 and 4.8 of SPC contain transparent warnings on this risk. Section 4 of PL advises patients on this risk.	N/A
Important potential risks: Development of resistance during long-term exposure in HBV infected patients	Sections 4.1 and 5.1 of SPC contain transparent warnings on this risk.	N/A
Missing information: Safety in children (including long-term safety)	Sections 4.2, 4.4 and 5.2 of SPC contain transparent warnings on this risk. Section 2 advises patients on this risk.	Educational brochure for physicians
Missing information: Safety in elderly patients	Sections 4.2, 4.4, 4.8 and 5.2 of SPC contain transparent warnings on this risk. Section 2 of PL advises patients on this risk.	N/A
Missing information: Safety in pregnancy	Section 4.6 of SPC contains transparent warnings on this risk.	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 2of PL advises patients on this risk.	
Missing information: Safety in lactation	Section 4.6 of SPC contains transparent warnings on this risk. Section 2of PL advises patients on this risk.	N/A
Missing information: Safety in patients with renal impairment	Sections 4.2, 4.4 and 5.2 of SPC contain transparent warnings on this risk. Section 2of PL advises patients on this risk.	Educational brochure for physicians
Missing information: Safety in patients with decompensated liver disease and CPT score >9 (including long-term safety)	Sections 4.4 and 4.8 of SPC contain transparent warnings on this risk. Sections 2, 3 and 4 of PL advise patients on this risk.	N/A
Missing information: Safety in liver transplant recipients infected with HBV	Sections 4.4 of SPC contain transparent warnings on this risk.	N/A

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable. The Applicant is in dialogue with the Antiretroviral Pregnancy Registry (APR) and once agreements have been concluded, the participation to the APR will be reflected in the RMP.

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 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.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of tenofovir disoproxil, 245 mg film coated tablet. The reference product, Viread, is indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected adults and adolescents as well as indicated for the treatment of chronic hepatitis B in adults and adolescents (see sections 4.4, 4.8 and 5.1). 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 two-period, two-treatment, two-sequence, balanced, single dose, crossover comparative bioequivalence study. 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 times as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

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

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

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

4. Recommendation

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

HIV 1 infection

Tenofovir disoproxil Zentiva is indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected adults.

In adults, the demonstration of the benefit of tenofovir disoproxil in HIV 1 infection is based on results of one

study in treatment naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which tenofovir disoproxil was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml).

Tenofovir disoproxil Zentiva is also indicated for the treatment of HIV 1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

The choice of Tenofovir disoproxil Zentiva to treat antiretroviral experienced patients with HIV 1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Hepatitis B infection

Tenofovir disoproxil Zentiva is indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).
- evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1).
- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

Tenofovir disoproxil Zentiva is indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with:

- compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis (see sections 4.4, 4.8 and 5.1).

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

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

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV adolescent educational brochure
- HBV adolescent educational brochure

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

- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil-containing products such as Tenofovir disoproxil Zentiva
- That Tenofovir disoproxil Zentiva should only be used in patients with impaired renal function if the potential benefits of treatment are considered to outweigh the potential risks
- The importance of dose interval adjustment using Tenofovir disoproxil Zentiva 245 mg film-coated tablets in adult patients with creatinine clearance of 30-49 ml/min
- That in adults with severe renal impairment (creatinine clearance <30 ml/min) and hemodialysis patients where adequate dose adjustments cannot be applied with this product due to lack of alternative tablet strengths, the use in this group of patients is not recommended. If no alternative treatment is available, it is possible to use Tenofovir disoproxil Zentiva 245 mg film-coated tablets in extended dosing intervals.
- Daily dose adjustment using other suitable formulation of tenofovir disoproxil 33 mg/g granules (check for availability) is recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min). For patients unable to use the granules formulation and with no alternative treatment available, prolonged dose intervals using Tenofovir disoproxil Zentiva 245 mg film-coated tablets may be used
- That use of Tenofovir disoproxil Zentiva should be avoided with concomitant or recent use of nephrotoxic medicinal products. If 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 Tenofovir disoproxil Zentiva therapy
- The importance of regular monitoring of renal function during Tenofovir disoproxil Zentiva therapy

- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function should be re-evaluated within one week. If creatinine clearance is confirmed as < 50 ml/min or serum phosphate decreases to < 1.0 mg/dl then consideration should be given to interrupting Tenofovir disoproxil Zentiva therapy. Interrupting treatment with Tenofovir disoproxil Zentiva should also be considered in case of progressive decline of renal function when no other cause has been identified.
- Instructions on the use of the creatinine clearance slide ruler

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

- That a multidisciplinary approach is recommended for the management of adolescent patients
- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil-containing products such as Tenofovir disoproxil Zentiva
- That Tenofovir disoproxil Zentiva is not recommended for use in paediatric patients with renal impairment
- That use of Tenofovir disoproxil Zentiva should be avoided with concomitant or recent use of nephrotoxic medicinal products. If 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 Tenofovir disoproxil Zentiva therapy
- The importance of regular monitoring of renal function during Tenofovir disoproxil Zentiva therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is confirmed to be < 1.5 mg/dl (0.48 mmol/l) in any adolescent patient receiving tenofovir disoproxil, renal function should be re-evaluated within one week.
- If renal abnormalities are detected or suspected then consultation with a nephrologist should be obtained to consider interruption of Tenofovir disoproxil Zentiva treatment. Interrupting treatment with Tenofovir disoproxil Zentiva should also be considered in case of progressive decline of renal function when no other cause has been identified.
- That Tenofovir disoproxil Zentiva may cause a reduction in BMD and the effects of Tenofovir disoproxil Zentiva associated changes in BMD on long term bone health and future fracture risk are currently unknown in adolescent patients
- That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained