CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

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

lamivudine

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/2268/001-002/DC
Registration number in the Netherlands: RVG 110409, 110414

22 October 2012

Pharmacotherapeutic group:	direct acting antivirals, nucleoside and nucleotide reverse transcriptase inhibitors
ATC code:	J05AF05
Route of administration:	oral
Therapeutic indication:	as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children
Prescription status:	prescription only
Date of authorisation in NL:	19 July 2012
Concerned Member States:	NL/H/2268/001/DC: decentralised procedure with DE, ES, FR, IT, MT, PT, RO and UK NL/H/2268/002/DC: decentralised procedure with DE, ES, FR, IT, MT, PT and 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 Aurobindo 150 mg and 300 mg film-coated tablets, from Aurobindo Pharma B.V. The date of authorisation was on 19 July 2012 in the Netherlands.

The product is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

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

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*, it 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 Epivir 150 mg/300 mg film-coated tablets which have been registered in the EEA by ViiV Healthcare UK Limited since 1996 (150 mg) and 2001 (300 mg) through a centralised procedure (MA-number EU/1/96/015/001 and EU/1/96/015/003).

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 Epivir 300 mg film-coated 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 these product types 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 substance is lamivudine is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white powder, which is soluble in water, sparingly soluble in methanol and slightly soluble in ethanol. Lamivudine appears in different polymorphic forms. Form II is produced.

The CEP procedure is used for the active substance. 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 new 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
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP. Additional tests for the polymorphic form II are included. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for seven batches.

Stability of drug substance
Stability data on the active substance were provided for three validation batches stored at long-term conditions (12 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 and the storage conditions (no specific storage conditions required) are justified.

** 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 Aurobindo 150 mg is a white to off-white, film coated, diamond shaped tablet, debossed with ‘Z’ and ‘25’ on either side of the score line on one side and plain with a score line on the other side. The size is 13.9 mm x 6.9 mm. The tablet can be divided into equal doses.

Lamivudine Aurobindo 300 mg is a grey, film-coated, diamond shaped tablet, debossed with ‘Z26’ on one side and plain on other side. The size is 17.5 mm x 8.6 mm.

The film-coated tablets are packed in clear PVC/Aclar – Aluminium foil blister packs and HDPE bottle packs with polypropylene closure.

The excipients are:

Tablet core - Microcrystalline Cellulose (E460), Sodium Starch Glycolate (Type A), Magnesium Stearate (E572).
Film-coating 150 mg - Hypromellose (E464), Macrogol (400), Titanium Dioxide (E171), Polysorbate 80 (E433).
Film-coating 300 mg - Hypromellose (3cps) (E464), Hypromellose (6cps) (E464), Titanium Dioxide (E171), Macrogol (400), Polysorbate 80 (E433), Iron Oxide Black (E172).

Both tablet strengths are fully dose proportional.

The excipients and packaging are usual for this type of dosage form.

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 Epivir®.
A wet granulation method was chosen and optimised during pharmaceutical development. The development was started with the 300 mg strength and the optimised formulation could be successfully applied to the 150 mg strength to obtain a dose proportional formulation.
A bioequivalence study for the 300 mg was carried out and a waiver is requested for the 150 mg. From a chemical-pharmaceutical point of view, there is no objection. Dissolution profiles at three different pH's were determined for test and reference batches used in the bioequivalence study. More than 85% of drug was released in 15 minutes in all three dissolution media for the test as well as the reference batch. The products can be regarded as similar without further mathematical evaluation.
Lamivudine Aurobindo 150 mg tablets bear a score line on the tablet to facilitate division of the tablets into two equal parts. A breakability study was performed as per Ph.Eur. on the three submission batches. All individual masses were within the acceptable limits of 85%-115% of the average mass.
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 maximum proposed batch size post authorisation.

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 weight, uniformity of dosage units, water content, subdivision of tablets, dissolution, assay, related substances, thickness and microbial contamination. Release and shelf-life limits are acceptable. The analytical methods were adequately described. Validation data was provided for the UV methods for identification and dissolution, the HPLC methods for assay and related substances and 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 for both tablet strengths stored at 25°C/60% (12 months), 30%/75%RH and 40ºC/75% RH (6 months). The batches were stored in the proposed commercial packaging (PVC/Aclar blisters and HDPE bottles). The conditions used in the

stability studies are according to the ICH stability guideline (or as required for Zone IV requirements). 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. Photostability was demonstrated. In the long-term and accelerated stability studies, no specific trends were observed for description, water content, dissolution, related substances and microbial contamination, all parameters remained within limits. The results for assay show variation that is addressed by the MAH. In view of the provided stability data, the claimed shelf-life of 24 months is justified, a storage condition reading “store below 30°C” is also justified. The lamivudine 150 mg and 300 mg tablets can be stored at long-term conditions in the simulated bulk pack for a period of 12 months.
No clear changes could be observed in the in-use stability study, the product remains stable for the intended period of use. The MAH states that 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
No material derived from or exposed to animals infected by TSE/BSE has been used in the manufacture of lamivudine tablets. Lamivudine tablets are thus free from potential risks associated with the transmission of TSE/BSE. TSE certificates for all excipients and for the drug substance are included.

II.2 Non-clinical aspects

This product is a generic formulation of Epivir, 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 lamivudine 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 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 in which the pharmacokinetic profile of the test product Lamivudine Aurobindo 300 mg film-coated tablets (Aurobindo Pharma B.V, the Netherlands) is compared with the pharmacokinetic profile of the reference product Epivir 300 mg film-coated tablets (GSK, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study from the German market is justified, as the product 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, 2-way cross-over study bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-45 years. Each subject received a single dose (300 mg) of one of the 2 lamivudine formulations. The formulations were administered in solid form with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 and 30 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence is 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
Twenty-eight healthy male subjects were included in this study. Three subjects did not report for check-in for Period II. Twenty-five subjects completed the study and were included in the analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	14765 ± 4355	15126 ± 4390	3562 ± 1182	1.18 ± 0.53	4.1 ± 1.6
Reference	14606 ± 4323	15028 ± 4367	3297 ± 1038	1.44 ± 0.74	4.6 ± 1.9
***Ratio (90% CI)**	1.01 (0.93 - 1.09)	1.00 (0.93 - 1.08)	1.07 (0.96 - 1.18)	-	-
CV (%)	15.6	15.2	21.4	-	-

$AUC_{0-\infty}$ 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 under fasted conditions, it can be concluded that Lamivudine Aurobindo 300 mg and Epivir 300 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Lamivudine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of lamivudine. 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.

Extrapolation to 150 mg strength
The 150 and 300 mg tablets are dose-proportional and have been manufactured by the same process. Dissolution profiles at three different pH's were shown to be comparable. Lamivudine shows linear pharmacokinetics. The results from the study with the 300 mg can be extrapolated to the 150 mg strength.
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

Lamivudine was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lamivudine 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 product Epivir 150 mg and 300 mg film coated tablets marketed by ViiV Healthcare UK Limited.

Readability test

The proposed PIL text of Lamivudine Aurobindo 150 mg and 300 mg film coated tablets is the same as the PIL text of Epivir, which has been Centrally approved throughout the EEA via EMA Product number EMEA/H/C/000107. A user test of this PIL was approved in August 2010.
Considering the above a waiver for conducting user testing on the PIL of Lamivudine Aurobindo 150 mg and 300 mg film coated tablets proposed for this DCP was requested and granted.

The lay-out of the Lamivudine Aurobindo 150 mg and 300 mg film coated tablets is identical to the User tested PILs of Aurobindo's in-house style and Aurobindo Pharma Limited has successfully performed User testing with the in-house lay-out for more than 40 products.
Regarding design and lay-out of the PILs of Lamivudine Aurobindo 150 mg and 300 mg film coated tablets, both PILs were bridged with Ramipril Aurobindo user tested PIL, which was approved during procedure MT/H/0103/001-002/DC. Justification for bridging was considered acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lamivudine Aurobindo 150 mg and 300 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Epivir 150 mg and 300 mg film coated tablets. Epivir 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 and are in agreement with other lamivudine containing products.

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 Aurobindo 150 mg and 300 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 25 June 2012. Lamivudine Aurobindo 150 mg and 300 mg film-coated tablets were authorised in the Netherlands on 19 July 2012.

The date for the first renewal will be: 25 June 2017.

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

Quality - active substance

- The MAH committed to continue the stability testing at least up to the proposed re-test period. At least one commercial scale batch (if manufactured) will be added annually to the stability program and shall be tested at least once a year to confirm the re-test period through the proposed stability duration. The authorities shall be informed immediately in case out of specification results are observed.

Quality - medicinal product

- The MAH committed to perform process validation studies on the first three production scale batches (maximum batch size) of lamivudine 150 mg and 300 mg tablets, as well as on the first three batches of common blend with different batch sizes. Results of these studies shall be reported to the authorities when unexpected events and/or out-of-specification results are observed.
- The MAH committed to provide batch analytical data of three consecutive production scaled batches of the drug product with the maximum batch size when available.
- The MAH committed to continue the stability testing up to the proposed shelf-life.
- The MAH committed to perform accelerated and long-term stability studies on the first three production batches of the maximum batch size for each strength of lamivudine as and when they are manufactured based on the commercial and demand requirements. The MAH also includes the intermediate conditions in the protocol, the samples stored at intermediate conditions (i.e. 30 °C/65 % RH) shall be analysed only if any significant change is observed in the stability data of samples stored at accelerated conditions (i.e. 40°C/75% RH). Furthermore, long-term stability studies will be conducted on a minimum of one marketed production batch per year in the marketed pack. Results will be submitted to the agency up tot the period of shelf-life.
- The MAH committed to continue the on-going in-use study (i.e. 24 months etc.), but results shall be used to substantiate the suitability of HDPE container after first opening in case shelf-life extension is considered for Lamivudine tablets in the future.

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