

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Lamivudine Hetero 100 mg, 150 mg and 300 mg,
film-coated tablets
Hetero Europe, Spain**

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/2661/001-003/DC
Registration number in the Netherlands: RVG 111863-111864, 111866**

7 October 2013

Pharmacotherapeutic group:	direct acting antivirals; nucleoside and nucleotide reverse transcriptase inhibitors
ATC code:	J05AF05
Route of administration:	oral
Therapeutic indication:	chronic hepatitis B in adults (100 mg); antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children (150/300 mg)
Prescription status:	prescription only
Date of authorisation in NL:	22 August 2013
Concerned Member States:	Decentralised procedure with DE, ES, IT, 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 Hetero 100 mg, 150 mg and 300 mg, film-coated tablets from Hetero Europe. The date of authorisation was on 22 August 2013 in the Netherlands.

The 100 mg product is indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis. Initiation of lamivudine treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier is not available or appropriate.
- decompensated liver disease in combination with a second agent without cross-resistance to lamivudine.

The 150 and 300 mg products are 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 HIV, and is also active against hepatitis B virus in all cell lines tested and in experimentally infected animals.

Lamivudine is metabolised by both infected and uninfected cells to the triphosphate (TP) derivative which is the active form of the parent compound. The intracellular half-life of the triphosphate in hepatocytes is 17-19 hours in vitro. Lamivudine-TP acts as a substrate for the HBV viral polymerase.

The formation of further viral DNA is blocked by incorporation of lamivudine-TP into the chain and subsequent chain termination.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zeffix 100 mg film-coated tablets, which is indicated for treatment of chronic hepatitis B, and Epivir 150 and 300 mg film-coated tablets, which are indicated as part of antiretroviral combination therapy for the treatment of HIV. Zeffix was authorized by GlaxoGroup Ltd on 29 July 1999 through Centralised Procedure EU/1/99/114/001-002. Epivir 150 mg and 300 mg were first registered by ViiV Healthcare UK on 8 August 1996 and 15 November 2001 through Centralised procedure EU/1/96/015/001&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 two bioequivalence studies in which the pharmacokinetic profile of the products is compared with the pharmacokinetic profile of the reference products Zeffix 100 mg film-coated tablets and Epivir 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 drug substance is lamivudine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Lamivudine is soluble in water, sparingly soluble in methanol, and slightly soluble in ethanol. Lamivudine appears in different polymorphic forms. Lamivudine form I is produced.

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 synthesis process of lamivudine including the used starting materials, solvents and reagents has been described.

Quality control of drug substance

For Lamivudine the drug substance specification is in-line with the Ph. Eur. monograph except for the specification on KF water content. However, it is stated in the Ph. Eur. monograph under Characters that lamivudine shows polymorphism. The difference is considered justified.

Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

For lamivudine stability studies were conducted on 4 batches for 18 months at 2-8°C, 6 months at 25°C/60% RH, and 12 months at 30°C/65% RH. All stability results meet the drug substance specification. One batch has been stored and tested at 40°C/75% RH during 6 months (with results meeting the requirements), and two other batches have been included in the accelerated study at 40°C/75% RH with 1 month results. The MAH committed that results of two additional batches drug substance in the accelerated studies at 40°C/75% RH will be submitted to the authorities. Based on this commitment the claimed re-test period of 2 years without specific storage condition, can be accepted.

* *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 Hetero 100 mg is a pink, capsule shaped, biconvex, film-coated tablet with a dimension of 12 x 6 mm, debossed with '37' on one side and 'I' on the other side.

Lamivudine Hetero 150 mg is a white, capsule shaped, biconvex scored film-coated tablet with a dimension of 15 x 6.5 mm, debossed with J on one side and 16 on the other side, 1 and 6 separated by a score line.

Lamivudine Hetero 300 mg is a white, capsule shaped, biconvex film-coated tablet with a dimension of 19.1 x 8.9 mm, debossed with 17 on one side and J on the other side.

The film-coated tablets are packed in Alu-Alu blister packs. The 150 and 300 mg tablets are also available in HDPE containers with a child resistant polypropylene cap.

The excipients are:

Tablet core - isomalt (E953), crospovidone type A, magnesium stearate (E572).

Coating 100 mg - hypromellose 6cp (E464), titanium dioxide (E171), macrogol 400, polysorbate 80 (E433), iron oxide red (E172), iron oxide yellow (E172).

Coating 150 mg and 300 mg - hypromellose 3cp (E464), hypromellose 6cp (E464), titanium dioxide (E171), macrogol 400, polysorbate 80 (E433).

The three strengths are dose proportional.

Pharmaceutical development

The pharmaceutical development of the product has been described, the choice of excipients is justified and their functions explained. The MAH discussed the choice for the polymorphic form I. In the majority of the countries lamivudine form II is protected by patents, *i.e.* form II cannot be considered for use. From the data provided it is concluded that potential issues with pharmaceutical processing of lamivudine form I are adequately covered. Breakability of the 150 mg tablet complies with the Ph.Eur. requirements.

Bioequivalence studies have been performed with the 100 mg and 300 mg strengths with the same composition as the commercial batches. The main development studies performed were comparative dissolution studies and optimising the manufacturing process. Bioequivalence and reference batches show comparable dissolution profiles at the three tested pH values and de-aerated water. The different dissolution conditions for the 100 mg and 150 mg tablet on the one hand and for the 300 mg tablets on the other hand are justified. All dissolution results for all 3 strengths in all used dissolution media were > 85% after 15 min. Regarding the performed bioequivalence studies the proposed product strengths were grouped into 1) 100 mg tablets (antiviral), and 2) 150 mg & 300 mg (anti-retroviral).

Manufacturing process

The manufacturing process is a standard process of sifting drug substance and all excipients, pre-lubrication blending, lubrication, compression, and film-coating. The standard process is well described. The proposed in-process controls and requirements are regarded acceptable. Two batches per strength have been validated. All results from the validation studies met the set acceptance criteria.

Control of excipients

All excipients are tested in accordance with their corresponding monograph, except for the Opadry film-coat mixtures, which are tested according to acceptable in-house procedures. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, water content by KF, average weight, uniformity of dosage units (based on weight), breakability for the 150 mg tablet, dissolution, HPLC assay, HPLC related substances, residual solvents and microbial contamination. The release and end of shelf-life requirements are identical, except for water content. In general, the analytical methods have been satisfactorily validated. Batch analytical data provided on two batches per strength comply with the specifications.

Stability of drug product

Stability data on the product has been provided on the same two validation batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) in Alu-Alu blister pack and HDPE bottle. The conditions used in the stability studies are according to the ICH stability guideline. In the stability studies no specific or significant changes have been observed; after 18 months the crystal form (Form-I) had not changed and the microbiological examination test met the specification. Based on the provided data, a shelf-life of 30 months can be granted.

Lamivudine was tested in a photo-degradation study. No significant change was observed. The product does not require any special storage conditions.

For the tablets in the HDPE containers the results of in-use stability studies were submitted. For the 100 mg strength for 2 batches in-use stability data at 25°C/60% RH has been provided for days 0, 30 and 60. For the 300 mg strength for 2 batches in-use stability data at 25°C/60% RH has been provided for days 0, 15 and 60. All results are satisfactory so far, no trends in the in-use stability data are observed. The proposed in-use shelf-life of 3 months, as mentioned in the corresponding SPCs, can be accepted.

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 is of vegetable origin.

II.2 Non-clinical aspects

These products are generic formulations of Zeffix and Epivir, which are 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 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 two bioequivalence studies in which the pharmacokinetic profile of the test products Lamivudine Hetero 100 mg and 300 mg (Hetero Europe, Spain) is compared with the pharmacokinetic profile of the reference products Zeffix 100 mg tablets (GSK, Germany) and Epivir 300 mg tablets (ViiV Healthcare, NL). There are two different Reference innovator products. Therefore two bioequivalence studies to support the application is considered adequate.

The choice of the reference product

The choice of the reference products in the bioequivalence studies is justified, as these have been registered through a Centralised Procedure across the EEA. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 100 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 20-44 years. Each subject received a single dose (100 mg) of one of the 2 lamivudine 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 at pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence is considered adequate.

Results

Two subjects were withdrawn due to adverse events and one due to protocol violation (tested positive for benzodiazepines). Furthermore two subjects did not check in for period II. Twenty-seven subjects completed the study and were included in the analysis.

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

Treatment N=27	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	4550 \pm 897	4710 \pm 910	1170 \pm 252	0.88 \pm 0.35	3.4 \pm 0.6
Reference	4580 \pm 1005	4730 \pm 1010	1140 \pm 318	1.12 \pm 0.50	3.3 \pm 0.9
*Ratio (90% CI)	1.00 (0.95 - 1.05)	1.00 (0.96 - 1.04)	1.05 (0.97 - 1.15)	--	--
CV (%)	9.9	9.3	18.6	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Hetero 100 mg and Zeffix 100 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.

Bioequivalence study II – 300 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 19-39 years. Each subject received a single dose (300 mg) of one of the 2 lamivudine 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 at 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, 16, 24 and 36 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence is considered adequate.

Results

One subject did not check-in for period II and one subject withdrew consent. Thirty subjects completed the study and were included in the analysis.

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

Treatment N=30	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	12130 \pm 2095	12380 \pm 2089	2770 \pm 731	1.07 \pm 0.41	5.4 \pm 2.7
Reference	12660 \pm 2547	1290 \pm 2540	2800 \pm 839	1.24 \pm 0.77	5.0 \pm 2.6
*Ratio (90% CI)	0.97 (0.91 - 1.03)	0.97 (0.91 - 1.03)	1.01 (0.92 - 1.10)	--	--
CV (%)	13.8	13.4	21.0	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Hetero 300 mg and EpiVir 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.

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 the 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 pHs 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. Lamivudine shows linear pharmacokinetics. All the criteria have been fulfilled for a biowaiver for the 150 mg strength.

The MEB has been assured that the bioequivalence studies have 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 SPCs approved during the decentralised procedure are in accordance with those accepted for the reference products Zeffix 100 mg and Epivir 150 and 300 mg film-coated tablets.

Readability test

The package leaflet has not been evaluated via a user consultation study. The MAH states that the readability of the PL for Lamivudine Hetero film-coated tablets is assured by using the originator's (Zeffix®) Package Leaflet (PL) text, and by applying the Hetero layout, which guarantees user friendliness as shown in several previously performed user-tests. This is considered acceptable.

It is agreed that an additional user test is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lamivudine Hetero 100 mg, 150 mg and 300 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zeffix 100 mg and Epivir 150 and 300 mg film-coated tablets. Zeffix and Epivir are well-known medicinal products 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 Hetero 100 mg, 150 mg and 300 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 9 May 2013. Lamivudine Hetero 100 mg, 150 mg and 300 mg, film-coated tablets were authorised in the Netherlands on 22 August 2013.

The date for the first renewal will be: 9 May 2018.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to submit results of two additional batches of drug substance in the accelerated studies at 40°C/75% RH.

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 _{1/2}	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