CBG MEB

Public Assessment Report

Scientific discussion

Iviverz 600 mg/300 mg film-coated tablets

(abacavir/lamivudine)

NL/H/3488/001/DC

Date: 4 October 2016

This module reflects the scientific discussion for the approval of Iviverz 600 mg/300 mg film-coated tablets. The procedure was finalised on 1 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EEA	European Economic Area
ERA	Environmental Risk Assessment
HIV	Human Immunodeficiency Virus
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
USP	United States Pharmacopeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Iviverz 600 mg/300 mg film-coated tablets from Actavis Group PTC ehf.

The product is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

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 Kivexa 600/300 mg film-coated tablets which has been registered in the EEA by ViiV Healthcare UK Limited since 17 December 2004 through a centralised procedure EMEA/H/C/000581. The individual active substances were registered as single component formulations in 1996 (lamivudine; centralised procedure) and 1999 (abacavir; centralised procedure).

The concerned member states (CMS) involved in this procedure were Austria, Cyprus, Czech Republic, Denmark, Estonia, Greece, Finland, Hungary, Ireland, Iceland, Lithuania, Latvia, Malta, Norway, Poland, 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

Iviverz is an orange, film-coated, modified capsule shaped tablet and contains as active substances 600 mg abacavir and 300 mg lamivudine.

The film-coated tablets are packed in Aluminium-PVC/PE/PVDC white opaque blisters and plastic HDPE bottles with a plastic PP cap.

The excipients are:
Tablet core – microcrystalline cellulose PH 102 (E460), microcrystalline cellulose PH 200 (E460), sodium starch glycolate (Type A), povidone K 90 (E1202) and magnesium stearate (E470b).
Tablet coating – hypromellose 5 (E464), macrogol 400 (E1521), titanium dioxide (E171) and sunset yellow FCF aluminium lake (E110).

II.2 Drug Substances

Abacavir
The active substance abacavir is not described in the European Pharmacopoeia (Ph.Eur.) and the United States Pharmacopoeia (USP), however there is a Ph.Eur. monograph for abacavir sulphate. Abacavir is not very soluble across the physiological pH range. It is a white to light brown powder and exhibits isomerism and polymorphism. The crystalline form of abacavir is manufactured. Its enantiomer and the two diasteriomers 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 consists of four steps and is described in sufficient detail. The proposed starting materials are acceptable. The crystalline form is stable during storage and no unwanted polymorphs are formed.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It was established in house and contains tests for appearance, identification, water content, sulphated ash, heavy metals, related compounds, enantiomeric purity, assay, residual solvents and polymorphic form. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three commercial scaled batches stored at 30°C/65% RH (18 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The batches were stored in the proposed packaging. No trends or significant changes were observed. The proposed re-test period of 30 months without any storage condition is acceptable.

Lamivudine
The active substance lamivudine is described in the Ph.Eur., USP and British Pharmacopoeia. Lamivudine is a white or almost white powder and contains two stereogenic carbon centres. It is manufactures as a pure enantiomer. The active substance is known to be very soluble. Form II was chosen to be the final polymorphic form due to its good flow property, bulk density and thermodynamic stability. The ASMF procedure is also used for this active substance.

Manufacturing process
The manufacturing process consists of five stages and is described in sufficient detail. The starting materials are acceptable. The solvents used in the manufacturing process are controlled by acceptable specifications.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meet the requirements of the Ph.Eur. monograph with respect to test parameters and limits. It is supplemented with additional tests and criteria for residual solvents, polymorphic form and particle size. A justification for the absence of a test for microbial contamination has been provided. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 30°C/65% RH (60 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The batches were stored in the proposed packaging. Additionally long term stability data (12 months) on three production scaled batches have been provided. A re-test period of 5 years with the storage condition “preserved in well-closed, light resistant container up to 30ºC” is acceptable.

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 and their functions is explained. The objective of the development was to create a stable formulation of abacavir and lamivudine in the form of a film-coated tablet comparable to that of the innovator product Kivexa.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Iviverz 600 mg/300 mg film-coated tablets and reference product, Kivexa 600/300 mg, film-coated tablets. The bioequivalence study test batch was manufactured according to the finalised manufacturing process

and composition. The composition of the batch used in the bioequivalence trial is identical to the final formulation chosen.

The dissolution profiles of the test and reference product that were used in the bioequivalence study were compared at three different buffers (0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8). The results demonstrate that the test batch is *in vitro* similar to the innovator product Kivexa in the three buffers tested. The comparative impurity and assay results were also found to be comparable.

Manufacturing process
The manufacturing process consists by wet granulation. This is considered a standard process and has been validated according to relevant European guidelines. Process validation data on the product have been presented for two full scaled batches. A commitment to perform validation of the manufacturing process on a third full scaled batch in accordance with the process validation protocol has been made.

Control of excipients
The excipients comply with their respective Ph.Eur. monographs. These 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, uniformity of mass, dissolution, content uniformity, related substances, crystalline form and microbial examination. 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 for two full scaled batches and one lab scaled 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 two full scaled batches and one pilot scaled batch stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The batches were stored in the proposed packaging. No changes or trends 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 30 months when stored in the proposed packaging. There are no special storage conditions. The in-use stability studies support an in-use shelf-life of 1 month when stored below 25ºC. The in-use stability studies will be repeated towards the end of the product's shelf life.

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 Iviverz 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 Iviverz 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 Kivexa 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 and lamivudine 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Iviverz 600 mg/300 mg film-coated tablets from (Actavis Group PTC ehf, Iceland) is compared with the pharmacokinetic profile of the reference product Kivexa 600/300 mg, film-coated tablets (ViiV Healthcare UK Limited, UK).

The choice of the reference product in the bioequivalence study is accepted, as Kivexa has been 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, open-label, balanced, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy male subjects, aged 19-41 years. Each subject received a single dose (600 mg/300 mg) of one of the 2 active substance 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 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 24 and 36 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 was withdrawn from the study due to an adverse event (elevated blood pressure), one subject due to vomiting and two subjects were withdrawn due to positive cotinine tests. One subject was a back-up to compensate for any drop-outs prior to dosing and did not complete the study. Therefore, a total of 29 subjects 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=29	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	16071 ± 2808	16393 ± 2804	5829 ± 1548	1.5 (0.5 - 3.5)	1.46 ± 0.19
Reference	16334 ± 3093	16698 ± 3069	5535 ± 1103	1.5 (0.5 – 4.0)	1.64 ± 0.88
***Ratio (90% CI)**	0.99 (0.96 – 1.02)	--	1.04 (0.97 – 1.13)	--	--
CV (%)	6.3	--	17.5	--	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 lamivudine under fasted conditions.

Treatment N=29	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	14100 ± 3245	14737 ± 3177	3001 ± 637	1.75 (1.0 – 4.0)	3.3 ± 1.3
Reference	14489 ± 3556	15086 ± 3522	3009 ± 718	2.0 (1.25 – 5.0)	3.5 ± 1.3
***Ratio (90% CI)**	0.98 (0.94 – 1.02)	--	1.01 (0.95 – 1.06)	--	--
CV (%)	8.4	--	11.8	--	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 Iviverz is considered bioequivalent with Kivexa.

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 Iviverz.

- Summary table of safety concerns as approved in RMP

Important identified risks	- ABC hypersensitivity reaction (including reduced vigilance following HLA-B*5701 testing) - Use in subjects with hepatic impairment
Important potential risks	- Long term risk of carcinogenicity and long term exposure to NRTIs - Use in pregnancy - Ischaemic cardiac events - Possible interaction of ABC with ribavirin - Possible interaction of ABC/3TC with tenofovir disoproxil fumarate - Risk of shorter time to virological failure
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 Kivexa. 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:
  - in the presence of skin rash; or
  - when developing 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 Kivexa. 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 PL 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.
In order to test the readability of the PL of Iviverz film-coated tablets, a total of 22 persons were questioned: 2 during the preliminary round of testing, and 2 groups of each 10 persons during the following 2 test rounds. A questionnaire of 15 questions on the leaflet content was used, addressing the safety and usage messages, and 4 additional questions to obtain feedback on the format of the leaflet. General and applicability questions were used to investigate the technical readability, comprehensibility of the text, traceability of the information and the applicability. During both test rounds with 10 participants in each round, information was located and understood by all subjects for all questions. All questions met criterion of 81% correct answers.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Iviverz 600 mg/300 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Kivexa 600 /300 mg film-coated tablets. Kivexa 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 Iviverz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 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
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product; Implementation of change(s) for which no new additional data is required to be submitted by the MAH	NL/H/3488/ 1/IB/001	IB	23-09-2016	23-12-2016	Approved	No