CBG MEB

Public Assessment Report

Scientific discussion

Abacavir Mylan 300 mg, film-coated tablets

(abacavir)

NL/H/3913/001/DC

Date: 26 January 2018

This module reflects the scientific discussion for the approval of Abacavir Mylan 300 mg, film-coated tablets. The procedure was finalised on 25 October 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
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 Abacavir Mylan 300 mg, film-coated tablets from Generics (UK) Ltd.

The product is indicated for in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children.

The demonstration of the benefit of abacavir is mainly based on results of studies performed with a twice daily regimen, in treatment-naïve adult patients on combination therapy.

Before initiating treatment with abacavir, screening for carriage of the *HLA-B*5701* allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the *HLA-B*5701* allele.

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 Ziagen 300 mg, film-coated tablets which has been centrally registered (EU/1/99/112/001) in the EEA by Viiv Healthcare UK Limited since 8 July 1999.

The concerned member states (CMS) involved in this procedure were France, Italy, Portugal 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

Abacavir Mylan is a yellow, capsule shaped, film-coated, biconvex tablet debossed with 'H' on one side and 'A' and '26' on the other side. Both sides are separated by a score line and the tablet can be divided into equal doses.

The tablets are packed in white opaque PVC/Aluminium blisters or Aluminium/Aluminium blisters.

The excipients are:
Tablet content – microcrystalline cellulose (PH102), sodium starch glycolate (Type A), colloidal anhydrous silica and magnesium stearate.
Tablet coating – hypromellose 6cP, triacetin, titanium dioxide (E171), yellow iron oxide (E172) and polysorbate 80.

II.2 Drug Substance

The active substance is abacavir, an established active substance not described in the European Pharmacopoeia (Ph.Eur.), but a monograph is available for abacavir sulphate. It is an off-white to pink coloured powder. Abacavir is sparingly soluble in methanol and insoluble in water or in buffers across the physiological pH range. The active substance contains two chiral centres. The same crystalline form is consistently manufactured. Enantiomeric purity and polymorphic form are controlled in the drug substance specification.

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 is described in sufficient detail. Adequate specifications have been provided. The proposed starting materials are acceptable. The active substance was sufficiently characterised with regard to chemical structure and polymorphic form. The impurities have been adequately discussed. No metal catalysts are used.

Quality control of drug substance
The active substance specification of the ASMF holder was established in house and is considered adequate to control the quality. It contains tests for description, solubility, identification, water content, x-ray diffraction, sulphated ash, heavy metals, related compounds, enantiomeric purity, assay and residual solvents. The drug substance specification of the MAH is in accordance with that of the ASMF holder with additional requirements for particle size and microbiological examination. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three commercial scale batches stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months), and 40°C/75% RH (6 months). The batches were stored in the proposed packaging. No trends or significant changes were seen. Based on the data submitted, a retest period could be granted of 36 months.

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.
A test for subdivision of tablets is included in the drug specification. The breakability is not more than 1 individual mass outside the limits of 85% to 115% of the average mass and no individual mass is outside the limits of 75% to 125% of the average mass. This is acceptable.
The dissolution profiles of the test product Abacavir Mylan 300 mg and the reference product Ziagen 300 mg used in the bioequivalence study showed that both products dissolve for more than 85% in 15 minutes in all three media tested (pH 1.2, 4.5 and 6.8). The profiles of the test product differ somewhat at pH 6.8, however no point is raised as dissolution exceeds 85% in 15 minutes.

Manufacturing process
The manufacturing process consists of dry mixing, lubrication, compression, film-coating and packing and has been validated according to relevant ICH guidelines. The process is considered to be standard and is described in sufficient detail. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients
Apart form the coating material, all excipients comply with the Ph.Eur. Additional requirements for particle size and bulk density were laid down for microcrystalline cellulose and magnesium stearate and additional requirements for residual solvents were laid down for sodium starch glycolate. These specifications and the specifications for the coating material 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, average weight, water content, uniformity of dosage units, dissolution, related compounds, assay, identification of colourants, breakability and microbiological examination. The microbiological contamination and identification of colourants tests are not routinely performed. The release and shelf life specifications differ with regard to the acceptance criteria for water content and total impurities. The proposed drug product specification is acceptable with regard to the release and shelf life limits for total impurities. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 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 three full scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The film-coated tablets were stored in the proposed packaging. No trends or significant changes were observed. Photostability studies showed that the product is not sensitive to light. Based on the data submitted, a shelf life was granted of 24 months without any specific storage conditions.

Specific measures for 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. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Abacavir Mylan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitment have been made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Abacavir Mylan 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 Ziagen 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

Abacavir 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 Abacavir Mylan 300 mg, film-coated tablets (Generics (UK) Ltd., UK) is compared with the pharmacokinetic profile of the reference product Ziagen 300 mg, film-coated tablets (ViiV Healthcare UK Limited, UK). The choice of the reference product is considered acceptable.

Bioequivalence study

Design

A single-dose, balanced, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 20-44 years. Each subject received a single dose (300 mg) of one of the 2 abacavir 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 5 days.

Blood samples were collected pre-dose and at 0.083, 0.167, 0.333, 0.667, 0.833, 1, 1.167, 1.333, 1.5, 1.667, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets can be taken with or without food. 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

One subject withdrew from the study due to protocol non-compliance and one subject withdrew on medical grounds. Therefore, 30 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 abacavir under fasted conditions.

Treatment N=30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	7559 ± 2537	7605 ± 2549	3303 ± 1058	0.75 (0.33 – 3.0)	1.5 ± 0.3
Reference	7551 ± 2441	7598 ± 2450	3600 ± 1280	0.50 (0.167 – 1.5)	1.6 ± 0.5
***Ratio (90% CI)**	0.99 (0.96 – 1.03)	--	0.93 (0.87 – 0.99)	--	--
CV (%)	8.4	--	15.5	--	--

$AUC_{0-\infty}$ 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 Abacavir Mylan 300 mg, film-coated tablets are considered bioequivalent with Ziagen 300 mg, film-coated 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 Abacavir Mylan.

- Summary table of safety concerns as approved in RMP

Important identified risks	• ABC hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing)
Important potential risks	• Use in subjects with moderate/severe hepatic impairment • Ischaemic cardiac events • Use in pregnancy • Long term risk of carcinogenicity and long term exposure to NRTIs
Missing information	None

As for the reference product Ziagen, educational material for healthcare professionals and a patient alert card should be provided in order to increase the understanding and awareness of abacavir hypersensitivity.

The educational material should contain the following key elements:

1. **Diagnosis of Abacavir Hypersensitivity Reaction**
   Major symptoms associated with ABC HSR are fever (~80%), rash (~70%), gastrointestinal symptoms (>50%) such as nausea, abdominal pain, vomiting, and diarrhoea, generalise malaise, fatigue, and headache (~50%) and other symptoms (~30%) such as respiratory, mucosal, and musculoskeletal symptoms.

   Based on the above patients are advised to contact their physician immediately to determine whether they should stop taking abacavir if:
   - presence of skin rash; OR
   - development of 1 or more symptom from at least 2 of the following groups:
     - Fever
     - Shortness of breath, sore throat or cough
     - Nausea or vomiting or diarrhoea or abdominal pain
     - Extreme tiredness or achiness or generally ill feeling

2. **Pharmacogenetic Testing**
   HLA-B*5701 is the only identified pharmacogenetic marker that is consistently associated with clinical diagnosis of an ABC HSR reaction. However, some patients with a suspected ABC hypersensitivity reaction may not have the HLA-B*5701 allele.

   Before initiating abacavir therapy, clinicians should screen for HLA-B*5701(in settings where validated screening methods are available). Clinical diagnosis of suspected hypersensitivity to ABC remains the basis for clinical decision making. HLA-B*5701 screening for risk of ABC hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving ABC. If ABC hypersensitivity cannot be ruled out on clinical grounds, ABC should be permanently discontinued and should not be restarted, regardless of the results of HLAB*5701 screening. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.

3. **Management of ABC HSR reaction**
   Regardless of HLA-B*5701 status, patients who are diagnosed with a hypersensitivity reaction must discontinue abacavir immediately. Symptoms can occur at any time during treatment with ABC, but usually occur within the first 6 weeks of therapy. Delay in stopping treatment with abacavir after the onset of hypersensitivity may result in an immediate and life-threatening reaction. Following discontinuation of abacavir, the symptoms of the reaction should be treated according to local standard of care. Rechallenge can result in a more rapid and severe reaction, which can be fatal, therefore rechallenge is contraindicated.

4. **Hypersensitivity case studies**
   The educational material includes 3 case studies to demonstrate different clinical scenarios and their management.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Ziagen. 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 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The developed questionnaire contained 18 questions specific to abacavir and 4 questions specific to the format of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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

Abacavir Mylan 300 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Ziagen 300 mg, film-coated tablets. Ziagen 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 Abacavir Mylan 300 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 25 October 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

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