CBG MEB

Public Assessment Report

Scientific discussion

Abacavir Hexal 300 mg, film-coated tablets

(abacavir)

NL/H/3436/001/DC

Date: 8 June 2017

This module reflects the scientific discussion for the approval of Abacavir Hexal 300 mg, film-coated tablets. The procedure was finalised on 23 March 2016. 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 Hexal 300 mg, film-coated tablets from Hexal AG.

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 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

Abacavir Hexal 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 PVC/Alu 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 (12 months), 30°C/75% RH (12 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 24 months when stored with the storage condition: Store at 25ºC excursions permitted between 15ºC and 30ºC, preserve in tight, light-resistant containers.

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 Hexal 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. The MAH

committed to evaluate the specification limits for total impurities on future batches. 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 (12 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. On basis of the data submitted, a shelf life was granted of 24 months without any specific storage conditions.

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 Abacavir Hexal has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment has been made during the procedure:
- The MAH committed to evaluate the specification limits for total impurities on future batches. It is pointed out that adjustment of the specification should be notified to the competent authority by means of a variation.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Abacavir Hexal 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 Hexal 300 mg, film-coated tablets (Hexal AG, Germany) 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 Hexal 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 Ziagen.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Abacavir hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing) - Use in subjects with hepatic impairment
Important potential risks	- Viral resistance in paediatric patients - Long term risk of carcinogenicity and long term exposure to NRTIs - Use in pregnancy - Ischaemic cardiac events - Possible interaction with ribavirin
Missing information	- None

It is considered that the following additional risk minimisation measures are necessary for the safe and effective use of the product:

- Educational materials for healthcare professionals to address the risk of abacavir hypersensitivity (website and slide set) covering the key points as stated in Annex II for Ziagen. The educational material should contain the following key elements:

  1. 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 general ill feeling

  2. Risk factors for ABC HSR
  *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.

  3. Recommendations for *HLA-B*5701* screening
  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.

4. Information on *HLA-B*5701* testing
The one-time *HLA-B*5701* test identifies people at high risk for this serious allergic reaction. The gold standards for *HLA-B*5701* screening are sequence-based genotyping and polymerase chain reaction sequencing of specific oligonucleotide probes. Blood or saliva samples are collected and tested for genetic sequences coding for the *HLA-B*5701* allele. Results of PREDICT-1 and SHAPE studies show that the presence of the *HLA-B*5701* allele is associated with increased risk of ABC hypersensitivity, regardless of race, screening for *HLA-B*5701* before starting treatment with ABC may identify subjects at increased risk of a HSR, avoiding treatment with ABC in subjects with the *HLA-B*5701* allele was shown to significantly reduce the incidence rate of clinically diagnosed cases of hypersensitivity. Data from these studies do not support the use of skin patch testing in routine clinical practice. Only patients found to lack the *HLA-B*5701* allele should begin therapy with ABC.

5. Management of ABC HSR reaction
Symptoms can occur at any time during treatment with ABC, but usually occur within the first 6 weeks of therapy. Symptoms are initially mild and evolve over days, becoming more severe with continued ABC therapy. Symptoms improve on cessation of ABC. Rechallenge can result in a more rapid and severe reaction, which can be fatal, therefore rechallenge is contraindicated.

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

- Patient alert card. Each pack of abacavir/lamivudine medication contains an Alert Card for patients and information on the risk in the packet leaflet (PL).

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

A user consultation with target patient groups on the PL has been performed on the basis of a bridging report. The MAH provided information that the content and wording of the PL the product under consideration is identical with the content and wording of the PL centrally authorised reference product Ziagen. In addition, the MAH provided a summary of design and layout details of approved leaflets. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Abacavir Hexal 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 Hexal 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 23 March 2016.

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
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site Change in immediate packaging of the finished product; qualitative and quantitative composition; solid pharmaceutical forms	NL/H/3436/IA/001/G	IA/G	29-11-2016	22-12-2016	Approved	No