CBG MEB

Public Assessment Report

Scientific discussion

Padviram 600 mg/200 mg/245 mg, film-coated tablets

(efavirenz/emtricitabine/tenofovir disoproxil succinate)

NL/H/3878/001/DC

Date: 26 October 2017

This module reflects the scientific discussion for the approval of Padviram 600 mg/200 mg/245 mg, film-coated tablets. The procedure was finalised on 5 July 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 Padviram 600 mg/200 mg/245 mg, film-coated tablets, from Sandoz B.V.

Padviram is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil succinate. 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 Padviram 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 (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 state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Padviram is a pink, capsule shaped, film-coated tablet, plain on both sides. Each film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300.6 mg of tenofovir disoproxil succinate or 136 mg of tenofovir).

The tablets are packed in high-density polyethylene bottles with a polypropylene child resistance cap and a plastic (HDPE) canister containing silica gel.

The excipients are:
tablet core – cellulose microcrystalline (E460), croscarmellose sodium Type A (E468), hydroxypropylcellulose (E463), sodium laurilsulfate (E487), magnesium stearate (E470b), poloxamer 407 and red iron oxide (E172).
film-coating – polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b) and black and red iron oxide (E172).

II.2 Drug Substances

The active substances are efavirenz, emtricitabine and tenofovir disoproxil succinate. 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 four stages. 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 drug substance specification has been established in-house by the MAH and is in line with the specification of the AMSF holder, including tests for particle size distribution and microbial quality. 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 3 batches

Stability of drug substance
Stability data on the active substance have been provided for multiple batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The stability data showed no clear trends or changes in any of the tested parameters. Based on the stability data provided the proposed re-test period of 60 months can be granted with the storage condition ‘Store below 25°C, protected from light, in well closed container’.

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 is 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 three 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 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 with slightly tighter limits for some impurities. 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 3 batches by the drug product manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for 9 batches stored at 30°C/65% RH (up to 60 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 48 months is acceptable, with the storage condition ‘Do not store above 30°C. Protect from light. Protect from moisture’.

Tenofovir disoproxil succinate

The active substance tenofovir disoproxil succinate 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 succinate has one chiral centre.
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Manufacturing process
The active substance is manufactured in four steps, of which the final step is a purification 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 tenofovir disoproxil succinate specification has been established in house by the MAH, and is line with, or tighter than, the (pending) monographs of the USP and WHO Pharmacopoeia International, including additional requirements 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 4 batches by the drug product manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for 6 commercial scaled batches stored at 5°C (18 months for 3 batches and 24 months for other 3 batches) and 30°C/65% RH (6 months). All results were within the specifications set. No clear up- or downward trends were observed, except for a slight increase over time in a impurity under accelerated conditions. Based on the provided stability data the retest period of 30 months with the storage condition “Store in a refrigerator at 2°- 8°C” 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, dissolution method development and performance of comparative dissolution studies complementary to the *in vivo* bioequivalence study. The choices of the packaging and manufacturing process are justified. The drug product batch used in the BE study was manufactured according to the finalized manufacturing process and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The main steps of the manufacturing process are wet granulation and preparation of the final blends of the separate efavirenz layer and emtricitabine and tenofovir disoproxil layer, compression, film-coating and packaging. Process validation data on the product have been presented for 3 pilot scaled 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., except for the iron oxides that comply with Regulation EU 231/2012. The 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 description, identification, dimensions, assay, related substances, residual solvents, dissolution, uniformity of dosage units, uniformity of mass, water content and microbiological purity. Except for water content and related substances, 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 from 3 pilot scaled batches and one smaller batch 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 3 pilot scaled batches and 1 smaller batch stored at 25°C/60% RH (up to 12 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 bottles.
No significant 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. Based on the data provided, the claimed shelf-life of 18 months without any special storage conditions is justified.
In-use stability data has been provided. Based on the results of the in-use stability study, the claimed in-use shelf-life after opening of 1 month 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 Padviram 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 Padviram 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 succinate 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 Padviram 600 mg/200 mg/245 mg, film-coated tablets (Sandoz 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 fasting conditions in 50 healthy male subjects, aged 20-44 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 21 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 24, 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 vomiting and one subject did not report for check-in before the second period. Therefore, 48 subjects completed the study and were eligible for pharmacokinetic analysis. As one subject had a pre-dose value of > 5% of the C_{max} value, his data were excluded from the statistical analysis for efavirenz (table 1).

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

Treatment N=47	**AUC_{0-72h}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	51241 ± 19757	2333 ± 599	3.67 (1.0 – 8.0)	61 ± 22
Reference	51871 ± 21532	2516 ± 698	3.33 (1.0 – 5.0)	64 ± 29
***Ratio (90% CI)**	1.00 (0.93 – 1.07)	0.94 (0.86 – 1.02)	--	--
CV (%)	20.2	24.1	--	--

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=48	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h

Test	11222 ± 2506	11726 ± 2512	2273 ± 580	1.67 (0.75 – 4.67)	4.8 ± 1.4
Reference	11183 ± 2372	11758 ± 2492	2263 ± 508	1.67 (0.75 – 3.0)	4.9 ± 2.1
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	--	1.00 (0.94 – 1.06)	--	--
CV (%)	15.0	--	18.5	--	--

$AUC_{0-\infty}$ 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=48	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2795 ± 923	3044 ± 971	331 ± 100	1.33 (0.50 – 4.33)	18 ± 4.0
Reference	2784 ± 803	3040 ± 872	356 ± 101	1.33 (0.50 – 2.0)	19 ± 4.0
***Ratio (90% CI)**	0.98 (0.91 – 1.06)	--	0.93 (0.87 – 1.00)	--	--
CV (%)	21.8	--	20.5	--	--

$AUC_{0-\infty}$ 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 Padviram 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 Padviram.

- 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 - 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 (occurring through accidental concurrent use of this medicinal product with any of its active components) - 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 Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Efavirenz/Emtricitabine/Tenofovir disoproxil 600mg/200mg/245mg film-coated tablets 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 600mg/200mg/245mg film-coated tablets
- Efavirenz/Emtricitabine/Tenofovir disoproxil 600mg/200mg/245mg film-coated tablets is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min)
- That use of Efavirenz/Emtricitabine/Tenofovir disoproxil 600mg/200mg/245mg film-coated tablets should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Efavirenz/Emtricitabine/Tenofovir disoproxil 600mg/200mg/245mg film-coated tablets 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 600mg/200mg/245mg film-coated tablets therapy
- The importance of regular monitoring of renal function during Efavirenz/Emtricitabine/Tenofovir disoproxil 600mg/200mg/245mg film-coated tablets 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 600mg/200mg/245mg film-coated tablets therapy should be interrupted. Interrupting treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil 600mg/200mg/245mg film-coated tablets 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

For the key safety information reference was made to the parent package leaflet (PL) of Atripla 600 mg mg/200 mg/245 mg film-coated tablets and for the lay-out to the parent PL of Ivabradine 5 mg and 7.5 film-coated tablets. The MAH concludes that there are not significant differences between the parent and the daughter PLs. Therefore, it is considered that the satisfactory results obtained in the user test conducted in the parent PLs can be applied to the daughter PL. In conclusion, the Efavirenz/Emtricitabine/Tenofovir disoproxil tablets package insert (daughter PL) does not necessitate further testing according to the “Guideline on the readability of the labelling and package leaflet of medicinal products for human use”.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Padviram 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 Padviram 600 mg/200 mg/245 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 July 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached