European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Lamivudine Teva

International Nonproprietary Name: **lamivudine**

Procedure No. EMEA/H/C/001113

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 5 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Lamivudine Teva, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to: Article 10(1) of Directive 2001/83/EC.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: **Epivir 150 mg film-coated tablets**
- Marketing authorisation holder: **Glaxo Group Ltd**
- Date of authorisation: **08-08-1996**
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation numbers: **EU/1/96/015/001 (Bottle), EU/1/96/015/004 (Blister pack)**

■ *Medicinal product authorised in the Community/Member State where the application is made or European reference medicinal product:*

- Product name, strength, pharmaceutical form: **Zeffix 100 mg film-coated tablets**
- Marketing authorisation holder: **Glaxo Group Ltd**
- Marketing authorisation numbers: **EU/1/99/114/001, EU/1/99/114/002**
- Marketing authorisation granted by:
  - Community

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: **Epivir 300 mg Tablets**
- Marketing authorisation holder: **GlaxoSmithKline**
- Date of authorisation: **08-08-1996**
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation numbers: **EU/1/96/015/003 (Bottle) EU/1/96/015/005 (Blister pack)**
- Bioavailability study number: **2008-1715**

The Rapporteur appointed by the CHMP was:
Rapporteur: Dr Dermolis

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 5 December 2008.
- The procedure started on 24 December 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 26 March 2009.
- During the meeting on 20 - 23 April 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 July 2009.
- During the meeting on 20 – 23 July 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Lamivudine Teva on 23 July 2009.

2 SCIENTIFIC DISCUSSION

3.1 Introduction

This is a generic medicinal product containing lamivudine as active substance. Each film-coated tablet contains 100 mg lamivudine; the product is indicated for the treatment of HBV infection. The reference medicinal product is Zeffix film-coated tablets which is part of the global marketing authorisation for lamivudine containing reference medicinal products.

Lamivudine is an antiviral agent with a pyrimidine nucleoside analogue structure, which suppresses HBV viral replication by terminating HBV DNA chain elongation. Lamivudine has been shown to enter HBV transfected and non-transfected HepG2cells (a human hepatoma-derived cell-line) where it is phosphorylated to lamivudine 5'-monophosphate (active form of the parent compound) by cytoplasmic deoxycytidine kinase. Intracellular phosphorylation of the monophosphate results in the formation of the 5'di- and 5'tri-phosphates. Lamivudine triphosphate acts as a substrate of HBV viral polymerase. The formation of further viral DNA is blocked by incorporation of lamivudine triphosphate into the chain.

The safety and efficacy profile of lamivudine for the treatment of HBV infection has been demonstrated in several clinical trials, details of which can be found in the EPAR for the reference medicinal product. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance. Since this application is a generic application referring to the reference medicinal product Zeffix, the pivotal basis is the demonstration of bioequivalence.

The indication proposed for Lamivudine Teva is the same as authorised for the reference medicinal product, which 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.
- decompensated liver disease.

3.2 Quality aspects

Introduction

The product is presented as film-coated tablets containing 100 mg lamivudine.

Other ingredients are:

Tablet core: microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate.

Film coating: hypromellose 3cP, hypromellose 6cP, titanium dioxide E171, macrogol 400, polysorbate 80, iron oxide yellow E172, iron oxide red E172.

The film coated tablets are packed in PVC/PVdC – Aluminium blisters and white HDPE containers with white opaque polyethylene child resistent screw cap with induction seal.

Active Substance

Lamivudine is a white or almost white powder that is soluble in water, sparingly soluble in methanol and slightly soluble in ethanol. Lamivudine has the chemical name 4-amino-1-[(2R,5S)-2-(hydroxymethyl]-1,3-oxathiolan-5-yl]pyrimidin-2(1H)-one hydrate (5:1). Lamivudine possesses two asymmetric carbons and is expected to be optically active. Lamivudine exists in two polymorphic forms.

- Manufacture

The manufacturing of lamivudine consists in two steps. The information on the manufacturing process is provided in an ASMF. Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory. Polymorphic forms and[c3] optical isomerism[c4]) are controlled during manufacture

- Specification

The specifications of the drug substance include description (Ph Eur), solubility (Ph Eur), identification (Specific Optical Rotation, IR, Enantiomeric purity), polymorphic identification (XRPD, DSC), absorbance, related substances, (Ph Eur), enantiomeric purity (Ph Eur), heavy metals (Ph Eur), water content (Ph Eur), residue on ignition (Ph Eur), assay (HPLC[c7]) and residual solvents (GC). The analytical methods used for control of active substance are methods described in the Ph Eur monograph 2217.

Batch analysis data (n=3) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

The stability studies have been carried out on four batches of active substance in long-term conditions (30°C/65% RH) and in accelerated conditions (40°C/75% RH). The data cover a period of 6 to 9 months in long term conditions and 6 months in accelerated conditions. The stability samples have been stored in a mini-size simulation of the original packing.
Parameters tested during stability studies are characterisation, identification (IR), polymorph identity XRPD), related substance (HPLC), water content and assay.
Forced degradation studies were performed by treatment with heat, light (UV light and visible light), under acidic and alkaline conditions, under oxidizing, reduction and hydrolysis conditions.
The stability results justify the proposed retest period.

Medicinal Product

- Pharmaceutical Development

The aim of the development pharmaceutics was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substance as the reference medicinal product. The dissolution tests described for the finished product were used as discriminating tests in order to select suitable formulations.
Different manufacturing processes for Lamivudine tablets (direct compression and wet granulation) were tested. Ultimately, the direct compression process was chosen based on appearance and quality attributes of the product, as well as the simplicity and effectiveness of this process.
The excipients used in the formulation are tablet core: microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate.film coating: hypromellose 3cP, hypromellose 6cP, titanium dioxide E171, macrogol 400, polysorbate 80, iron oxide yellow E172, iron oxide red E172.
All the excipients are tested according to the current European Pharmacopoeial specifications except the colorants which are tested as per in-house methods.
Tablets are packaged either with PVC/ PVdC blister or white opaque HDPE container with child resistant screw cap.The suppliers declare that their materials comply with the Ph. Eur. and Commission Directive 2002/72/EC as amended (relating to plastic materials intended to come into contact with foodstuffs).

- Manufacture of the Product

The manufacturing process is a standard direct compression. The manufacturing is divided into 6 main steps: initial blending, intermediate blending, final blending: lubrification, compression, coating and packaging.

- Product Specification

The finished product specifications include appropriate tests for description, identification of active substance (HPLC, UV), identification of Opadry colorants (HPLC), uniformity of dosage units (Ph Eur), dissolution (Ph Eur), assay ([c8]%, HPLC), impurities/degradation products (HPLC), microbial limit test (Ph Eur).

Batch analysis results (n = 2) confirm consistency and uniformity of manufacture and indicate that the process is under control.

- Stability of the Product

Two batches of the finished packed in the intended for marketing primary packaging (blisters and HDPE containers) were put on long-term (25°C/60%RH) for up 12 months for blisters and for up 9 months for HDPE containers, and accelerated (40°C/75%RH) for up 6 months stability testing ICH conditions. The following parameters were tested: description, assay, dissolution, impurities/degradation products, and microbiological quality.

The results support the shelf life in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3.3 Non-clinical aspects

No new non-clinical data were submitted in support of this application. The applicant provided an acceptable summary of the pharmacological, pharmacodynamic and toxicological properties of lamivudine from recent literature sources and on a literature research for recent non-clinical information relevant to the safety of lamivudine. The non-clinical aspects of the SPC are in line with the SPC of the reference product. No further studies are required and the applicant has justified why no such data was provided.

The impurity profile has been discussed and it was concluded that there are no significant differences between the impurity profiles of the generic product and reference products. The applicant provided a suitable justification for the absence of a formal environmental risk assessment, based on the expectation that introduction of these generic products onto the market is unlikely to result in an increase in the combined sales of all lamivudine-containing products, which in turn is unlikely to increase exposure of the environment to lamivudine.

3.4 Clinical aspects

Introduction

This is an abridged application for film-coated tablets containing 100 mg lamivudine. To support the marketing authorisation the applicant conducted a single dose bioequivalence study with cross-over design under fasting conditions using the 300 mg strength. This study was the pivotal study for the assessment. For the 100 mg strength the applicant then applied for a biowaiver.

A clinical overview was provided summarising the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of lamivudine based on a literature search; this overview was considered adequate. The SPC is in line with the SPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are of particular relevance.

GCP:

The pivotal study was complying with GCP, as claimed by the applicant. The applicant provided a statement to the effect that clinical trial 2008-1715 was conducted outside the community and was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant requested a biowaiver for the conduct of a bioequivalence study for the 100 mg strength based on the following justification related to the comparison with the 300 mg strength as well as characteristics of the active substance:

Both strengths of the generic medicinal product are manufactured by the same manufacturer and process, have the same qualitative composition, same ratio between amounts of active substance and excipients, and similar dissolution profile under identical conditions. Adequate dissolution profiles were provided. From a pharmacokinetic view point, lamivudine shows dose-linearity over the therapeutic range.

A bioequivalence study was conducted with the 300 mg strength. Based on the above information and taking into account the criteria laid out in the applicable Note for Guidance, the CHMP considered that a bioequivalence study with the 100 mg strength is not necessary. It was noted that the reference product used for the bioequivalence study is different from the reference product for the SPC; any potential differences between these formulations have been taken into account and were considered acceptable for the application of the biowaiver concept.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study; the details of this study are summarised in Table 1:

Table 1 Summary of study 2008-1715

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treat-ment
Determination of bioavailability between a generic medicinal product and a reference product under fasting conditions	Open-label, randomized, two period, two sequence, two treatment, crossover study	Two film-coated tablet formulations, 300 mg, oral	40 enrolled (38 comple-ted)	Healthy subjects	Single-dose

Pharmacokinetics

- Methods

STUDY DESIGN

Study 2008-1715 was an open label, randomised two-treatment, two-period, two-sequence, single-dose, crossover study conducted under fasting conditions.

The subjects were confined to the clinical facility for at least 10 hours prior to each drug administration until 24 hours after dosing. Subjects were randomly assigned to one of two dosing sequences.

In each period, an optional pre-study snack was provided to each subject after check-in and prior to fasting. Subjects fasted overnight for at least 10 hours prior to drug administration and for at least 4 hours following drug administration. Study drugs were administered with 240 ml of room temperature potable water. Standardized xanthine-free meals with caffeine-free beverages were provided to subjects at least 4 hours after drug administration in each period. Other standardized meals were served throughout the remainder of the confinement period. Other than the optional pre-study snack and the protocol specified meals, subjects were not allowed any other food or drink while confined in the clinic. With the exception of the water ingested during drug administration, water was not allowed from 2 hours prior to drug administration, until 2 hours post-dose.

Concentrations of lamivudine were measured from samples collected over a 24-hour interval after dosing in each period. Blood samples were collected pre-dosing and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post-dosing. [EMEA10]

The washout interval between both periods was 7 days.

The clinical part of the study, the bioanalytical analyses as well as the statistical analyses were performed by contract research organisations. [EMEA11]

The study protocol and consent form were reviewed and approved [EMEA13]by an ethics review board. [EMEA14]

TEST AND REFERENCE PRODUCTS:

Test Product:	Lamivudine 300 mg film-coated tablets
Manufactured by:	TEVA Pharm. Works Private Ltd, Hungary
Batch No.:	0110408
Manufacturing date:	04/2008

Reference Product:	Epivir 300 mg, film-coated tablets
Manufactured by:	Glaxo Smith Kline, France
Batch No.:	R314477
Expiry date:	06/2010

POPULATION(S) STUDIED

40 healthy volunteers, male and female, 18-55 years of age, with a BMI between 19 and 30 (inclusive), were randomised and enrolled into the study in order to allow for dropouts and withdrawals. The mean demographic data for all enrolled subjects are presented in Table 2.

Inclusion and exclusion criteria were acceptable for the product and for this type of study. Subjects abstained from ingesting products containing grapefruit, alcohol, caffeine, and/or xanthine for 48 hours prior to each drug administration and until after the last sample from each period was

collected. Subjects were not allowed to use any medications (prescription or over-the-counter), herbal/natural products and nutritional supplements for the 14 days preceding drug administration until completion of the entire study. Hormonal contraceptives, non-systemic, topically applied products (prescription or otherwise) or occasional use of common analgesics were allowed.

38 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Table 2 Summary of mean demographic data for enrolled subject (N = 40)

	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Mean	35	167.7	70.5	24.9
+/- SD	10	8.7	12.5	2.9
Median	35	168.5	67.7	25.4
Range	20-54	151.0-187.0	49.8-95.5	19.1-29.8

ANALYTICAL METHODS

The blood samples were analyzed using a LC-MS/MS Technique.
[EMEA17]
The analytical method was considered adequately validated.

PHARMACOKINETIC VARIABLES

The pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, C_{max} and T_{max} were determined. AUC was calculated by the trapezoidal rule. C_{max} and T_{max} were directly estimated from the individual concentration time profiles.

STATISTICAL METHODS

The statistical analysis was performed using SAS software.

Descriptive statistics were estimated for the pharmacokinetic parameters in each treatment. The least square means, the differences between the treatments least square means, and the corresponding standard errors of these differences were estimated for log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}.

ANOVA was performed on the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. In addition, ANOVA was applied to untransformed K_{el} and $T_{1/2}$ parameters. The ANOVA model included sequence, subject nested within sequence, period and treatment. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated. For the bioequivalence conclusion it was predefined that 90% geometric intervals of the ratio (Test/Reference) of least square means from the ln-transformed values for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} had to be within the range of 80-125%.

Non-transformed T_{max} was tested using the non parametric Wilcoxon test.

The statistical methods were adequately described and were deemed acceptable. There were no major protocol deviations.

- Results

38 out of 40 enrolled subjects completed the study and were included in the pharmacokinetic and statistical data analysis. Two subjects were excluded during the conduct of the study for the following reasons:
- One subject was tested positive for cotinine (exclusion criteria) at period II check-in and was therefore dismissed for non-compliance;
- One subject experienced nausea and loose stool after period II and was dismissed without being dosed.

At the beginning of period II, all pre-dose concentrations were below LLOQ except for one subject where pre-dose concentration was lower than 5% for C_{max}.

The pharmacokinetic parameters obtained in the 38 subjects who were included in the analysis are presented in Table 3. The results of the statistical analysis for ln-transformed data are displayed in Table 4.

Table 3 Pharmacokinetic parameters of study 2008-1715 (non-transformed values)

	Test			Reference		
	N	**Mean***	**SD****	**N**	**Mean***	**SD****
AUC_{0-t} [ng×h/ml]	38	14269.42	20	38	13926.42	21
$AUC_{0-\infty}$ [ng×h/ml]	38	14538.32	19	38	14212.01	20
C_{max} [ng/ml]	38	3672.89	27	38	3673.95	26
T_{max} [h]	38	1.19	47	38	1.27	74

$AUC_{0-\infty}$ 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
* Arithmetic mean
** Standard deviation

Table 4 Statistical analysis of study 2008-1715 (ln-transformed data)

Parameter	**Ratio of geometric means (%)**	**90% CI***		**Intra-subject CV (%)**
		Lower	**Upper**	
AUC_{0-t} (ng×h/ml)	101.93	98.20	105.80	10
$AUC_{0-\infty}$ (ng×h/ml)	101.81	98.29	105.45	9
C_{max} (ng/ml)	99.19	93.44	105.30	16

* 90% confidence intervals based on ln transformed values.

The 90% confidence intervals for the ratio of geometric means of AUC_{0-t}, AUC_{0-inf} and C_{max} (ln-transformed data) are within the limits of 80% to 125%.

A statistically significant difference (α =0.05) was detected between the two periods of the study in the analysis of AUC_{0-t} (p=0.0116) and AUC_{0-inf} (p=0.0144). No objective explanation could be given for this period effect. It is possible that the observed effect is due solely to chance. The least-squares means of the formulation effect were adjusted for the period effect. The final results are not influenced by the statistically period effect noticed for these parameters.

With regard to the individual plasma concentration time profiles, it was noted that the concentrations values measured for two subjects in period I appeared to have spurious concentration at four hours post-dose. This was explained by a possible sample switch, and a graphical analysis switching theses values in the profiles was performed to support this assumption. An additional statistical analysis was performed with the measured values for the lamivudine concentration at 4 hours post-dose in period I switched between these two subjects. It was confirmed that also in this analysis the 90% confidence intervals of the relative mean plasma lamivudine AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were within the 80-125% range.

Safety data

There were 29 adverse events (11 with the test product and 18 with the reference product) involving 15 subjects in the study. All adverse events were mild. 18 events were considered unrelated and 11 events possibly related.

One subject had a bruised left hand finger after period I dosing. The subject was not dismissed from the study, but deemed lost to follow up. Another subject experienced serious adverse events. These occurred after the completion of the clinical portion of the study and were considered not related to the product.

None of the AEs was considered to have a significant impact on the safety of the subjects or on the integrity of the study results.

- Conclusions

Based on the presented bioequivalence study Lamivudine Teva is considered bioequivalent with Epivir. The results of study 2008-1715 with the 300 mg film-coated tablet formulation can be extrapolated to other strengths of 100 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), section 5.4.

Pharmacodynamics

No new pharmacodynamic data have been provided by the applicant. These data are not required for this particular application.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring specific risk minimization activities have been identified. Therefore, a risk management plan was not considered necessary for this generic medicinal product.

- User consultation

The results of user consultation provided indicates that the Package leaflet is well structured and organized, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable in patients /users are able to act upon the information that it contains.

Discussion on Clinical aspects

A single dose bioequivalence study – randomized, two-sequence, two-period, two-treatment, cross-over study under fasting conditions – has been conducted with the 300 mg film-coated tablets. The design of the study is considered adequate.

The sampling period of 24 hours is sufficient to characterize the plasma concentration-time profile and to ensure measurements over a period of at least 5 half-lives based on the minimum expected $t_{½}$ of 5 hours. Blood sample timing is appropriate to allow an accurate measurement of T_{max}. The wash-out period of 7 days is long enough to avoid any carry over effect to the second period.

The 90% confidence intervals of AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were within the 80-125% range hence bioequivalence is concluded. The same statistical outcome was observed if the obtained values for the two subjects at 4 hours post-dose in period I, where an inadvertent switch is assumed, were switched. An observed statistical period effect did not impact on the final outcome and is considered a chance finding.

A biowaiver was applied for the 100 mg strength, which is subject to the present application. The conditions for a biowaiver (same manufacturer and process, linearity over the therapeutic range, same qualitative composition, same ratio between amounts of active substance and excipients, similar dissolution profile under identical conditions) have been fulfilled. Regarding the dissolution characteristics, it should be noted that the dissolution is not a rate-limiting step due to the high solubility of lamivudine and the solubility of lamivudine, which is practically pH independent. It was noted that the reference product used for the bioequivalence study is different from the reference product for the SPC; any potential differences between these formulations have been taken into account and were considered acceptable for the application of the biowaiver concept. Therefore, it is concluded that the biowaiver for the 100 mg film-coated tablet is acceptable and that no dedicated bioequivalence study is required.

3.6 Overall conclusions, risk/benefit assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality data. No new nonclinical data have been presented but an acceptable summary of the pharmacology, pharmacokinetics and toxicology of lamivudine has been provided. This is considered acceptable. From a clinical perspective, an appropriate summary of publicly available information regarding the pharmacokinetic and pharmacodynamics properties as well as the clinical efficacy and safety profile of lamivudine for the treatment of HBV infection has been presented.

The pivotal basis of this application is a bioequivalence study conducted with a single dose in fasting state against a reference product. The overall study design as well as the bioanalytical methods were acceptable for this purpose. Based on the statistical analysis of the obtained pharmacokinetic data, bioequivalence between the test and the reference product can be concluded as the 90% confidence intervals of the relative mean plasma lamivudine AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were within the 80-125% range. This study was conducted with the 300 mg film-coated tablet whereas the strength applied for is the 100 mg film-coated tablet. Since the applicable criteria related to the manufacturing of the product as well as the pharmacokinetic properties are fulfilled, the application of the biowaiver concept is acceptable hence bioequivalence can be considered demonstrated for this formulation.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Recommendation

Based on the CHMP review of available data, the CHMP considered that the benefit/risk ratio of Lamivudine Teva in 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.
- decompensated liver disease.

was positive and therefore recommended the granting of the marketing authorisation.