CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lamivudine/Zidovudine Aurobindo 150/300 mg, film-coated tablets Aurobindo Pharma B.V, the Netherlands

lamivudine/zidovudine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2590/001/DC
Registration number in the Netherlands: RVG 111576

21 May 2013

Pharmacotherapeutic group:	antivirals for treatment of HIV infections, combinations
ATC code:	J05AR01
Route of administration:	oral
Therapeutic indication:	Human Immunodeficiency Virus (HIV) infection
Prescription status:	prescription only
Date of authorisation in NL:	18 February 2013
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, MT, PT, RO, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Lamivudine/Zidovudine Aurobindo 150/300 mg, film-coated tablets from Aurobindo Pharma B.V. The date of authorisation was on 18 February 2013 in the Netherlands.

The product is indicated for antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

A comprehensive description of the indications and posology is given in the SPC.

Lamivudine and zidovudine are nucleoside analogues which have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both medicinal products are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-TP respectively. Their main modes of action are as chain terminators of viral reverse transcription. Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication in vitro; lamivudine is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Combivir 150/300 mg tablets, which has been registered in the EEA by ViiV Healthcare UK Limited since 19 March 1998 (original product). The product was authorised through centralised procedure EMEA/H/C/000190. The individual active substances were registered as single component formulations in 1987 (zidovudine; national registration in the Netherlands) and 1996 (lamivudine; centralised procedure).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Combivir 150/300 mg tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substances are lamivudine and zidovudine, established active substances described in the European Pharmacopoeia (Ph.Eur.*). Lamivudine is a white or almost white powder, which is soluble in water, sparingly soluble in methanol and slightly soluble in ethanol. Lamivudine appears in two crystalline polymorphic forms. The polymorphic form manufactured by the drug substance manufacturer is polymorph form II. Zidovudine is a white or brownish powder, which is sparingly soluble in water and soluble in anhydrous ethanol. Zidovudine shows no evidence of polymorphism.

The CEP procedure is used for both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
For both lamivudine and zidovudine the drug substance specification is in line with the Ph.Eur. and the CEP. Appropriate testing for additional parameters is performed. The specifications are 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 batches of lamivudine and for sixteen batches of zidovudine.

Stability of drug substance
For lamivudine, stability data were provided for three validation batches stored at long-term conditions (18 months) and accelerated conditions (6 months). The batches remained stable under accelerated and long-term storage conditions for all parameters tested. No specific trends were observed. In view of the stability data provided the claimed re-test period of 24 months is justified. No specific storage conditions are required.
For zidovudine, as stated on the CEP, the re-test period of the substance is 48 months in the proposed package.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Lamivudine/Zidovudine Aurobindo 150/300 mg is a white to off-white modified capsule-shaped, biconvex film-coated tablet with deep break line in between ‘J’ and ’59 on one side and break line on other side. The tablet can be divided into equal doses.

The film-coated tablets are packed in PVC/PVdC-Aluminium foil blisters and HDPE bottles with polypropylene closures.

The excipients are:
Tablet core - cellulose microcrystalline, sodium starch glycolate (Type A), silica colloidal anhydrous, magnesium stearate
Tablet coat - hypromellose (E464), titanium dioxide (E171), macrogol 400, polysorbate 80

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The product development objective was to develop a film-coated tablet that would be bioequivalent to the innovator product Combivir®. A wet granulation method was chosen and optimised during pharmaceutical development.
A bioequivalence study was carried out and sufficient *in-vitro* data complementary to the bioequivalence study have been provided. Dissolution profiles at three different pH values were determined for test and reference batches used in the bioequivalence study. More than 85% of both drug substances was released in 15 minutes in all three dissolution media for the test as well as the reference batch. The products can therefore be regarded as similar on quality grounds.
A breakability study was performed as per Ph.Eur. on the three submission batches. All individual masses were within the acceptance limits. The packaging material is commonly used for solid oral dosage forms. Moreover, the suitability of the packaging material was tested in stability studies. The pharmaceutical development of the product was adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation, followed by compression and coating, which are regarded as conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European Guidelines. Process validation data on the product was presented for three batches with the minimum proposed batch size. The MAH committed to validate three consecutive production-scale batches with the other proposed batch sizes post authorization.

Control of excipients
With the exception of the coating material, all excipients comply with the European Pharmacopoeia. For the coating material, a separate specification was provided. The analytical methods are adequately described. Specifications of the excipients are acceptable.

Quality control of drug product
The drug product specification includes tests for description, identification, average mass, uniformity of dosage units (by content uniformity), water content, subdivision of tablets, dissolution, assay, related substances, thickness and microbial contamination. Release and shelf-life limits for description, identification, average mass, uniformity of dosage units, subdivision of tablets, assay, identification of titanium dioxide, thickness and microbial quality are identical and acceptable. The analytical methods were adequately described. Validation data was provided for the method for identification, the methods for assay and related substances, the method for dissolution and for the harmonised method for the microbial contamination. Batch analytical data were provided for three batches with the minimum proposed batch size, demonstrating compliance with the proposed release specification.

Stability of drug product
Stability data on the drug product was provided on three batches stored at 25°C/60% (12 months) and 40ºC/75% RH (6 months). The batches were stored in the proposed commercial packaging (PVC/PVdC-aluminium blisters and HDPE bottles). The conditions used in the stability studies are according to the ICH stability guideline. Furthermore a long-term stability study in simulated bulk pack, a photostability study and an in-use stability study (under long-term conditions) in HDPE bottles have been performed. In the long-term and accelerated stability studies, no specific trends were observed for any of the tested parameters; all parameters remained within limits. In-use stability testing was also performed on the drug product packed in HDPE bottles (500's count) over a period of 12 months. No clear changes could be observed. In view of the provided stability data, the claimed shelf-life of 24 months is justified. The product

is not sensitive to light. No specific storage conditions are required. No clear changes could be observed in the in-use stability study.
The expiry dates are calculated in line with the *Note for Guidance on Start of the Shelf-life of the Finished Dosage Form*.

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.2 Non-clinical aspects

This product is a generic formulation of Combivir, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of the active substances released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Lamivudine and zidovudine are 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 in which the pharmacokinetic profile of the test product Lamivudine/Zidovudine Aurobindo 150/300 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Combivir 150/300 mg tablets (GlaxoSmithKline Pharmaceuticals S.A., Poland).

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

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 54 healthy male adults, aged 20-44 years. Each subject received a single dose (150/300 mg) of one of the 2 lamivudine/zidovudine formulations. The tablet was orally administered with 240 ml water after an overnight fast of approximately 10 hours. Fasting was continued for at least 4 hours. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00 and 30.00 hours after administration of the products.

The study design is acceptable, and the washout period is considered adequate ($t_{1/2}$ of lamivudine is 5-7 hours, and $t_{1/2}$ of zidovudine is 1-2 hours).

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

In total, 50 subjects completed both Period I and Period II. One subject was voluntarily withdrawn from the study in Period I before dosing. Two subjects were withdrawn from the study as they were absent for Period II check-in. A fourth subject withdrew his consent in Period II before dosing.

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

Treatment N=50	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6853.1 ± 1608.6	7178.8 ± 1631.4	1899.7 ± 584.1	1.00 (0.50 – 2.50)	3.23 ± 0.87
Reference	6679.7 ± 1568.0	6997.3 ± 1572.5	1775.5 ± 742.0	1.00 (0.50 – 2.50)	3.28 ± 0.86
***Ratio (90% CI)**	1.02 (0.98 – 1.07)	1.03 (0.99 – 1.07)	1.09 (1.01 – 1.16)	--	--
CV (%)	11.9	12.6	20.8	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of zidovudine under fasted conditions.

Treatment N=50	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2544.3 ± 599.7	2676.1 ± 604.9	2244.2 ± 1040.1	0.5 (0.17 – 1.50)	1.30 ± 0.20
Reference	2569.2 ± 721.0	2707.6 ± 736.4	2186.8 ± 1095.6	0.5 (0.17 – 2.00)	1.28 ± 0.20
***Ratio (90% CI)**	1.00 (0.96 – 1.04)	1.00 (0.96 – 1.04)	1.04 (0.92 – 1.18)	--	-
CV (%)	12.2	12.1	38.8	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of lamivudine and zidovudine under fasted conditions, it can be concluded that Lamivudine/Zidovudine Aurobindo 150/300 mg and Combivir 150/300 mg tablets are bioequivalent

with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
No deaths or serious adverse events were reported during this study. Four adverse events were reported in four subjects during the entire duration of the study. Two adverse events were reported during in-house stay of Period II and two adverse events were reported during post study evaluations.
In two subjects an adverse event of giddiness was reported on the day of dosing in Period II (Test product for one subject, reference for the other), which was mild and possibly related to the study drug, and was resolved on the same day. No concomitant medications were applied.
One subject experienced an adverse event of elevated platelet count level which was mild in nature and possibly related to the study drug. This subject did not report to the facility for further follow-up.
In a fourth subject an adverse event was observed of elevated eosinophil level which was mild in nature and possibly related to the study drug. The normal range was restored after 20 days.

Lamivudine and zidovudine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substances. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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).

Risk management plan
The combination of lamivudine and zidovudine was first approved in 1998, and there is now more than 10 years post-authorisation experience with the combination of these active substances. The safety profile of this product can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Combivir.

Readability test
The package leaflet has not been evaluated via a user consultation study. The PL of Lamivudine/ Zidovudine Aurobindo is identical to the centrally approved PL of Combivir 150/300 mg film-coated tablets.A waiver for user testing is approvable if both text and layout/design are in line with an already user tested and approved PIL. This is the case for the layout and design, which are the same has been user tested for another product in another decentralised procedure. Bridging is justified; separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lamivudine/Zidovudine Aurobindo 150/300 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is generic form of Combivir 150/300 mg tablet. Combivir 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Lamivudine/Zidovudine Aurobindo 150/300 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 January 2013. Lamivudine/Zidovudine Aurobindo 150/300 mg, film-coated tablets was authorised in the Netherlands on 18 February 2013.

The date for the first renewal will be: 20 January 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform process validation studies on the first three batches of Lamivudine and Zidovudine 150 mg/300 mg tablets.
- The MAH committed to continue the stability testing at long-term conditions (25ºC±2ºC/ 60%±5%RH) for up to 60 months.
- The MAH committed to perform accelerated and long-term stability studies on the first three production batches of the maximum batch size. Furthermore, long-term stability studies will be conducted on a minimum of one marketed production batch per year in the marketed pack.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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