CBG MEB

Public Assessment Report

Scientific discussion

Efavirenz Aurobindo 600 mg, film-coated tablets

(efavirenz)

NL/H/2950/001/DC

Date: 17 November 2014

This module reflects the scientific discussion for the approval of Efavirenz Aurobindo 600 mg, film-coated tablets. The procedure was finalised on 13 May 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Efavirenz Aurobindo 600 mg, film-coated tablets from Aurobindo Pharma B.V.

The product is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 years of age and older.

Efavirenz has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm^3, or after failure of protease inhibitor (PI) containing regimens. Although cross-resistance of efavirenz with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based combination therapy after failure of regimens containing efavirenz.

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 Sustiva 600 mg film-coated tablets which has been registered in the EEA by Bristol-Myers Squibb Pharma EEIG through a centralised procedure since 1999 (MA numbers EU/1/99/110/008-010).

The concerned member states (CMS) involved in this procedure were Cyprus, Denmark, Finland, Germany, Italy, Malta, Portugal, 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 Aurobindo 600 mg is a yellow coloured, oval shaped, beveled edge, biconvex, film-coated tablet, debossed with 'L' on one side and '11' on the other side.

The tablets are packed in clear PVC/PVdC-Aluminium foil blister packs and white opaque HDPE bottle packs with white opaque polypropylene closure.

The excipients are:
Tablet core - microcrystalline cellulose, low-substituted hydroxypropyl cellulose, lactose monohydrate, hydroxypropyl cellulose, crospovidone, sodium lauryl sulfate, magnesium stearate, anhydrous colloidal silica
Coating - hypromellose, macrogol, titanium dioxide and iron oxide yellow.

II.2 Drug Substance

The active substance is efavirenz, an established active substance described in the United States Pharmacopoeia (USP). The active substance is a white to off-white powder, which is practically insoluble in water. Efavirenz contains one chiral centre. The drug substance consists of the S-enantiomer. Efavirenz exhibits polymorphism and Form β is used in the drug product.

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.

Manufacturing process
The manufacturing process consists of two synthetics steps and multiple purification steps. The active substance has been adequately characterised and acceptable specifications have been included for reagents, intermediates and starting materials.

Quality control of drug substance
The drug substance specification has been established in-house. The specification is based on the USP monograph and the specification of the ASMF-holder, with additional requirements such as particle size and specific impurities. 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 six full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for five batches stored at 25°/60% RH (24 months) and 40°C/75% RH (6 months). All parameters tested remain relatively stable 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.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials and dissolution studies.
Bioequivalence studies were performed with the drug product. The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. The bioequivalence batch is of sufficient size in relation to the intended commercial batch size. Comparative dissolution data have been provided, demonstrating similarity to the reference product. The pharmaceutical development of the product has been adequately performed and the discriminatory power of the routine dissolution method has been demonstrated.

Manufacturing process
The manufacturing process is divided into the following steps: dry mixing, wet granulation, lubrication, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques and is regarded as a standard process. Process validation data on the product has been presented for two batches of the smallest commercial scale.

Control of excipients
All excipients used comply with the requirements of their respective Ph.Eur. or USP/NF monographs, except for the ready to use coating material. In-house specification have been provided for the coating material. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, average weight, water content, uniformity of dosage units, dissolution, assay, related substances, thickness, microbial limits and identification of colorants. The release specification is identical to the shelf life specification, except for water content. The drug product specification is acceptable..
The analytical methods been adequately described and validated. The stability indicating nature of the method for assay and related substance has been demonstrated. Batch analytical data from the proposed production site have been provided on two batches of the smallest commercial size, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two batches of the smallest commercial size stored at 25°C/60% RH (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 marketing packs (blisters and HDPE bottles).
A slight increase in one impurity was observed in all containers and at both conditions. An increase in water content was observed in the blister. The increase was more pronounced at accelerated conditions. Water content remained relatively stable in the HDPE bottles. All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits. The product was demonstrated to be photostable.
Based on the 12 months stability data provided, the proposed shelf life of 24 months can be granted. The proposed storage condition 'No special storage conditions' is considered acceptable.
Stability data has been provided demonstrating that the product remains stable for 12 months after first opening of the container, when stored at 25°C/60% RH. An in-use shelf-life period is therefore not considered necessary to be stated in the SmPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin. Milk used in the manufacturing process is sourced from healthy animals in the same conditions as milk collected for human consumption. Also, calf rennet used in manufacture of lactose is produced in accordance with the applicable EU requirements.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Efavirenz Aurobindo 600 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to conduct validation on the first three batches of Efavirenz Aurobindo 600 mg tablets of different batch sizes.
- The MAH committed to continue the on going long-term stability studies.
- The MAH committed to include three consecutive commercial-scale batches of the minimum and maximum batch size.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Efavirenz Aurobindo 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 Sustiva which is available on the European market. Reference is made tot 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 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 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 Efavirenz Aurobindo 600 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Sustiva 600 mg tablets (Bristol-Myers Squibb Pharma, Germany).

The choice of the reference product in the bioequivalence study is justified, as the reference product is registered through a centralised procedure.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 19-44 years. Each subject received a single dose (600 mg) of one of the 2 efavirenz 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 33 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence for efavirenz is considered adequate. Efavirenz should be taken without food according to the SmPC, as the increased efavirenz concentrations observed following administration with food may lead to an increase in frequency of adverse reactions.

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. Efavirenz has a very long elimination half-life (about 65h) and therefore and in accordance with the guideline, AUC_{0-72h} was taken as main variable for the extent of absorption.

Results
Seven subjects dropped out: one subject for personal reasons, three subjects due to vomiting in Period I and three subjects did not check in for Period II. The remaining 41 subjects completed the study and were included in the analysis.

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

Treatment N=41	**AUC_{0-72h}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	52971 ± 19491	2362 ± 915	4.0 (1.0 – 5.0)
Reference	55694 ± 20308	2584 ± 932	3.0 (1.0 – 7.0)
***Ratio (90% CI)**	0.95 (0.90-1.01)	0.91 (0.85-0.98)	--
CV (%)	16.2	18.5	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **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			

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. Based on the submitted bioequivalence study Efavirenz Aurobindo 600 mg is considered bioequivalent with Sustiva 600 mg tablets.

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 Aurobindo.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Psychiatric and nervous system symptoms • Skin rash and severe skin reactions • High-grade hepatic enzyme elevation and severe hepatic events • Neural tube development abnormalities • Alteration in blood levels and CYP2B6 generic polymorphism
Important potential risks	• Urolithiasis/Nephrolithiasis
Missing information	• Safety in children (< 3 years old) • Safety in elderly patients • Safety in pregnancy and lactation • Safety in patients with hepatic impairment • Safety in patients with renal impairment

In line with the RMP of the reference product no additional pharmacovigilance activity is currently warranted. The member states agree that routine risk management measures are sufficient.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sustiva 600 mg. 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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the parent leaflet Efavirenz Teva 600 mg film-coated tablets (EMEA/H/C/002352). The results of testing on the parent leaflet are extrapolated to the daughter leaflet Efavirenz Aurobindo. There is also a bridging submitted to the lay

out of Efavirenz Aurobindo 600 mg film coated tablets (daughter PIL) with Metoprolol aurobindo 50 mg & 100 mg film coated tablets (parent PIL) which was assessed and approved during procedure SE/H/1201/001-002/DC. The bridging report of the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Efavirenz Teva 600 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Sustiva 600 mg film-coated tablets. Sustiva 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 Teva 600 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 May 2014.

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