LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s. (tenofovir disoproxil fumarate, efavirenz, emtricitabine)

SE/H/2158/01/DC

This module reflects the scientific discussion for the approval of Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s.. The procedure was finalised at 2023-03-13. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s., 600 mg/200 mg/245 mg, Film-coated tablet.

The active substance is tenofovir disoproxil fumarate, efavirenz, tenofovir disoproxil, emtricitabine. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

The product belongs to antivirals for systemic use for treatment of HIV infections, ATC code: J05AR06.
A fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil. It is indicated for 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 the product prior to initiation of their first antiretroviral treatment regimen.

II.2 General comments on the submitted dossier

The application for Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s., 600 mg/200 mg/245 mg, film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, DK, EE, FR, IT and RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Atripla 600 mg/200 mg/245 mg, film-coated tablets authorised in the EU since 2007, with Gilead Sciences Ireland UC as marketing authorisation holder.

The reference product used in the bioequivalence study is Atripla 600 mg/200 mg/245 mg, film-coated tablets from the UK with Gilead Sciences Ireland UC as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that

acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the UK authority and WHO in 2017 and 2020, without any critical findings. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of the active substances are well known. As active substances are a widely used, well-known combination, no further studies are

required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s. is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s. from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Efavirenz/Emtricitabine/Tenofovir disoproxil with the reference product Atripla.

Study (BEQ-2149-EET (F)-2017)
Methods
The study was an open label, randomised, balanced, analyst-blind, two-treatment, two-period, two-sequence single-dose crossover study conducted in 36 healthy volunteers under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of efavirenz, emtricitabine and tenofovir were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for C_{max} and AUC_{0-t} for emtricitabine and tenofovir (AUC_{0-72} was used instead of AUC_{0-t} for efavirenz). The study was conducted between 01 June 2017 and 08 August 2017.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1, 2 and 3 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for efavirenz, n=29.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**50106 ± 14309**	**2342 ± 546**	**3.50 (1.00 - 5.00)**
Reference	**50230 ± 17763**	**2368 ± 902**	**4.50 (1.00 - 5.02)**
***Ratio (90% CI)**	**104.48 (97.21 - 112.29)**	**105.80 (96.74 - 115.71)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for emtricitabine, n=29.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**12210 ± 2742**	**2365 ± 711**	**1.75 (0.75 - 3.50)**
Reference	**12042 ± 2252**	**2213 ± 512**	**1.50 (0.75 - 4.00)**
***Ratio (90% CI)**	**100.99 (97.57 – 104.53)**	**105.95 (98.46 – 114.02)**	**-**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for tenofovir disoproxil, n=29.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2272 ± 730**	**289 ± 82**	**1.25 (0.75 - 3.00)**
Reference	**2314 ± 606**	**277 ± 59**	**1.25 (0.50 - 3.52)**
***Ratio (90% CI)**	**95.05 (86.33 – 104.64)**	**99.80 (90.10 – 110.54)**	**-**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} or AUC_{0-72} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

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

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the

Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s.

Safety specification
The MAH has submitted the version 0.1 RMP dated 9 November 2022 and proposed the following summary of sate concerns:

Summary of safety concerns	
Important identified risks	• High-grade hepatic enzyme elevation and severe hepatic events (EFV) • Neural tube developmental abnormalities (EFV) • Psychiatric and nervous system symptoms (EFV) • Skin rashes and severe skin reactions (EFV) • Alteration in EFV blood levels and CYP2B6 genetic polymorphisms (EFV) • Renal toxicity (TD) • Bone events due to proximal renal tubulopathy/loss of BMD (TD)
Important potential risks	• Urolithiasis/nephrolithiasis (EFV)
Missing information	• Safety in pregnancy and lactation (EFV, TD)

Assessor's comment: The submitted in line with the last published RMP of the originator (Atripla) and is therefore considered acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 9 November 2022 is considered acceptable.

An updated RMP should be submitted:
- At the request of the RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s., is found adequate. There are no objections to approval of Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva k.s., from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  N/A
- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**
  N/A

V.3 Summary of Product Characteristics (SmPC)

The separately attached SmPC is considered acceptable.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva, EMEA/H/C/004250 (content) and Ibuprofen Zentiva, SE/H/2057/001-3 (layout). Assessment of the Bridging proposed by the applicant is attached in Appendix I.

The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-