CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lamivudine/Zidovudine Mylan 150/300 mg, film-coated tablets Mylan 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/2059/001/DC
Registration number in the Netherlands: RVG 107779

21 September 2011

Pharmacotherapeutic group:	antivirals for treatment of HIV infections, combinations
ATC code:	J05AR01
Route of administration:	oral
Therapeutic indication:	antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection
Prescription status:	prescription only
Date of authorisation in NL:	31 August 2011
Concerned Member States:	Decentralised procedure with BE, CZ, DE, ES, FR, IT, LU, MT, PL, PT, RO, SK, 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 Mylan 150/300 mg, film-coated tablets from Mylan B.V. The date of authorisation was on 31 August 2011 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 mg/300 mg film-coated tablets which has been registered in the EEA since 1998 by Glaxo Group Limited through a centralised procedure (MA number EU/I/98/058/001-002)

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 mg/300 mg, 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 lamivudine
The active substance 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 Active Substance Master File (ASMF) procedure is used for lamivudine. 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 synthesis process of lamivudine has been described in sufficient detail, including the used starting materials, solvents and reagents. Lamivudine is formed in a three-step process. The active substance has been adequately characterized. No class 1 organic substances are used in the manufacturing processes.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur monograph and ICH requirements. Batch analytical data demonstrating compliance with the drug substance specification have been provided on nine batches.

Stability of drug substance
For lamivudine stability studies were conducted on 18 batches in the commercial packaging under long-term (up to 60 months) and accelerated conditions (6 months). The stability results show that under both conditions all parameters comply with the proposed specification and no significant changes or trends has been observed. Also no degradation was observed after exposure of the solid product to heat and light (fluorescence and UV).
Based on the above observations a re-tests period of 60 months was granted and no special storage conditions are required.

** 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.*

Active substance zidovudine
The active substance zidovudine is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or brownish powder, which is sparingly soluble in water and soluble in anhydrous ethanol.

For zidovudine the CEP procedure is used. 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 monograph and the additional requirements from the CEP. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Lamivudine/Zidovudine Mylan 150/300 mg is a white to off-white, capsule shaped, biconvex film-coated tablet, debossed with “M” on the left of the scoreline and “103” on the right, on one side of the tablet, and scored on the other side.
The tablet can be divided into equal halves.

The film-coated tablets are packed in PVdC-PVC / Aluminium foil blisters or HDPE bottles with PP screw cap with desiccant.

The excipients are:
Tablet core - cellulose microcrystalline (E460), colloidal anhydrous silica (E551), sodium starch glycolate, magnesium stearate (E572)
Film-coating - hypromellose (E464), titanium dioxide (E171), propylene glycol (E1520).

Pharmaceutical development
The pharmaceutical development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were comparative dissolution studies and optimising the manufacturing process. The bioequivalence study was performed on one batch with the same composition as the commercial batches. Bioequivalence and reference batches have comparable dissolution profiles at the three tested pH values, which were in line with the guideline on “the investigation of bioequivalence”. Breakability is tested in accordance with Ph.Eur. requirements.

Manufacturing process
The tablets are made by blending of the ingredients followed by direct compression and film coating. Adequate in-process controls have been specified. Validation protocols and reports for the first three batches of tablets manufactured have been provided. The MAH committed to perform process validation studies on the first 3 production-scale batches of tablets.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, uniformity of dosage units, loss on drying, dissolution, assay, related substances, uniformity of mass and microbial contamination.
The release and end of shelf-life requirements are identical, except for loss of drying. The analytical methods have been satisfactory validated. Batch analytical data have been provided on 4 full-scale batches, demonstration compliance with the specifications.

Stability of drug product

Stability data on the product has been provided for three full-scale batches stored at 30°C/75% RH (36 months) and 40°C/25% RH (6 months) in blister pack and for four full-scale batches stored at 30°C/75% RH (3 and 36 months) and 40°C/25% RH (6 months) in HDPE bottle pack. In simulated bulk stability data has been provided for three full-scale batches stored at 30°C/75% RH (12 months) and 40°C/25% RH (6 months) The conditions used in the stability studies are according to the ICH stability guideline.
All tested parameters are within specifications. In general an upwards trend is seen in the percentage for the loss of drying under all storage conditions for the blister and HPDE packaging. For none of the other tested parameters a clear change is observed.
The in-use stability data included in provided indicate that no in-use shelf-life is necessary. Furthermore the data have been provided, demonstrating that the drug product is photostable.
The proposed shelf-life of 48 months (blister and bottle) or 12 months (bulk) was granted, without special 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. Magnesium stearate used in the formulation does not contain any material from animal origin and therefore is free from any TSE/BSE risk. The stearic acid used as a raw material in the manufacture of magnesium stearate is produced from natural palm oil. A certificate is included.

II.2 Non-clinical aspects

This product is a generic formulation of Combivir, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 and zidovudine 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 substances with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Lamivudine/Zidovudine Mylan 150/300 mg (Mylan B.V., NL) is compared with the pharmacokinetic profile of the reference product Combivir 150/300 mg film-coated tablets (GSK, UK).

The choice of the reference product
The reference product has been registered through a centralised procedure and is therefore the same across the EEA.
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 46 healthy male subjects, aged 21-44 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. A subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24 and 36 hours after administration of the products.
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

Forty-four healthy male subjects (+ 2 stand-by) were included in this study. Two subjects were withdrawn before start of the study because of AEs. These were replaced by the 2 stand-by subjects. Forty-four subjects completed the study and were included in the analysis as described in the protocol.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of lamivudine under fasted conditions

Treatment N=44	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6234 ± 1662	6647 ± 1424**	1729 ± 559	1.17 ± 0.53	2.6 ± 1.0**
Reference	6313 ± 1400	6600 ± 1467	1792 ± 559	1.00 ± 0.51	2.6 ± 0.6
***Ratio (90% CI)**	1.02 (0.98-1.06)	1.01 (0.98-1.05)	1.00 (0.94-1.06)	--	--
CV (%)	10.1	10.1	16.8	--	--

$AUC_{0-\infty}$ 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*
***43 subjects*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of zidovudine under fasted conditions

Treatment N=44	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2440 ± 764	2571 ± 671**	2119 ± 1150	0.64 ± 0.41	1.3 ± 0.2**
Reference	2531 ± 649	2605 ± 653	2341 ± 1109	0.56 ± 0.40	1.3 ± 0.2
***Ratio (90% CI)**	0.99 (0.94-1.04)	0.99 (0.95-1.04)	0.92 (0.82-1.05)	--	--
CV (%)	13.2	12.7	35.0	--	--

$AUC_{0-\infty}$ 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*
***43 subjects*

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 Mylan 150/300 mg and Combivir 150/300 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.

From the literature it is known that the extent of lamivudine and zidovudine absorption (AUC) and estimates of half-life following administration of the product with food were similar when compared to fasting subjects, although the rates of absorption (C_{max}, t_{max}) were slowed. Based on these data lamivudine/zidovudine may be administered with or without food. 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 active substance. The safety profile of lamivudine/ zidovudine can be considered to be well established. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.
At a European level, a Risk Management Plan (RMP) has been agreed for lamivudine/zidovudine combination in children weighing 14 kg or more in view of potential safety concerns (see EPAR on the EMA website).
The MAH committed to develop and implement the Risk Management Plan (RMP) following the grant of the license and before the launch of the product onto the market. The following safety concerns will be covered:

- Dosing recommendations resulting in over exposure
- Inhomogeneous dosing regimen in children weighing 21 to 30 kg
- Risk of choking associated with tablets in younger children
- Carcinogenicity in children exposed to NRTIs.

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 been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each.
A total of 18 questions specific to Lamivudine/Zidovudine Mylan were asked. Additionally the questionnaire included three questions on the presentation of the information. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both test rounds, more than 90% of the questions were correctly located and answered. The user test demonstrates that the leaflet complies with the requirements.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lamivudine/Zidovudine Mylan 150/300 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Combivir 150/300 mg. 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 Mylan 150/300 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 July 2011. Lamivudine/Zidovudine Mylan 150/300 mg, film-coated tablets was authorised in the Netherlands on 31 August 2011.

The date for the first renewal will be: 5 July 2016.

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 3 production-scale batches of tablets.
- The MAH committed to place one production batch of the highest batch size packed in blister material on stability at long-term conditions over the proposed shelf life and at accelerated conditions over 6 months.

Risk Management Plan

- The MAH committed to develop and implement the Risk Management Plan (RMP) following the grant of the license and before the launch of the product onto the market.

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