CBG MEB

Public Assessment Report

Scientific discussion

Efavirenz Hetero 600 mg film-coated tablets

(efavirenz)

NL/H/3033/001/DC

Date: 23 April 2015

This module reflects the scientific discussion for the approval of Efavirenz Hetero 600 mg film-coated tablets. The procedure was finalised on 7 November 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 Hetero 600 mg film-coated tablets from Hetero Europe S.L.

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 is a non-competitive inhibitor of HIV-1 reverse transcriptase (NNRTI) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α, β, γ or δ). 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 Croatia, Germany, Spain, 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 Hetero 600 mg is a yellow coloured, capsule shaped, biconvex, film-coated tablet, debossed with ‘H’ on one side and ‘E8’ on the other side.

The tablets are packed in Alu/Alu blister packs, white opaque PVC-Alu blister packs and white opaque HDPE bottle packs with polypropylene closure.

The excipients are:
Tablet core - microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate
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 substance is a white to slightly pink powder freely soluble in methanol and practically insoluble in water. Efavirenz possesses one asymmetric carbon atom and is expected to be optically active. Efavirenz exists in five polymorphic forms known as Form-I, Form-II, Form-III, Form-IV and Form-V as reported in literature.

Efavirenz is manufactured using a synthetic route described in an Active Substance Master File (ASMF). Another synthetic route that has been proposed was not approved. The current synthetic processes yield materials of a single crystalline form, which remains unchanged throughout the subsequent formulation and manufacture of the finished products.

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 has been subscribed in sufficient detail in the ASMF. The active substance processed using the approved synthetic route has been adequately characterised and acceptable specifications have been included for solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house. The specification is based on the specifications of the ASMF-holder, with additional requirements for microbiological purity and 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 three batches produced by the approved synthetic route.

Stability of drug substance
Stability data on the active substance have been provided by the ASMF holder. Stability studies at long-term and accelerated conditions did not show any up- or downward trends, indicating that the batches remain stable throughout the tested period.
The claimed re-test period of 2 years is acceptable, based on available completed 12 months long-term stability studies. No specific temperature restrictions are required as the drug substance is found stable when stored at both 25°C/60%RH and 40°C/75%RH.

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. Comparative dissolution data have been provided, demonstrating similarity to the reference product: for both the test and the reference product more than 85% is dissolved after 30 minutes. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: sifting, dry mixing, wet granulation, lubrication, (air) drying, sifting and milling, extra granular sifting, (pre)-lubrication, blend sample analysis, compression, film-coating, finished product analysis, 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.

Control of excipients
All excipients used comply with the requirements of their respective Ph.Eur. 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 description, identity, average weight, water content, dissolution, uniformity of dosage units, assay, related compounds, microbial examination, 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 full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two full-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The batches were stored in the proposed marketing packs (Alu/Alu-blister packs, PVC/Alu-blister packs and HDPE bottles with PP caps). Additionally, a stability study of the film-coated tablets stored in the bulk packaging material was performed at long-term conditions (25°C/60% RH for 12 months).
The conditions used in the stability studies are according to the ICH stability guideline.
The stability results show that no up- or downward trends were observed in the stability data of all batches after storage for up to 18 months under long term, and up to 6 months accelerated conditions. Photostability studies demonstrated that there is no effect of light on the product stability. Based on the accelerated and real time stability data a shelf-life of 30 months, without the need for special storage conditions, is justified. No additional stability data are needed. In-use stability for 30 days for the HDPE-containers has been sufficiently demonstrated.

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 Hetero 600 mg film-coated tablets have 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 Hetero 600 mg tablets of different batch sizes.
- The MAH committed to carry out stability studies on the first three commercial batches at accelerated and long-term conditions.
- The MAH committed to analyse in-use stability at the end of shelf-life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Efavirenz Hetero 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 Hetero 600 mg (Hetero Europe S.L., Spain) 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
An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 19-38 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. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 1, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.33, 4.66, 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
Nine subjects dropped out: one subject due to vomiting in Period I, four subjects did not check in for Period II, two subjects tested positive for breath alcohol, and two subjects withdrew for personal reasons. The remaining 33 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=33	**AUC_{0-72h}** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	54.8 ± 17.7	3.27 ± 1.11	3.2 ± 1.0	72 ± 34
Reference	57.9 ± 17.5	3.16 ± 1.34	3.0 ± 1.1	61 ± 27
***Ratio (90% CI)**	0.94 (0.87-1.01)	1.05 (0.96-1.16)	--	--
CV (%)	17.9	23.6	--	--

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 Hetero 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 Hetero.

- 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 • Fetal neural tube abnormalities (including m meningomyelocele, spina bifida, or hydrocephalus) associated with first trimester exposure to EFV • Alteration in blood levels and CYP2B6 generic polymorphism
Important potential risks	• Urolithiasis/Nephrolithiasis • Malignant neoplasms
Missing information	• Use in pediatric populations (< 3 years old) • Use in in elderly patients • Patients with renal impairment • Safety in patients with renal insufficiency • Patients with hepatic 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 Hetero. There is also a bridging submitted to the lay out of Efavirenz Hetero 600 mg film coated tablets (daughter PIL) with Levetiracetam Hetero 750 mg film-coated tablets (parent PIL) which was assessed and approved during procedure PT/H/0515/003/DC. The bridging report of the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Efavirenz Hetero 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 Hetero 600 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 November 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