COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark 600 mg/200 mg/245 mg film-coated tablets

(efavirenz/emtricitabine/tenofovir disoproxil fumarate)

NL/H/4283/001/DC

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This module reflects the scientific discussion for the approval of Efavirenz/ Emtricitabine/Tenofovir disoproxil Glenmark 600 mg/200 mg/245 mg film-coated tablets. The procedure was finalised at 17 April 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark 600 mg/200 mg/245 mg film-coated tablets, from Glenmark Arzneimittel GmbH.

The product is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. 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 Efavirenz/Emtricitabine/Tenofovirdisoproxil Glenmark prior to initiation of their first antiretroviral treatment regimen.

The demonstration of the benefit of efavirenz/emtricitabine/tenofovir disoproxil is primarily based on 48-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to efavirenz/emtricitabine/tenofovir disoproxil. No data are currently available from clinical studies with efavirenz/emtricitabine/tenofovir disoproxil in treatment-naïve or in heavily pretreated patients.

No data are available to support the combination of this product and other antiretroviral agents.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Atripla 600 mg/200 mg/245 mg film-coated tablets (EU/1/07/430), which has been registered in the EEA by Gilead Sciences International Ltd since 13 December 2007 through a centralised procedure.

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Spain, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark is a pink, capsule shaped, biconvex, film-coated tablet, debossed with "CL 81" on one side and plain on the other side. Each film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate).

The film-coated tablets are packed in high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure and including a silica gel desiccant.

The excipients are:
Tablet core - microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, magnesium stearate and pregelatinised starch.
Film-coating - polyvinyl alcohol part hydrolysed, titanium dioxide (E171), macrogol, talc (E553b), iron oxide red (E172) and iron oxide black (E172).

II.2 Drug Substances

The active substances are efavirenz, emtricitabine and tenofovir disoproxil fumarate. All three active substances are established, however not described in the European Pharmacopoeia (Ph. Eur.). Efavirenz is described in the United Stated Pharmacopoeia (USP) and emtricitabine and tenofovir disoproxil fumarate (related salt) are described in a pending draft USP monograph and in the WHO international pharmacopoeia.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Efavirenz
Efavirenz is a white to off-white powder, non-hygroscopic and practically insoluble in water. Efavirenz exhibits stereoisomerism due to the presence of 1 chiral centre and corresponds to the S-enantiomer. Enantiomeric purity is controlled routinely in the specifications. Polymorphism has been observed for efavirenz. The polymorphic form consistently manufactured is Form I.

Manufacturing process

The active substance is synthesised in four main steps using well defined starting materials with acceptable specifications. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Quality control of drug substance

The active substance specification include tests for appearance, solubility, completeness of solution, identification, water content, residue on ignition, enantiomeric purity, impurities, assay, residual solvents, optical rotation, melting range, particle size distribution and density. Absence of control of microbiological quality has been justified. The specification is considered adequate to control the quality and meets the requirements of the European guidelines on chemistry of new active substances. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

With respect to the reference standards, container closure system and stability reference is made to the corresponding sections of the ASMF-holder. The ASMF includes stability studies performed with the drug substance according to ICH conditions. No significant changes in any parameters were observed. The proposed retest period of 5 years with the storage condition 'store below 25 °C, protected from light, in well closed container' is justified.

Emtricitabine

Emtricitabine is a white to almost white crystalline powder, freely soluble in water. Emtricitabine exhibits stereoisomerism, the 2R, 5S absolute configuration corresponds to most active enantiomer. Polymorphism has been observed for emtricitabine. The polymorphic form consistently manufactured is declared as Form I. Information on the control of the stereochemistry as well as on the polymorph is provided.

Manufacturing process

The first steps of the synthesis leading to the intermediate are performed by one manufacturer and the last two steps by a different manufacturer. The starting materials are adequately defined. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and is considered sufficient.

Quality control of drug substance

The active substance specification include tests for appearance, solubility, identification, water content, residue on ignition, heavy metals, enantiomeric purity, impurities, assay, residual solvents, particle size, polymorphism and boron content. Absence of control of microbiological quality should be justified. The analytical methods used have been adequately described. The methods are identical to those of the ASMF holder. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 24 months when stored preserved in well closed containers, protect from light and stored at controlled room temperature.

Tenofovir disoproxil fumarate

The active substance tenofovir disoproxil fumarate is a white to off-white crystalline powder and very slightly soluble in water. Five polymorphs have been reported, however only one polymorph is consistently produced. Tenofovir disoproxil fumarate has one chiral centre.

Manufacturing process

The starting materials are adequately defined. The first steps of the synthesis leading to the intermediate are performed by two manufacturers and the last two steps by a third manufacturer. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and is considered sufficient.

Quality control of drug substance

The active substance specification include tests for appearance, solubility, identification, melting range, water content, residue on ignition, heavy metals, fumaric acid content, impurities, assay, enantiomeric purity, residual solvents, particle size, density, polymorphism (XRD) and microbiological quality. The analytical methods used have been adequately described. The methods are identical to those of the ASMF holder. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for six commercial scaled batches stored at 25°C/60% RH (6 months) and at 2-8°C (up to 18 months). No significant changes in any parameters were observed. The proposed retest period of 2 years with the storage condition 'Store in tightly closed, airtight containers, protect from light and at temperature between 2-8°C' is not supported, i.e. 18 months could be acceptable based on the available data.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The excipients used are well known and of pharmacopoeial quality. Particle size of the drug substances is relevant because all three exhibit poor flow properties, and efavirenz is also poorly soluble.

The results of the comparative *in vitro* dissolution studies between the bioequivalence study test and reference shows similarity in dissolution in all three media within the physiological pH range (no dissolution of efavirenz is observed within the physiological pH range studied) but not for efavirenz. Although the results of the *in vivo* bioequivalence study prevail, the

MAH has discussed the possible reasons for the discrepancy in dissolution behaviour between test and reference product at the quality control medium which is acceptable.

Manufacturing process

The manufacturing process is divided into three main parts. The first two steps concern the manufacturing of the efavirenz blend and emtricitabine and tenofovir disoproxil fumarate blend by granulation, followed by compression of the two lubricated blends. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. including the functionality related characteristics. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of the active substances, identification of colourants, average weight, water content, dissolution, uniformity of dosage units, assay, impurities, residual solvent and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two pilot scale and three full-scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two full-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). . The stability studies have been performed using ICH storage conditions. Relevant stability parameters have been evaluated as part of the stability studies. No significant changes are observed during the stability studies. The proposed 24 months shelf life is acceptable. Given the apparent need to use a desiccant in the bottle packs, the storage condition is 'Store in the original package to protect from moisture. Keep the bottle tightly closed' together with 'Do not store above 30°C'.

Stability data has been provided for two batches packed in 250 cc containers (90 tabs) demonstrating that the product remains stable for 90 days after initial opening when stored at 25°C/60% RH. Since no degradation occurs no in-use shelf life claim is required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Atripla which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Efavirenz/Emtricitabine/Tenofovir disoproxil is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark 600 mg/200 mg/245 mg

film-coated tablets (Glenmark Arzneimittel GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Atripla 600 mg/200 mg/245 mg film-coated tablets (Gilead Sciences International Ltd, UK).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-44 years. Each subject received a single dose (600 mg/200 mg/300 mg) of one of the 2 efavirenz/emtricitabine/tenofovir disoproxil formulations. The tablet was orally administered with 240 ml water an overnight fast. There were 2 dosing periods, separated by a washout period of 42 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablets should be taken under fasting conditions. As such, the fasting conditions applied in the study are considered adequate.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Five subjects were withdrawn from the study on principal investigator advice due to an adverse event and two subjects did not report to the facility for the second period due to personal reasons. Therefore, 29 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of efavirenz under fasted conditions.

Treatment N=29	**AUC_{0-72h} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	50106 ± 14309	2342 ± 546	3.50 (1.0-5.0)
Reference	50230 ± 17762	2368 ± 902	4.50 (1.0-5.0)

***Ratio (90% CI)**	1.04 (0.97-1.12)	1.06 (0.97-1.16)	--
CV (%)	16.0	19.9	--

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 concentration
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of emtricitabine under fasted conditions.

Treatment N=29	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	12210 ± 2742	12688 ± 2749	2365 ± 710	1.75 (0.75-3.5)	5.3 ± 1.4
Reference	12042 ± 2252	12551 ± 2236	2213 ± 512	1.50 (0.75-4.0)	4.8 ± 1.5
***Ratio (90% CI)**	1.01 (0.98-1.05)	--	1.06 (0.98-1.14)	--	--
CV (%)	7.6	--	16.3	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tenofovir under fasted conditions.

Treatment N=29	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	2272 ± 730	2478 ± 739	289 ± 82	1.25 (0.75-3.0)	19.3 ± 2.3
Reference	2314 ± 606	2509 ± 596	277 ± 59	1.25 (0.50-3.5)	19.3 ± 3.0
***Ratio (90% CI)**	0.95 (0.86-1.05)	--	1.00 (0.90-1.11)	--	--
CV (%)	21.4	--	22.8	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark is considered bioequivalent with Atripla.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Glenmark.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	- High-grade hepatic enzyme elevation and severe haptic events - Neural tube development abnormalities - Psychiatric and nervous system symptoms - Skin rashes and severe skin reactions - Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms - Renal toxicity - Bone events due to proximal renal tubulopathy/loss of BMD
Important potential risks	- Urolithiasis/nephrolithiasis
Missing information	- Safety in pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Atripla. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark 600 mg/200 mg/245 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Atripla 600 mg/200 mg/245 mg film-coated tablets. Atripla is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Efavirenz/Emtricitabine/Tenofovir disoproxil Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 April 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse