CBG MEB

Public Assessment Report

Scientific discussion

Atrilesto, film-coated tablets

(efavirenz/emtricitabine/tenofovir disoproxil)

NL/H/3688/001/DC

Date: 28 September 2017

This module reflects the scientific discussion for the approval of Atrilesto 600 mg/200 mg/245 mg, film-coated tablets. The procedure was finalised on 12 January 2017. 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 Atrilesto 600 mg/200 mg/245 mg, film-coated tablets, from Teva Nederland B.V.

Atrilesto is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil phosphate. 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 Atrilesto prior to initiation of their first antiretroviral treatment regimen.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Atripla 600 mg/200 mg/245 mg film-coated tablets (EMEA/H/C/000797) which has been registered in EEA by Gilead Sciences International Ltd since 13 December 2007, through a centralised procedure.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Czech Republic, Germany, Denmark, Greece, Finland, Iceland, Poland and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Atrilesto is a pink, oval shaped, film-coated tablet, debossed with “TEE” 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 (equivalent to 291.22 mg of tenofovir disoproxil phosphate or 136 mg of tenofovir).

The tablets are packed in OPA/Alu/PE+ desiccant – Alu/PE blister and high-density polyethylene bottles with a polypropylene child resistance cap and a desiccant in the bottle.

The excipients are:
Tablet core – cellulose microcrystalline, croscarmellose sodium, mannitol (E421), hydroxypropylcellulose, low substituted hydroxypropylcellulose, poloxamer 407, crospovidone, hypromellose, hydrogenated vegetable oil and sodium stearyl fumarate.
Film coating (Opadry II 85F240144 Pink) – polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc and carmine (E120).

II.2 Drug Substances

The active substances are efavirenz, emtricitabine and tenofovir disoproxil phosphate. 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 all three active substances. 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

The active substance Efavirenz is a white to off-white powder and freely soluble in methanol and in dichloromethane and practically insoluble in water in the pH range 1-8. Efavirenz has one chiral centre and contains the S-enantiomer. The R-enantiomer is controlled in the specification. The substance is not hygroscopic and exhibits polymorphism. One polymorphic form is consistently manufactured.

Manufacturing process
The manufacturing process consists of two synthetic steps and multiple purification steps. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents. No class I solvents are used in the process.

Quality control of drug substance
The efavirenz specification is in line with the specification of the AMSF holder.. In addition, an in-house specification for particle size distribution was set. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided by the drug product manufacturer on 4 batches.

Stability of drug substance
Stability data on the active substance have been provided for 5 batches stored at 30°/65% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. All parameters tested remain relatively stable (with the exception of some analytical variance) at both storage conditions. Based on the stability data provided the proposed re-test period of 36 months can be granted when stored in a well closed container at controlled room temperature, protected from light.

Emtricitabine

The active substance emtricitabine is a white to almost white crystalline powder and freely soluble in methanol and water and practically insoluble in dichloromethane. Emtricitabine has two chiral centres and is the cis-enantiomer. The substance exhibits polymorphism and one polymorphic form is consistently manufactured.

Manufacturing process
The active substance is manufactured in two stages and a final purifications step. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents. No class I solvents or heavy metal catalysts are used in the process.

Quality control of drug substance
The specification applied by the drug product manufacturer is in line with the specification of the AMSF holder.. In addition, an in-house specification for particle size distribution was set. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 2 batches by the drug product manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for 15 batches stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. No clear up- or downward trends were observed, under both long term and accelerated conditions. The proposed retest period of 60 months is acceptable, without the need for special storage conditions.

Tenofovir disoproxil phosphate

The active substance tenofovir disoproxil phosphate is a white to off-white powder and freely soluble in dimethylformamide and soluble in methanol. The substance is slightly hygroscopic and only one polymorph is known and manufactured.

Manufacturing process
The active substance is manufactured in three stages, consisting of four chemical steps and a final salt formation and purification. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents. No class I solvents or heavy metal catalysts are used in the process.

Quality control of drug substance
The tenofovir disoproxil phosphate specification as adopted by the drug product manufacturer is fully in line with the specification of the AMSF holder including the limits for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 2 batches by the drug product manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for 2 pilot scaled batches and 3 full scaled batches stored at 5°C (18 months for the full scale batches and 36 months for the pilot batches) and 25°C/60% RH (6 months). All results were within the specifications set. Based on the provided stability data the retest period of 24 months with the storage condition “Store at 2°-8°C” as proposed by the drug substance supplier is justified.

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 main development studies concerned the characterisation of the reference product, formulation optimization studies, manufacturing process development studies and the performance of comparative dissolution studies.
One *in vivo* bioequivalence was performed. The results of the comparative *in vitro* dissolution studies between the bioequivalence study test and reference did not show similarity in dissolution in all three media within the physiological pH range and in the QC medium. However, the results of the *in-vivo* bioequivalence study prevail. The possible reasons for the difference has been sufficiently discussed and is justified.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The main steps of the manufacturing process are the separate wet granulation of the three active substances, drying and screening, blending of the three granulates, compression and film-coating. Process validation data on the product have been presented for 2 pilot scale batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur., USP or in-house specifications. 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, dissolution, uniformity of dosage units, assay, related substances, water content and microbial quality. Except for some of the impurities, the release and shelf-life limits are identical. 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 2 pilot scaled 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 2 pilot scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed blisters and bottles. No clear

trends or changes were seen in any of the tested parameters at both storage conditions. Results of a photostability study showed that the drug product is not sensitive to light exposure. The proposed shelf-life of 2 years and storage condition 'Store in the original blister in order to protect from moisture. This medicinal product does not require any special temperature storage conditions' for the blister and 'Store in the original bottle in order to protect from moisture. Keep the bottle tightly closed. This medicinal product does not require any special temperature storage conditions' for the bottle are justified.

Stability data has been provided demonstrating that the product remains stable for 30 days following first opening of the container when stored at 25°C/60% RH. No separate in-use shelf-life was laid down. This is justified.

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 Atrilesto 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 Atrilesto 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 and tenofovir disoproxil phosphate are well-known active substances 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atrilesto 600 mg/200 mg/245 mg, film-coated tablets (Teva Nederland B.V,, NL) 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 60 healthy (40 males/20 females) subjects, aged 21-80 years. Each subject received a single dose (600 mg/200 mg/245 mg) of one of the 2 efavirenz/emtricitabine/tenofovir disoproxil formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.67, 0.83, 1, 1.25, 1.50, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 36, 48 and 72 after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence is considered adequate. According to the SmPC, the tablets should be taken under fasting conditions. As such, the fasting conditions applied in the study is 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.

Tenofovir instead of tenofovir disoproxil was analysed, as tenofovir disoproxil is very rapidly converted into tenofovir, which is agreed.

Results

One subject was withdrawn due to a positive alcohol test result and one subjects withdrew consent for personal reasons (not related to clinical events). Therefore, 58 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 evafirenz under fasted conditions.

Treatment N=58	**AUC_{0-72h}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	57328 ± 11512	2624 ± 722	3.5 (0.83 – 6.0)	18.7 ± 2.7
Reference	54961 ± 13051	2470 ± 861	3.0 (1.25 – 12.0)	18.7 ± 4.1
***Ratio (90% CI)**	1.06 (1.02 – 1.10)	1.09 (1.00 – 1.18)	--	--
CV (%)	13.2	26.6	--	--

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

Treatment N=58	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** <x>g.h/ml	**C_{max}** <x>g/ml	**t_{max}** h	**$t_{1/2}$** h
Test	11479 ± 3496	11799 ± 3586	2122 ± 670	1.5 (0.83 – 4.5)	16.9 ± 7.6
Reference	11629 ± 3640	11904 ± 3703	2188 ± 716	1.5 (0.67 – 4.0)	15.8 ± 6.3
***Ratio (90% CI)**	0.99 (0.97 – 1.02)	--	0.97 (0.93 – 1.02)	--	--
CV (%)	7.8	--	16.1	--	--

$AUC_{0-\infty}$ 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=58	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2008 ± 909	2157 ± 971	262 ± 100	0.83 (0.50 – 3.0)	19.1 ± 4.0
Reference	2196 ± 926	2352 ± 980	276 ± 107	0.83 (0.50 – 4.0)	18.8 ± 3.7
***Ratio (90% CI)**	0.91 (0.88 – 0.95)	--	0.95 (0.91 – 1.00)	--	--
CV (%)	13.6	--	15.3	--	--

$AUC_{0-\infty}$ 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*

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 Atrilesto 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 Atrilesto.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Renal toxicity - Bone events due to proximal renal tubulopathy/loss of bone mineral density - Psychiatric and nervous system symptoms - Skin rash and skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme - High grade hepatic enzyme elevation and severe hepatic events - Neural tube developmental abnormalities - Post-treatment hepatic flares in human immunodeficiency/hepatitis B virus co-infected patients - Interaction with didanosine - Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms - Pancreatitis
Important potential risks	- Lack of efficacy - Overdose - Urolithiasis/nephrolithiasis - Malignant neoplasms
Missing information	- Safety in children (<3 months old for efavirenz, including long-term safety for tenofovir disoproxil) - Safety in elderly patients - Safety in pregnancy - Safety in lactation - Safety in patient with hepatic impairment - Safety in patients with renal impairment

The MAH has followed the innovator product Atripla in the development of the educational material and has adopted the key elements that need to be included in the educational material.

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Atrilesto 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 Atrilesto
- Atrilesto is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min)
- That use of Atrilesto should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Atrilesto 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 Atrilesto therapy
- The importance of regular monitoring of renal function during Atrilesto 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 Atrilesto therapy

should be interrupted. Interrupting treatment with Atrilesto 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

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. It included an appropriate testing panel of 11 male and 12 female subjects of various age and education. The questions covered various sections of the PL and addressed key messages. The data shows the participants were able to correctly locate the answer the questions in 99% of the time and to correctly answer the questions 100% of the time. The participants were given ample time to answer each question. The interviewer performed the testing in an appropriate fashion. No issues have been identified. The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atrilesto 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 Atrilesto, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 January 2017.

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
NL/H/3688/IB/001/G	• Change in the name and/or address of: a manufacture (including where relevant quality control testing sites). • Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier. • Changes in the manufacturing process of the active substance	-	11-07-2017	Approved	-
NL/H/3688/IB/002/G	• Change in the name and/or address of: a manufacture (including where relevant quality control testing sites). • Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance; up to 10-fold increase compared to the originally approved batch size • Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance; minor changes to an approved test procedure • Extension or introduction of a re-test period/storage period supported by real time data	-	11-07-2017	Approved	-
NL/H/3688/1/IB/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product; Implementation of change(s) for which no new additional data is required to be submitted by the MAH	PL	24-09-2017	Approved	-
NL/H/3688/1/IA/004	Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)*	-	10-09-2017	Approved	-
NL/H/3688/1/IB/005	Change in the (invented) name of the medicinal product; for Nationally Authorised Product; A change from the product name in all markets within the DCP procedure from a trade name to a name following an "INN + MAH" naming convention.	-	05-10-2017	Approved	-