18 May 2017
EMA/454542/2017

Assessment report

Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva

International non-proprietary name: efavirenz / emtricitabine / tenofovir disoproxil

Procedure No. EMEA/H/C/004250/0000

Note

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

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Administrative information

Name of the medicinal product:	Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva
Applicant:	Zentiva k.s. U kabelovny 130 Dolni Mecholupy 102 37 Prague 10 CZECH REPUBLIC
Active substance:	efavirenz / emtricitabine / tenofovir disoproxil phosphate
International non-proprietary name/Common name:	efavirenz / emtricitabine / tenofovir disoproxil
Pharmaco-therapeutic group (ATC Code):	Antiviral for systemic use, antivirals for treatment of HIV infections, combinations (J05AR06)
Therapeutic indication(s):	Treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva prior to initiation of their first antiretroviral treatment regimen.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	600 mg / 200 mg / 245 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	30 tablets

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List of abbreviations

3TC lamivudine
ABC abacavir
AEs adverse events
AIDS acquired immunodeficiency syndrome
AOR adjusted odds ratio
ART active antiretroviral therapy
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 area under the plasma concentration-time curve from zero to the last measurable concentration
AUC0-∞ area under the plasma concentration-time curve from zero to infinity
AZT zidovudine
bis[POC]PMPA tenofovir disoproxil fumarate
BE bioequivalence
BMD bone mineral density
cART combination antiretroviral therapy
CDC Centers for Disease Control and Prevention
CI confidence interval
Cmax maximum plasma concentration
Cmin minimal plasma concentration
CYP cytochrome P450
DART Development of AntiRetroviral Therapy in Africa
DDI didanosine
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
GA gestational age
GCP good clinical practise
GFR glomerular filtration rate
h hour
HAART highly active antiretroviral therapy
HBV hepatitis B virus
HDL high-density lipoprotein
HDRD HIV Drug Resistance Database
HIV human immunodeficiency virus
HPLC high performance liquid chromatography

CHB chronic hepatitis B
IQR interquartile range
ITT the intent-to-treat
LDL low-density lipoprotein
LC/MS/MS liquid chromatography-tandem mass spectrometry
LPV lopinavir
NNRTI nonnucleoside reverse-transcriptase inhibitor
NRTI nucleoside reverse transcriptase inhibitor
PBMC peripheral blood mononuclear cells
PD pharmacodynamic(s)
PK pharmacokinetic(s)
PMPA 9-(2-phosphonomethoxypropyl)adenine
p.o. peroral
PTD preterm delivery
PYFU person years follow up
r ritonavir
RNA ribonucleic acid
RPV rilpivirine
RR rate ratio
SAEs serious adverse events
SB stillbirths
SPC 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 tenofovir
TFV-DP tenofovir diphosphate
Tmax time to maximum plasma concentration
TP triphosphate
VAT visceral adipose tissue
VL viral load
vs. versus
ZDV zidovudine
PAH Pulmonary arterial hypertension
AE Adverse event
BMPR2 Bone morphogenetic protein receptor type 2
BNP Brain natriuretic peptide
BPH Benign prostatic hyperplasia
ED Erectile dysfunction
IIEF International Index of Erectile Function
ALK1 Activin receptor-like kinase type 1
PVOD Pulmonary veno-occlusive disease
PCH Pulmonary capillary hemangiomatosis
CTEPH Chronic thromboembolic pulmonary hypertension

CO Cardiac output.
PDE-5 Phosphodiesterase type 5 inhibitors
WHO World Health Organization
q.d. once-daily
t.i.d 3-times-daily
IEC Independent Ethics committee
GLP Good Laboratory Practice
L Liters
CrCl Creatinine clearance
mL/min Milliliter per minute
mL milliliters
mg milligrams
BP Blood pressure
g/kg grams per kilograms
cGMP Cyclic guanosine monophosphate
NO Nitric oxide
NAION Non-arteritic anterior ischaemic optic neuropathy
sGC soluble Guanylate Cyclase
NP Natriuretic peptides
GTP Guanosine triphosphate;
6MWT 6-minute walk test
MPAP Mean pulmonary arterial hypertension
MedDRA Medical Dictionary for Regulatory Activities
CI Confidence interval
CI Cardiac index
CW Clinical worsening
PASP Pulmonary artery systolic pressure
PBO Placebo-controlled trial
PVR Pulmonary vascular resistance
PHIRST Pulmonary Arterial
NYHA New York Heart Association
RVSP Right ventricle systolic pressure
mPAP mean Pulmonary arterial pressure
MC Multicenter
QoL Quality of life
SVR Systemic vascular resistance
NR Not reported
TSQM Treatment satisfaction questionnaire for medication
AP Applicant's Part of ASMF
API Active Pharmaceutical Ingredient
AR Assessment Report
ASM Active Substance Manufacturer
ASMF Active Substance Master File = Drug Master File
CoA Certificate of Analysis
DMF Drug Master File = Active Substance Master File

DP Decentralised (Application) Procedure
DSC Differential Scanning Calorimetry
FPM Finish Product Manufacturer
HDPE High Density Polyethylene
HPLC High Pressure Liquid Chromatography
INN International Non-proprietary Name
IPC In-process control test
IR Infrared
LOA Letter of Access
LOD Limit of Detection
LOQ (1) Limit of Quantification, (2) List of Questions
MA Marketing Authorisation
MAH Marketing Authorisation holder
MS Mass Spectrometry
ND Not detected
NMR Nuclear Magnetic Resonance
NMT Not more than
OOS Out of Specifications
PDE Permitted Daily Exposure
PE Polyethylene
Ph.Eur. European Pharmacopoeia
PIL Patient Information Leaflet
PP Polypropylene
PVC Poly vinyl chloride
PVDC Polyvinylidene chloride
QOS Quality Overall Summary
QP Qualified Person
Rf Retention factor
RH Relative Humidity
RMS Reference Member State
RRT Relative retention time
RSD Relative standard deviation
Rt Retention time
TSE Transmissible spongiform encephalopathy
UV Ultraviolet
XRPD
X-ray powder diffraction

Not all abbreviations might be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva k.s. submitted on 8 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Efavirenz/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 25 June 2015.

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, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 10b of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva prior to initiation of their first antiretroviral treatment regimen.

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 Atripla instead of non-clinical and clinical unless justified otherwise.

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: Atripla, 600/200/245 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Science Ltd., UK
- Date of authorisation: 13.12.2007
- Marketing authorisation granted by:
    - Community
- Community Marketing authorisation number: EU/1/07/430

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

- Product name, strength, pharmaceutical form: Atripla, 600/200/245 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Science Ltd., UK
- Date of authorisation: 13.12.2007
- Marketing authorisation granted by:
    - Community
- Community Marketing authorisation number: EU/1/07/430

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: Atripla, 600/200/245 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb and Gilead Science Ltd., UK
- Date of authorisation: 13.12.2007
- Marketing authorisation granted by:
    - Community
- Community Marketing authorisation number: EU/1/07/430

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.

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: Radka Montoniová

- The application was received by the EMA on 8 June 2016.
- The procedure started on 14 July 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 29 September 2016.
- PRAC Rapporteur's first Assessment Report was circulated to all CHMP members on 14 October 2016.
- During the meeting on 10 November 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 January 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 February 2017.
- During the PRAC meeting on 9 March 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.

- During the CHMP meeting on 23 March 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 18 April 2017.
- During the meeting on 18 May 2017, 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 Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva.

2. Scientific discussion

2.1. Introduction

Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva 600-200-245 mg film-coated tablets were developed as a generic equivalent to the innovator´s product Atripla 600/200/245 mg film-coated tablets. The innovator´s product was authorized in EU on 13.12.2007 as a fixed dose combination for treatment of HIV-1 infected adults aged 18 years and over. The marketing authorization holder is Bristol-Myers Squibb and Gilead Science Ltd., UK.

Efavirenz/Emtricitabine/Tenofovir is a well-known, well-described antiviral combination for the treatment of HIV. The pharmacodynamics and pharmacokinetics are currently well described and a number of PK data in less frequently studied compartments and in special populations have been published recently.

Efavirenz binds directly to the HIV-1 reverse transcriptase resulting in allosteric inhibition of DNA- and RNA- dependent DNA polymerase.

Emtricitabine is a synthetic nucleoside analogue of cytidine and undergoes intracellular phosphorylation to form the active metabolite, emtricitabine 5´-triphosphate, which competes with deoxycytidine 5´-triphosphate and becomes incorporated into HIV-1 DNA, resulting in viral DNA chain termination and the inhibition of HIV-1 reverse transcriptase activity.

Tenofovir is a nucleotide analogue of adenosine monophosphate. Its active metabolite, tenofovir diphosphate, competes with natural deoxyadenosine triphosphate for the active binding site on the HIV-induced reverse transcriptase (HIV DNA polymerase). Incorporation of tenofovir diphosphate into viral DNA results in chain termination, since tenofovir diphosphate lacks the hydroxyl group in the 3´-position, which acts as the point of attachment for the next deoxyribonucleoside triphosphate. Hence, reverse transcription, the key step in HIV proliferation, is inhibited.

The indication applied is for the use of Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva in the treatment of Human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva prior to initiation of their first antiretroviral treatment regimen.

2.2. Quality aspects

2.2.1. Introduction

Efavirenz / Emtricitabine / Tenofovir disoproxil Zentiva is presented as film coated tablet containing, in a fixed-dose combination, 600 mg of efavirenz, 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 core tablets are cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, sodium laurilsulfate, magnesium stearate, talc and colloidal anhydrous silica. The film coating is composed of polyvinyl alcohol, titanium dioxide (E171), macrogol, talc and iron oxide red (E172), yellow (E172) and black (E172).

The product is available in high density polyethylene (HDPE) bottles with polypropylene child-resistant screw caps, induction heat sealing (with aluminium foil) and silica gel desiccants (in a HDPE canister), as

described in section 6.5 of the SmPC.

2.2.2. Active substance

Efavirenz

General information

The chemical name of efavirenz is (4S)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-H-3,1-benzoxazin-2-one corresponding to the molecular formula $C_{14}H_9ClF_3NO_2$. It has a relative molecular mass of 315.68 g/mol and the following structure:

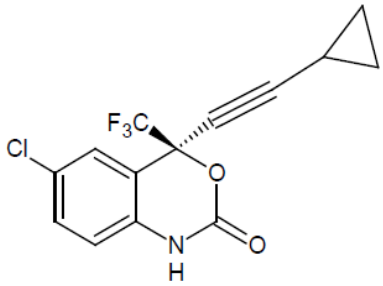

Figure 1. Structure of efavirenz.

The active substance is supplied by two suppliers.

Both manufactures sufficiently elucidated the structure of the active substance (AS) by a combination of IR, UV, 1H-NMR, 13C-NMR, XRPD and mass spectroscopy (MS). Additionally specific optical rotation was performed by one supplier, whereas the other performed elemental analysis (C, H, N) and DSC.

Efavirenz appears as a white to slightly pink non-hygroscopic crystalline powder. It is soluble in methanol, practically insoluble in water and insoluble in pH range 1.2-8.0. Its pKa was found to be around 10.

It contains one chiral centre resulting in two enantiomers. S-enantiomer is the desired one and the R-enantiomer is controlled in the specification as an impurity.

Efavirenz exhibits polymorphism. The same polymorphic form is manufactured and was confirmed by XRPD and controlled by DSC.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance by both suppliers has been provided in the restricted part of the two ASMFs and it was considered satisfactory.

Efavirenz is synthesized in three main chemical steps followed by milling, drying, micronizing, sifting and packing. The starting materials are well-defined with acceptable specifications.

The second supplier manufactures efavirenz in four main chemical steps. The key intermediate aminocarbinol is manufactured in three stages and then it is further converted to efavirenz in one step. The choice of the starting materials has been justified and they are controlled by appropriate specification.

Reagents and intermediates in both manufacturing processes are also controlled by acceptable specifications. Adequate in-process controls (IPC) 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. It has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance.

Efavirenz is packaged in double LDPE bags placed in a HDPE drum. For the primary packaging material specifications including IR identification have been provided. The materials comply with the relevant European requirements.

Specification

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

The potential impurities and possible genotoxic impurities which are possible from the defined starting materials are controlled in the final active substance by validated test methods. 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 active substance. 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 results from six production scale batches of the active substance were provided by one supplier. Batch analysis results from 18 production batch of efavirenz was provided by the other supplier. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three production scale batches of active substance from one supplier stored in the intended commercial packaging for up to 48 months under long term conditions (25±2 °C / 60±5% RH), for up to 6 months under accelerated conditions (40±2 °C / 75±5% RH) and also intermediate studies (30±2 °C; 75±5% RH) according to the ICH guidelines were provided. Proposed retest period of 5 years and storage conditions preserving in tight, light resistant container, stored at 25 °C with excursions permitted between 15 °C and 30 °C are accepted.

Stability data on three production scale batches from the second supplier stored in the intended commercial packaging for up to 60 months under long term conditions (25±2 °C / 60±5% RH) and for up to 6 months under accelerated conditions (40±2 °C / 75±5% RH) according to the ICH guidelines were also provided. The Proposed retest period 5 years and storage conditions not exceeding 25 °C, protected from light, in well closed container are accepted.

Samples were tested for description, identification, polymorphic form, limit of Efavirenz enantiomer, water content, assay, related substances and specific optical rotation (tested by). 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 (long term and accelerated conditions).

Photostability testing following the ICH guideline Q1B was performed on one batch by both manufacturers. The active substance is not sensitive to light.

Stress testing (to basic and acidic hydrolysis, oxidation, and thermal and photo degradation) was also performed on one batch by each manufacturer. Varying degrees of degradation were observed under the conditions tested, which were more prominent under base hydrolysis. 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.

Emtricitabine

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-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:

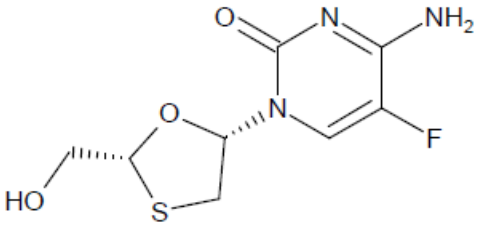

Figure 2. Structure of emtricitabine.

The active substance is supplied by two suppliers.

The structure of the active substance was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, UV spectroscopy, IR spectroscopy, mass spectrometry. In addition specific optical rotation was performed by the first supplier whereas the secondperformed identification by HPLC, and X-Ray Powder Diffraction methods as well.

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 between 2.15 and 2.27 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 2R,5S is commercially produced. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation in the intermediate product and in the final active substance.

Emtricitabine exhibits polymorphism. The same crystalline is consistently manufactured by both suppliers, and is characterised and controlled by XRD method (by the fisrt manufacturer) and DSC method (by the second manufacturer) at release and during stability studies.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance by both suppliers has been provided in the restricted part of the two ASMFs and it was considered satisfactory.

The starting materials used by the two manufacturers are well-defined with acceptable specifications.

The synthesis of the key intermediate is performed using slightly different solvents in the chemical reactions by the two ASMF Holders.

The synthetic scheme of the final active substance from the key intermediate is the same for both active substance manufacturers. It is synthesized in three main chemical steps. In addition, the first supplier has

a milling step before packaging. The key intermediate, solvents and reagents are described and are controlled by appropriate specifications. A satisfactory brief description of the micronisation step performed has also been provided.

The synthetic route was described in sufficient detail. 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. They are controlled in the final active substance by validated test methods and the results from commercial scale active substance batches were summarised. As the results were either below detection limit or not detected, it has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance.

Emtricitabine is packed by both suppliers in two layers of LDPE bags placed in an HDPE container. 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 specifications 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, Specific Optical Rotation), polymorphism (XRD), specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), heavy metals, chloride content (potentiometry), related substances (HPLC, TLC), enatiomeric purity (HPLC), assay (HPLC) and residual solvents (GC). Some of the tests are performed depending on the source of the active substance

The potential impurities and possible genotoxic impurities which are possible from the defined starting material are controlled in the final active substance by validated test methods and the results from three commercial scale emtricitabine batches (first supplier) and several batches, including 10 commercial scale batches from the other supplier 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 active substance. 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 results from three commercial scale batches from the first supplier and from 13 batches (including 10 commercial scale) from the second supplier were 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 first the manufacturer stored in the intended commercial packaging for up to 60 months under long term conditions (25±2 °C / 60±5 % RH) was provided. Three of the above batches were stored for up to 6 months under accelerated conditions (40±2 °C / 75±5 % RH) according to the ICH guidelines.

The second manufacturer has also provided stability data from fifteen pilot and commercial scale batches stored in the intended commercial packaging for up to 60 months under long term conditions (25±2 °C /

60±5 % RH) and for up to 6 months under accelerated conditions (40±2 °C / 75±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 by each manufacturer on one commercial scale batch. The results showed that the active substance is not sensitive to light.

Stress testing (thermal, light, hydrolysis, acidic, basic, oxidative and reductive conditions) was also performed on one commercial scale batch by each manufacturer. Samples were tested for description, identification, specific optical rotation (only performed by the first supplier), 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 7:

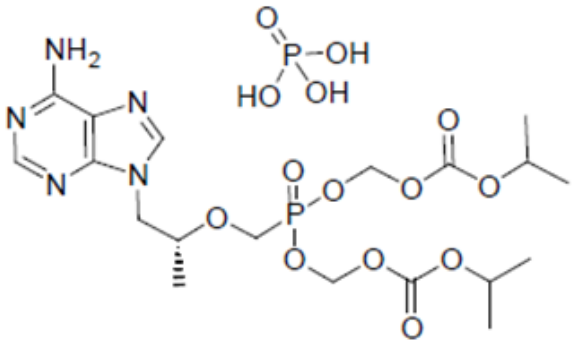

Figure 3. Structure of tenofovir disoproxil phosphate.

The molecular structure of Tenofovir disoproxil phosphate has been confirmed by use of spectroscopic methods as IR, MS, NMR (^{13}C and ^{1}H), and UV.

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 that a wet granulation process is used to manufacture the 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 (visual), identity (IR), water content (KF), heavy metals (ICP-AES), phosphoric acid assay (titration), assay (titration), related compounds (HPLC), 9-propenyladenine (HPLC), fumaric acid (HPLC), enantiomeric purity (chiral HPLC), residual solvents (GC), and microbiological purity (Ph. Eur.) particle size (Ph. Eur.).

The mono-POC PMPA impurity present at higher than the qualification threshold according to ICH Q3A is a known metabolite and thus considered to be qualified. Other impurities are adequately controlled by the specifications. There are no controls for polymorphic form as the produced crystalline form is the only one 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 °C) and for up to 6 months under accelerated conditions (25±2 °C/ 60±5 % RH) according to the ICH guidelines were provided. Samples were tested for 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 production scale batch. The active substance is not photosensitive but is slightly sensitive to heat and extremely sensitive to combination of 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 supplier 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 pink, 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 600 mg of Efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (phosphate), which would be bioequivalent to the reference product Atripla 600mg/200mg/245mg film-coated tablets.

The reference product was characterised with respect to qualitative composition, physico-chemical characterisation and dissolution behaviour. The reference medicinal product contains tenofovir disoproxil as a fumarate salt, whereas the phosphate salt of tenofovir disoproxil is used in the Zentiva generic formulation. This is acceptable since both salts result in exposure to the same active metabolite, they are salts of the same prodrug and they have a very similar impurity profile. Phosphate salt is a frequently used salt in pharmaceutical applications which is not expected to cause any toxic effects. Furthermore according to the performed bioequivalence study, both molecules have the same bioavailability after oral administration.

The qualitative composition was determined based on information from the literature and from development formulations trials considering the different properties of the raw materials and finished product characteristics. The qualitative composition of the generic product is comparable to that of reference product except for the presence of talc and colloidal anhydrous silica, only in the generic product. Talc is used as glidant to improve the flowability of Emtricitabine+Tenofovir Disoproxil layer; colloidal anhydrous silica, was chosen as the anti-tacking agent to eliminate tenofovir disoproxil phosphate's tendency of sticking on metal surfaces. Sodium laurilsulfate (SLS) was used as surfactant in order to facilitate the dissolution of efavirenz which has low water solubility. It is known from the literature that tenofovir disoproxil is incompatible with sodium laurilsulfate. Thus, the reference product is designed as bilayer tablet in order to minimise the physical contact between SLS and tenofovir disoproxil. The same approach was adopted for the dosage form design of the Zentiva generic product. Excipients used are well known and are commonly used for this type of medicinal product; they are of Ph.Eur. quality except Opadry II white which is of in-house quality. The colorants used in the formulation of finished product meet the requirement of the EC Regulation No. 231/2012. Based on the presented information, efavirenz, 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 accelerated stability studies.

Based on literature information, emtricitabine is a Class I (high solubility, high permeability), tenofovir disoproxil phosphate is a Class III (high solubility, low permeability) and efavirenz is a Class II (low solubility, high permeability) according to the Biopharmaceutics Classification system (BCS). Solubility of emtricitabine and tenofovir disoproxil phosphate are quite high and independent of pH; whereas efavirenz shows pH dependent solubility. Amounts of SLS to achieve sink conditions decrease inversely with pH. In

order to select the most suitable dissolution conditions, the solubility and the influence of pH on the solubility of the three active substances were determined. Individual solubility of active substances in purified water, 0.1N HCl and acetate buffers of pH 4.5 and 6.8 with and without surfactant were evaluated. The lowest amount of surfactant to be used to dissolve it in the dissolution media was determined, Considering SLS and phosphate interactions, acetate buffers were preferred instead of phosphate buffers for pHs 4.5 and 6.8. Dissolution behaviour of efavirenz was the limiting factor to determine the SLS amount in the media and it was observed that SLS did not affect the dissolved amounts of emtricitabine and tenofovir disoproxil. It was also confirmed that, with the increase of pH, the amount of SLS to achieve complete dissolution decreased. Based on the results of solubility and dissolution method development studies, the proposed dissolution method (paddle apparatus, 100 rpm, 1000 ml, 2% SLS in water) is considered sufficiently justified. The discriminatory power of the method was adequately demonstrated with regard to the efavirenz particle size, changes to the composition of the emtricitabine tenofovir layer and tablet hardness.

It was further confirmed that the Opadry coating material, a polyvinyl alcohol (PVA) based solid preparation, for tablet coating, has no effect on the dissolution behaviour of the tablets.

The impurity profiles of Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva and Atripla were determined using an HPLC method. The impurity profiles can be considered essentially similar based on the submitted results.

The bioequivalence of the generic vs the reference product was demonstrated by bioequivalence study ZNV-PO-673. Comparison of dissolution profiles of four pilot batches of the test drug product (including the biobatch) showed that all three active substances release was more than 85 % within 15 minutes in all tested media.

Since the drug product contained relatively high contents of active substances which had poor flowability, low bulk density and consequently were weak in compressibility direct compression method was not tried. Additionally, efavirenz and tenofovir disoproxil phosphate had the tendency to stick on metal surfaces which had to be eliminated via granulation techniques. It is also known from the literature and from the basic patent of Atripla that the original product is a bi-layer tablet. For Efavirenz/Emtricitabine/Tenofovir Disoproxil Zentiva the same approach was followed. Both the manufacturing method for emtricitabine/tenofovir layer (dry granulation by roller compaction) and that for efavirenz layer (wet granulation by high-shear granulation) are widely used processes of granulation in the pharmaceutical industry and are conducted to improve flowability and density of powder mixture, uniformity of contents and compressibility.

The primary packaging of Efavirenz/Emtricitabine/Tenofovir Disoproxil Zentiva 600/200/245 mg film coated tablets was selected as HDPE bottles with child resistant polypropylene (PP) screw caps with induction heat sealing (with aluminium foil). Three grams of silica gel 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 of bilayer tablets comprises the following main steps:

1. Preparation of the efavirenz layer by weighing, pre-mixing, wet granulation (high shear granulation), drying, sifting (oscillating mill), blending, lubrication (final blending).
2. Preparation of the emtricitabine / tenofovir disoproxil layer by weighing, sieving, blending, dry granulation (roller compaction), sifting (oscillating mill), blending, lubrication (final blending).

3. Compression of bilayer tablets
4. Film coating of tablets
5. Packaging

The manufacturing process follows the conventional approach for solid dosage forms, employing widely used, non-specialized manufacturing equipment, consistent with that available within the proposed manufacturer's facilities. The manufacturing process is considered a standard process and it has been described satisfactorily.

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 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.

Holding times have been specified for final blend, core tablets and film coated tablets.

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

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 efavirenz, emtricitabine and tenofovir disoproxil (HPLC, TLC), identification of colourants (chemical), identification of phosphoric acid (HPLC), disintegration (Ph. Eur.), water content (Ph. Eur.), hardness (Ph. Eur.), average mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution (HPLC), assay of efavirenz, emtricitabine and tenofovir disoproxil (HPLC), related substances of efavirenz, emtricitabine and tenofovir disoproxil (HPLC) and microbial purity (Ph. Eur.).

The proposed specification is acceptable and provides an adequate control of the product quality. The analytical methods used have been adequately described and validated. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data of four commercial scale batches used for process validation were presented. All batches are representative of the commercial formula and process and the results show that the finished product meets the proposed specification limits.

Stability of the product

Stability data of four commercial scale batches used for process validation stored under long term conditions for up to 18 months (25 °C / 60% RH), for up to 12 months under intermediate conditions (30 °C / 65% RH) and up to 18 months under 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. Stability commitment to conduct stability studies with the first three commercial batches of Efavirenz/ Emtricitabine/Tenofovir Disoproxil film coated tablet was provided and this is acceptable.

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.

Stability data of in-use stability testing has been provided demonstrating that the product remains stable for 30 days following first opening of the container, when stored at laboratory temperature, exposed to daylight. The product does not require any special temperature storage conditions. In-use shelf-life 30 days was established.

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 acidic, basic, oxidative conditions, elevated temperature, and 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. Recommendations for future quality development

None.

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.

2.3.2. Ecotoxicity/environmental risk assessment

No full Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Efavirenz-Emtricitabine-Tenofovir disoproxil manufactured by Zentiva k.s. is considered unlikely to result in any significant increase in the combined sales volumes for Efavirenz-Emtricitabine-Tenofovir disoproxil containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on the non-clinical aspects

Based on the data provided, the active substances efavirenz, emtricitabine and tenofovir disoproxil as well as the drug product comply with the International Council for Harmonisation (ICH) requirements for the quality concerning the impurities and residual solvents. There are no safety risks associated with the impurities, with respect to the use of the drug substance and the finalised drug product.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablet containing efavirenz / emtricitabine / tenofovir disoproxil. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

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

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) in their current version, are of particular relevance.

GCP

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

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

Exemption

Not applicable.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study, Study ZN-P0-673.

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	ZNV-P0-673	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 efavirenz/emtricitabine/tenofovir after a single oral dose administration under fasting conditions.	Crossover; Fasting State	Two tablet formulations; Efavirenz+Emtricitabine+Tenofovir Disoproxil 600/200/245 mg single dose; oral	50	Healthy Subjects	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Study ZN-P0-673: Stud Title: Study ZNV-P0-673: Single Dose Crossover Comparative Bioavailability Study Of Efavirenz+Emtricitabine+Tenofovir Disoproxil (Phosphate) 600/200/245 mg, Film-Coated Tablets In Healthy Male And Female Volunteers

Methods

Study design

The study was a single centre, randomized, single dose, laboratory-blinded, 2-period, 2 sequence, crossover design in healthy male and postmenopausal or surgically sterile female subjects. The following investigational products were to be administered under fasting conditions:

Test: 1 x Efavirenz+Emtricitabine+Tenofovir Disoproxil (phosphate) 600/200/245 mg film-coated tablet

Reference: 1 x Atripla® 600/200/245 mg (Efavirenz/Emtricitabine/Tenofovir Disoproxil (fumarate)) film-coated tablet

The investigational products were administered: group A (subjects 001-025) on 2015/11/07 for period 1 and on 2015/12/12 for period 2, and group B (subjects 026-050) on 2015/11/14 for period 1 and on 2015/12/19 for period 2.

Test and reference products

Drug Code:	Test	Reference
Formulation:	Efavirenz+Emtricitabine+Tenofovir Disoproxil (phosphate) 600/200/245 mg film-coated tablet	Atripla® (efavirenz+emtricitabine+tenofovir disoproxil (fumarate)) 600/200/245 mg film-coated tablet
Manufacturer:	ZENTİVA k.s., Turkey	Bristol-Myers Squibb and Gilead Sciences Limited, Ireland
Marketing Authorization Holder:	N/AP	Bristol-Myers Squibb and Gilead Sciences Limited, Ireland
Batch No.:	P01092015	12AT096D
Manufacturing Date:	04/09/2015	12/2012
Expiry Date:	03/03/2016	11/2016
Measured Content:		
Efavirenz	607 mg/tablet	589 mg/tablet
Emtricitabine	195 mg/tablet	202 mg/tablet
Tenofovir Disoproxil	240.09 mg/tablet	247.07 mg/tablet

Test product : Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva 600/200/245 film-coated tablets manufactured by Zentiva k.s. (batch No. P01092015, manufacturing date: 04/09/2015, exp. date: 03/03/2016)
Reference product: Atripla 600/200/245film-coated tablets manufactured by Bristol-Meers Squibb and Gilead Science Limited, Ireland (Batch No:12AT096D, exp. date 11/2016).
The assay content of the test product does not differ more than 5% from reference product Atripla for all drug substances.

Population studied

Subjects were male or postmenopausal or surgically sterile female, at least 18 years of age but not older than 55 years. The main inclusion criteria were:

- light-, non- or ex-smokers
- body mass index (BMI) ≥18.50 kg/m2 and <30.00 kg/m2
- no clinically significant abnormality found in the 12-lead ECG performed at study entry negative pregnancy test for female subjects
- healthy according to medical history, complete physical examination (including vital signs) and laboratory tests (general biochemistry, haematology and urinalysis)
- menopausal status was confirmed by measurement of estradiol and follicle-stimulating hormone (FSH), and absence of menses for one year

A total of 50 subjects were included in this study and, after randomization, 49 (98%) subjects received the Test and 49 (98%) subjects received the Reference.

Two subjects (4%) discontinued the study; one for personal reasons (related to clinical events), and one due to safety reasons (investigator's decision); 48 (96%) subjects completed the study.

One subject was withdrawn from the study before dosing of period 2 for safety reasons (due to severe gastroenteritis judged possibly related to the administration of Atripla) as decided by the study investigator and only received the Reference in period 1.

One subject withdrew consent from the study before dosing of period 2 for personal reasons related to clinical events (mild nausea and mild diarrhoea). The subject only received the Test in period 1.

Protocol deviations were documented during the study. 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. 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.

Analytical methods

The method for the determination of Efavirenz, Emtricitabine and Tenofovir in human plasma using HPLC with MS/MS detection has met acceptance criteria with respect to specificity, sensitivity, precision, accuracy, matrix effect, linearity, percent extraction yields and dilution integrity, spanning a theoretical concentration range of 25.0 ng/mL to 6000.0 ng/mL for Efavirenz, 10.0 ng/mL to 4000.0 ng/mL for Emtricitabine and 2.50 ng/mL to 800.00 ng/mL for Tenofovir. Stability evaluations in matrix and solutions have also met acceptance criteria, demonstrating insignificant degradation of Efavirenz, Emtricitabine, Tenofovir, Efavirenz-D5, Emtricitabine-15N-D2 and Tenofovir-D6 over the specified storage durations and conditions.

Pharmacokinetic variables

A single 600 mg/200 mg/245 mg oral dose of efavirenz/emtricitabine/tenofovir was administered under fasting conditions in each study period. The drug administrations were separated by a wash-out of 35 calendar days.

In each study period, 24 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.

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.

Efavirenz:

The pharmacokinetic parameters of interest for this study were to be the ln-transformed Cmax and AUC0-72. Tmax was to be calculated and provided for information purposes only.

Emtricitabine and tenofovir:

The pharmacokinetic parameters of interest for this study were to be the ln-transformed Cmax and AUC0-T. Other parameters including T_{max}, AUC0-∞, Residual Area, λ Z and T_{half} were to be calculated and provided for information purposes only.

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, AUC0-72 and AUC0-∞ was based on ln-transformed data; T_{max} was based on a non-parametric approach.

ANOVA model:

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

Criteria for Bioequivalence:

Statistical inference of efavirenz was to be 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 for the ln-transformed parameters C_{max} and AUC_{0-72} were all to be within the 80.00 to 125.00% bioequivalence range

Statistical inference of emtricitabine and tenofovir was to be 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 for the ln-transformed parameters C_{max} and AUC_{0-T} were all to be within the 80.00 to 125.00% equivalence range.

Results

All 50 subjects were analyzed and 48 subjects were included in the pharmacokinetic and statistical analysis.

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

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-72)}$ (N=48)	49807.27	12067.86	49298.55	14131.04
$AUC_{(0-\infty)}$ (N=48)	---	---	---	---
C_{max} (N=48)	1775.83	600.80	1825.21	663.40
T_{max}* (N=48)	2.67 (1.00 – 12.00)		3.53 (1.00 – 8.00)	

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours (units in ng*h/ml)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity (units in ng*h/ml)

C_{max} maximum plasma concentration (units in ng/ml)

T_{max} time for maximum concentration (* median, range) (units in hours)

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

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0-72)}$	102.12%	(97.91%, 106.52%)	12.34%

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
C_{max}	98.37%	(89.46%, 108.16%)	28.23%
* estimated from the Residual Mean Squares			

For efavirenz, the ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference for the ln-transformed parameters C_{max} and AUC_{0-72} were all within the 80.00 to 125.00% bioequivalence range.

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

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-T)}$ (N=48)	10280.66	2217.17	9957.23	2551.18
$AUC_{(0-\infty)}$ (N=47)	10599.62	2253.91	10311.62	2555.11
C_{max} (N=48)	1829.32	542.35	1968.31	558.00
T_{max}* (N=48)	1.63 (0.75 – 4.00)		1.75 (0.75 – 4.00)	

AUC_{0-T}	area under the plasma concentration-time curve from time zero to T hours (units in ng*h/ml)
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity (units in ng*h/ml)
C_{max}	maximum plasma concentration (units in ng)
T_{max}	time for maximum concentration (* median, range) (units in hours)

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

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-T)}$	103.89%	(100.35%, 107.55%)	10.13%
C_{max}	107.09%	(100.98%, 113.57%)	17.27%
* estimated from the Residual Mean Squares			

For emtricitabine, the ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference for the ln-transformed parameters C_{max} and AUC_{0-T} were all within the 80.00 to 125.00% bioequivalence range.

Table 6. Pharmacokinetic parameters for Tenofovir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-T)}$ (N=48)	1887.71	599.27	1865.50	699.51
$AUC_{(0-\infty)}$ (N=48)	2009.75	635.38	1988.96	742.44
C_{max} (N=48)	233.98	92.15	219.33	86.36
T_{max}* (N=48)	1.00 (0.50 – 4.50)		1.25 (0.50 – 3.00)	
AUC_{0-T}	area under the plasma concentration-time curve from time zero to T hours (units in ng*h/ml)			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity (units in ng*h/ml)			
C_{max}	maximum plasma concentration (units in ng)			
T_{max}	time for maximum concentration (* median, range) (units in hours)			

Table 7. Statistical analysis for Tenofovir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-T)}$	102.55%	(96.25%, 109.25%)	18.65%
C_{max}	106.06%	(99.63%, 112.91%)	18.41%
* estimated from the Residual Mean Squares			

For tenofovir, the ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference for the ln-transformed parameters C_{max} and AUC_{0-T} were all within the 80.00 to 125.00% bioequivalence range.

Therefore, the Test formulation (Efavirenz + Emtricitabine + Tenofovir Disoproxil (Phosphate) 600/200/245 mg film-coated tablets, Zentiva, k.s., Czech Republic) was judged to be bioequivalent to the Reference formulation (Atripla [Efavirenz + Emtricitabine + Tenofovir Disoproxil (Fumarate)]) 600/200/245 mg film-coated tablets, Bristol-Myers Squibb and Gilead Sciences limited, Ireland) under fasting conditions.

Based on the presented bioequivalence study (ZNV-P0-673) Efavirenz/emtricitabine/tenofovir disoproxil 600/200/245 mg is considered to be essentially similar to Atripla.

Safety data

A total of 72 adverse events were reported by 32 (64%) of the 50 subjects who participated in this study. Of these events, 41 occurred after administration of the Test and the other 31 after administration of the Reference.

Twenty-one (43%) of the 49 subjects who received the Test experienced AEs, the most common of which was somnolence (9 subjects; 18%). The AEs experienced following the administration of the Test were mild (37/41; 90%) or moderate in severity (4/41; 10%).

Twenty (41%) of the 49 subjects who received the Reference experienced AEs, the most common of which was dizziness (6 subjects; 12%). The majority of the AEs experienced following the administration of the Reference were mild (26/31; 84%) or moderate (4/31; 13%) in severity. One subject (1/31; 3%) experienced a severe AE: gastroenteritis.

Table 8. Summary of Adverse Events by System Organ Class Experienced by at Least Two Subjects

System Organ Class MedDRA Preferred term	Test (N=49) N (%)	Reference (N=49) N (%)
Subjects with at least one AE	21 (43)	20 (41)
Nervous system disorders	14 (29)	13 (27)
Somnolence	9 (18)	5 (10)
Dizziness	7 (14)	6 (12)
Headache	5 (10)	3 (6)
General disorders and administration site conditions	4 (8)	5 (10)
Fatigue	2 (4)	3 (6)
Gastrointestinal disorders	5 (10)	1 (2)
Nausea	3 (6)	1 (2)
Musculoskeletal and connective tissue disorders	1 (2)	3 (6)
Injury, poisoning and procedural complications	2 (4)	1 (2)
Vascular disorders	2 (4)	0

Conclusions

Based on the presented bioequivalence study Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva is considered bioequivalent with Atripla.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

The applicant has presented one bioequivalence study. The results concluded that the test product is bioequivalent to the chosen reference product. There are no major issues in the bioequivalence study.

2.4.6. Conclusions on clinical aspects

Based on the submitted bioequivalence study ZNV-P0-673) results the test product Efavirenz+Emtricitabine+Tenofovir Disoproxil (Phosphate) 600/200/245 mg film coated tablets of Zentiva k.s. and the reference Atripla film coated tablets (MAHs: Bristol-Myers Squibb and Gilead Science Ltd) are considered bioequivalent in healthy, adult, human subjects under fasting conditions.

2.5. Risk management plan

Safety concerns

Important identified risks	High-grade hepatic enzyme elevation and severe hepatic events Neural tube developmental abnormalities Psychiatric and nervous system symptoms Skin rashes and severe skin reactions Alteration in EFV blood levels and CYP2B6 genetic polymorphisms Post-treatment hepatic flares in HIV-1/HBV coinfected patients Renal toxicity Bone events due to proximal renal tubulopathy/loss of BMD Interaction with didanosine Pancreatitis
Important potential risks	Lack of efficacy Overdose (occurring through accidental concurrent use of the product with any of its active components) Urolithiasis/nephrolithiasis Malignant neoplasms
Missing information	Safety in patients with hepatic impairment Safety in children (< 3 months old for EFV, including long-term safety for TDF) Safety in elderly patients Safety in pregnancy Safety in lactation Safety in patients with renal impairment

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for Submission of interim or final reports (planned or actual)**

The Antiretroviral Pregnancy Registry (category 3)	The Antiretroviral Pregnancy Registry is intended to provide an early signal of any major teratogenic effect associated with a prenatal exposure to the products monitored through the Registry. The Registry is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products.	Safety in pregnancy	Planned	To be decided

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
High-grade hepatic enzyme elevation and severe hepatic events	<u>Proposed text in SmPC</u> Posology and method of administration in section 4.2 Contraindications in section 4.3 Special warnings and precautions for use in section 4.4 Undesirable effects in section 4.8 Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Neural tube developmental abnormalities	Proposed text in SmPC Fertility, pregnancy and lactation in section 4.6 Prescription only medicine	None proposed
Psychiatric and nervous system symptoms	Proposed text in SmPC Posology and method of administration in 4.2 Special warnings and precautions for use in 4.4 Undesirable effects in 4.8 Overdose in section 4.9 Preclinical safety data in section 5.3 Prescription only medicine	None proposed
Skin rashes and severe skin reactions	Proposed text in SmPC Special warnings and precautions for use in section 4.4 Undesirable effects in section 4.8 Prescription only medicine	None proposed
Alteration in EFV blood levels and CYP2B6 genetic polymorphisms	Proposed text in SmPC Interactions with other medicinal products and other forms of interactions in section 4.5 Pharmacokinetic properties in section 5.2 Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Post-treatment hepatic flares in HIV-1/HBV coinfected patients	Proposed text in SmPC Posology and method of administration in section 4.2 Special warnings and precautions for use in section 4.4 Undesirable effects in section 4.8 Prescription only medicine	None proposed
Renal toxicity	Proposed text in SmPC Special warnings and precautions for use in section 4.4 Interaction with other medicinal products and other forms of interaction in section 4.5 Undesirable effects in section 4.8. Prescription only medicine	Educational materials for healthcare professionals and patients
Bone events due to proximal renal tubulopathy/loss of BMD	Proposed text in SmPC Special warnings and precautions for use in section 4.4 Undesirable effects in section 4.8 Preclinical safety data in section 5.3 Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Interaction with didanosine	Proposed text in SmPC Special warnings and precautions for use in section 4.4 Interaction with other medicinal products and other forms of interaction in section 4.5 Undesirable effects in section 4.8. 5.1 Pharmacodynamic properties Prescription only medicine	None proposed
Pancreatitis	Proposed text in SmPC Special warnings and precautions for use in section 4.4 Interaction with other medicinal products and other forms of interaction in section 4.5 Undesirable effects in section 4.8. Prescription only medicine	None proposed
Lack of efficacy	Proposed text in SmPC 5.1 Pharmacodynamic properties Prescription only medicine	None proposed
Overdose (occurring through accidental concurrent use of the product with any of its active components)	Proposed text in SmPC 4.9 Overdose Prescription only medicine	None proposed
Urolithiasis/ nephrolithiasis	Prescription only medicine	None proposed
Malignant neoplasms	Proposed text in SmPC 5.3 Preclinical safety data Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with hepatic impairment	Proposed text in SmPC Posology and method of administration in section 4.2 Contraindications in section 4.3 Special warnings and precautions for use in section 4.4 Pharmacokinetic properties in section 5.2 Prescription only medicine	None proposed
Safety in children (< 3 months old for EFV, including long-term safety for TDF)	Proposed text in SmPC Posology and method of administration in section 4.2 Pharmacodynamic properties in section 5.1 Pharmacokinetic properties in section 5.2 Prescription only medicine	None proposed
Safety in elderly patients	Proposed text in SmPC Posology and method of administration in section 4.2 Special warnings and precautions for use in section 4.4 Undesirable effects in section 4.8 Pharmacokinetic properties in section 5.2 Prescription only medicine	None proposed
Safety in pregnancy	Proposed text in SmPC Pregnancy and lactation in section 4.6 Prescription only medicine	None proposed
Safety in lactation	Proposed text in SmPC Pregnancy and lactation in section 4.6 Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety in patients with renal impairment	Proposed text in SmPC Posology and method of administration in section 4.2 Special warnings and precautions for use in section 4.4 Undesirable effects in section 4.8 Pharmacokinetic properties in section 5.2 Prescription only medicine	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. PSUR submission

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

2.7. Pharmacovigilance

Pharmacovigilance system

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

2.8. Product information

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 Efavirenz+Emtricitabine+Tenofovir Disoproxil (Phosphate) 600/200/245 mg film coated tablets of Zentiva k.s. The reference product Atripla is indicated for treatment 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 single dose, two-period, two-sequence, two-way cross-over design under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation Efavirenz+Emtricitabine+Tenofovir Disoproxil (Phosphate) 600/200/245 mg film coated tablets of met the protocol-defined criteria for bioequivalence when compared with Atripla. 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 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 Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva is favourable in the following indication:

Treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva prior to initiation of their first antiretroviral treatment regimen.

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 Efavirenz/Emtricitabine /Tenofovir disoproxil Zentiva are provided with a physician educational pack containing the following:

- The Summary of Product Characteristics
- HIV renal educational brochure, including the creatinine clearance slide ruler

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 Efavirenz/Emtricitabine /Tenofovir disoproxil Zentiva
- Efavirenz/Emtricitabine /Tenofovir disoproxil Zentiva is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min)
- That use of Efavirenz/Emtricitabine /Tenofovir disoproxil Zentiva should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Efavirenz/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 Efavirenz/Emtricitabine /Tenofovir disoproxil Zentiva therapy
- The importance of regular monitoring of renal function during Efavirenz/Emtricitabine /Tenofovir disoproxil Zentiva therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- If serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function must 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 Efavirenz/Emtricitabine /Tenofovir disoproxil Zentiva therapy should be interrupted. Interrupting treatment with Efavirenz/Emtricitabine /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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.