EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2010
EMA/41752/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lamivudine / Zidovudine Teva

International nonproprietary name: lamivudine / zidovudine

Procedure No. EMEA/H/C/001236

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 October 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lamivudine / Zidovudine Teva , through the centralised procedure falling within the scope of the Article 3 (3) – 'Generic of a Centrally authorised product' of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 June 2008

The legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC, as amended.

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Combivir instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Combivir 150/300 mg Film-coated Tablets
- Marketing authorisation holder: Glaxo Group Ltd.
- Date of authorisation: 18 March 1998
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation numbers: EU/1/98/058/001-002

■ 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: Combivir 150/300 mg Film-coated Tablets
- Marketing authorisation holder: Glaxo Group Ltd.
- Date of authorisation: 18 March 1998
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation numbers: EU/1/98/058/001-002
- Bioavailability study number(s): 2009-2018

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 Rapporteur appointed by the CHMP was:

Rapporteur: Dr. P. Demolis

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- The application was received by the Agency on 2 October 2009.
- The procedure started on 21 October 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 January 2010
- During the meeting on 15 – 18 February 2010, 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 22 February 2010
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 July 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 September 2010
- During the CHMP meeting on 20-23 September 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP list of outstanding issues on 18 October 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 5 November 2010
- During the meeting on 15-18 November 2010, 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 / Zidovudine Teva on 18 November 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 November 2010

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2. Scientific discussion

2.1. Introduction

Problem statement

Lamivudine/Zidovudine TEVA 150/300 mg, film-coated tablets is a generic medicinal product containing lamivudine and Zidovudine as active substances. The product is intended for the treatment of HIV infection. For this application, the reference medicinal product is Combivir.

Lamivudine and zidovudine are nucleoside analogues which have activity against HIV. 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.

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

The indication proposed for Lamivudine/Zidovudine TEVA is the same as authorised for the reference medicinal product, which is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

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2.2. Quality aspects

2.2.1. Introduction

The product is presented as scored film-coated tablets containing 150 mg of lamivudine and 300 mg of zidovudine as active substances.

Other ingredients are:
Tablet core: Microcrystalline cellulose, sodium starch glycolate (Type A), sodium stearyl fumerate
Tablet coat: Hypromellose, hypromellose, polysorbate 80, macrogol 400, titanium dioxide E171

The film-coated tablets are packed in OPA/Alu/PVC Aluminium blisters or HDPE tablet-containers with polyethylene child resistant screw cap with induction seal.

2.2.2. Active Substance

<u>Lamivudine</u>

The active substance lamivudine is described in the Ph. Eur.

Lamivudine is a white or almost white powder that is soluble in water, sparingly soluble in methanol and slightly soluble in ethanol. Its chemical name is 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 and are controlled during manufacture.

The information on the manufacturing process is provided in an ASMF. Two different manufacturing processes are presented. Lamivudine is controlled by the manufacturers according to the Ph Eur monograph with additional tests which concern technical properties of the active substance The specifications of the drug substance include appearance (Ph Eur), identification (specific optical rotation, IR, enantiomeric purity), absorbance, related substance (HPLC), enantiomeric purity (HPLC), heavy metals, water content (Karl Fischer), sulphated ash, assay, residual solvents (GC), particle size, bulk density (Ph Eur) and tapped density (Ph Eur). The analytical methods and the specifications used for control of active substance are the same as in the Ph Eur monograph except loss on drying (water content instead). Batch analysis data (n=2) of the active substance is provided. The results are within the specifications and consistent from batch to batch.

Stability studies were carried out on 7 batches of lamivudine obtained with the two manufacturing processes applied for (4 batches and 3 batches). Up to 18 months under ICH long-term conditions (30°C/65% RH) for and 6 months under ICH accelerated conditions (40°C/75% RH) were provided. The stability samples were stored in a mini-size simulation of the original packing. Parameters tested during stability studies were character, identification (IR), polymorph identity (XRPD), related substances (HPLC), water content and assay. Forced degradation was studied under different stress conditions: treatment with heat, treatment with light (UV light and visible light), acidic conditions, alkaline conditions, and hydrolysis conditions. In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA. The stability results justify the proposed retest period when stored in the original packaging material.

Zidovudine

The active substance zidovudine is described in the Ph. Eur.

Zidovudine is a white or brownish powder that is sparingly soluble in water and soluble in anhydrous in ethanol. Its chemical name is 1-(3-azido-2, 3-dideoxy-ß-Derythro- pentofuranosyl)-5-methylpyrimidine-2, 4(1H, 3H)-dione. Zidovudine possesses one asymmetric carbon and is expected to be optically active. Zidovudine shows polymorphism.

The information on the two different manufacturing processes proposed is provided in an ASMF. In addition to the tests detailed in zidovudine Ph. Eur. monograph, tests for particle size distribution, density, residual solvents and microbial testing are performed. The specifications of the drug substance include appearance (Ph Eur), identification (IR), appearance of solution, specific optical rotation, related substances (TLC, HPLC), heavy metals, loss on drying, sulphated ash, assay, residual solvents (GC), particle size distribution, bulk density, tapped density and microbiological quality (Ph Eur). The analytical methods used for control of active substance are methods described in the Ph Eur. Batch analysis data (n=3) of the active substance is provided. The results are within the specifications and consistent from batch to batch.

The stability studies were carried out for zidovudine on 6 batches at long-term conditions (30°C/65% RH) for up to 48 months and at accelerated conditions (40°C/75% RH) for 6 months. The stability samples were stored in a mini-size simulation of the original packing. Parameters tested during

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stability studies are description, identification by IR, specific optical rotation, water content, related substance by TLC and HPLC and assay. Forced degradation was studied under different stress conditions: treatment with heat, treatment with light (UV light and visible light), acidic conditions, alkaline conditions, and hydrolysis conditions. In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA. The stability results justify the proposed retest period when stored in the original packaging material.

2.2.3. Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to obtain immediate-release scored tablets containing qualitatively and quantitatively the same active substance as the reference medicinal product and exhibiting the same bioavailability. Dissolution studies were performed in order to demonstrate equivalence between the reference medicinal product and the generic with regard to lamivudine and zidovudine release, and as discriminating tests in order to select suitable formulations. The choice of dissolution conditions was well demonstrated. Lamivudine and Zidovudine can be classified as a Class 3 drug according to the Biopharmaceutics Classification System (BCS). These active substances are characterized by a high solubility and a low permeability and in these cases the dissolution is not rate-limiting step.

Different manufacturing processes for the finished product (direct compression, low shear wet granulation and fluid bed granulation) were tested. Ultimately, a dry roller compaction process was chosen. The final formulation was selected where zidovudine, microcrystalline cellulose, and half of magnesium stearate in the formula were pre-blended, roller compacted and milled prior to incorporation of the rest of the ingredients.

The excipients used in the formulation are tablet core: microcrystalline cellulose, sodium starch glycolate (Type A), sodium stearyl fumarate, and tablet coating: hypromellose, hypromellose, polysorbate 80, macrogol 400, titanium dioxide E171. All the excipients are tested according to their current Ph. Eur. specification except the colorants which are tested as per in-house methods. The excipients selected are all standard and commonly used in the pharmaceutical industry. Most of them are also present in the formulation of the innovator product. Therefore they are expected to be compatible.

Tablets are packaged either with OPA/Alu/PVC Aluminium blisters or HDPE tablet-containers with polyethylene child-resistant screw cap with induction seal. The choice of the primary packaging was justified by stability studies.

Adventitious agents

Lamivudine-Zidovudine tablets do not contain ingredients derived from animals. TSE/BSE statements from each supplier were provided.

Manufacture of the Product

The manufacturing process is a standard compaction and direct compression. The manufacturing is divided into 9 main steps: initial blending, intermediate blending I, roller compaction, milling, intermediate blending II, final blending, compression, coating and packaging.

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The process validation protocol provided is satisfactory.

The manufacturing process will be validated according to this protocol on three consecutive production batches before marketing and after any major change of the process or equipment used.

Product Specification

The finished product specifications include appropriate tests for description, identification of active

substance (UPLC, TLC), identification of Opadry colorants (HPLC), uniformity of dosage units (Ph Eur), subdivision of tablets (Ph Eur), dissolution of the active substances (UPLC), assay, impurities/degradation products (UPLC), microbiological quality (Ph Eur).

Batch analysis results (n = 5) confirms consistency and uniformity of manufacture and indicates that the process is under control.

Stability of the Product

Stability studies were carried out on three pilot batches of non-scored tablets packed in the intended marketing primary packaging (blisters and HDPE tablet containers) stored at ICH long-term stability conditions (25°C/60%RH) for up 18 months, and at ICH accelerated stability conditions (40°C/75%RH) for up 6 months.

Stability studies were also carried out on three pilot batches of scored tablets in the intended marketing primary packaging (blisters and HDPE tablet containers) stored at ICH long-term stability conditions (25°C/60%RH) for up 3 months, and at ICH accelerated stability conditions (40°C/75%RH) for up 1 month.

In use stability studies were performed in HPDE tablet containers stored at 25°C/60%RH for up to 6 months.

The following parameters were tested: description, assay, dissolution, impurities/degradation products, and microbiological quality.

Additional stability studies were provided for one pilot batch of bulk tablets stored at 15-25°C max/70%RH.

In general, the results support the shelf life and storage conditions as defined in the SPC. In accordance with EU GMP guidelines[3], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has 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.

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2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

2.3. Non-Clinical aspects

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is based on literature searches and adequate scientific literature has been provided. The overview justifies why there is no need to generate new non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. There is thus no need for conducting tests on animals.

The Applicant has provided a statement to the effect that the preclinical studies reviewed from the literature and the data presented on stability and comparative impurity profile (originated from the laboratories or affiliates of TEVA Pharmaceuticals Europe) had been conducted according to GLP standards.

2.3.1. Ecotoxicity/environmental risk assessment

The applicant provided a suitable justification for the absence of a formal environmental risk assessment, based on the expectation that the introduction of Lamivudine/Zidovudine Teva manufactured by Teva Pharma B.V. onto the market is unlikely to result in any significant increase in the combined sales volumes for all lamivudine and zidovudine containing products and the exposure of the environment to the active substance. Thus, the CHMP endorsed that the ERA is expected to be similar and not increased.

2.4. Clinical Aspects

2.4.1. Introduction

To support the marketing authorisation the applicant conducted one bioequivalence study. Study 2009-2018 investigated the relative bioavailability of 150/300 mg Lamivudine/zidovudine film coated tablets (Teva Pharmaceutical Works Private Limited Company Ltd.) with that of 150/300 mg Combivir, film-coated tablets (GlaxoSmithKline, France) following a single oral dose (1 x 150/300 mg tablet) in healthy adult subjects when administered under fasting conditions.

A clinical overview was provided summarising the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of lamivudine and zidovudine based on a literature search; this overview was considered adequate. The SmPC is in line with the SmPC of the reference medicinal 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/EPW/QWP/1401/98) in its current version as well as the Questions & Answers on the

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Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are of particular relevance.

GCP

The bioequivalence study performed in accordance with GCP as claimed by the applicant.

Clinical studies

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

- Tabular overview of clinical studies

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 Treatment
Evaluate the comparative bioavailability between a generic medicinal product and a reference product under fasting conditions	Open-label, randomized, two period, two sequence, two treatment, crossover study	One film-coated tablet formulation, 300 mg, oral	62 enrolled (58 comple-ted)	Healthy subjects	Single-dose

2.4.2. Pharmacokinetics

This application contains a generic version of lamivudine tablets. Pharmacokinetic and pharmacodynamic properties of lamivudine and zidovudine have been demonstrated for the reference product. With the exception of bioequivalence data, this application contains no new data on the pharmacokinetics and pharmacodynamics of lamivudine and zidovudine. The Applicant's clinical overview of the clinical pharmacology is considered sufficient.

- Methods

Study design

The study was an open label, two-treatment, two-period, two-sequence, single-dose, crossover study conducted under fasting conditions with a wash out period of 7 days between administrations. 150/300 mg of lamivudine/zidovudine were administered in each period with 240 ml water after an overnight of at least 10 hours fasting period.

Subjects were randomly assigned to one of the two dosing sequences AB or BA (where treatment A is test product and treatment B is reference product) under fasting conditions. Pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and T_{half} were estimated based on plasma lamivudine and zidovudine levels for each subject included in the data set.

21 blood samples were collected pre-dosing and up to 36 h post-dosing (at 0 , 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, 24 and 36 hours) in each period.

Concentrations of lamivudine were measured from the samples collected over a 36-hour period after dosing in each period. Concentrations of zidovudine were measured from the samples collected over an

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8-hour interval after dosing in each period (at 0, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, and 8 hours).

Samples were assayed for lamivudine and zidovudine.

Study period:

March 30, 2009 to May 30, 2009.

Test and reference products

Test product:

Lamivudine/zidovudine 150/300 mg film-coated tablets (TEVA Pharm. Works Private Ltd, Hungary).

Mode of administration: 1 film-coated (=150/300 mg) administered with 240 ml of room temperature potable water. Batch number: 0190109. Manufacturing date: 01/2009.

Reference product:

Combivir 150/300 mg, film-coated tablets (Glaxo Smith Kline, France).

Mode of administration: 1 film-coated (=300 mg) administered with 240 ml of room temperature potable water. Batch number: R327048. Expiry date: 09/2009.

Population(s) studied

Based on historical data available to the sponsor regarding the intra-individual variability of AUC and C_{max} of lamivudine and zidovudine (35%) by oral route, the number of subjects to be included in an adequately powered study was estimated to be 58. Sixty-two healthy volunteers (i.e. 58 subjects + 4 extra subjects to account for dropouts) were randomised and enrolled into the study. Fifty-eighth volunteers completed the entire study and were thus analyzed.

The study population included non-smoking male and female volunteers from 18 to 55 years of age, with a BMI from 19 to 30, who were judged to be healthy based on medical history, ECG, laboratory evaluation and physical examination. Classical inclusion and exclusion criteria were followed.

The outcome of the study showed that a sufficient number of subjects was included in the study.

Four subjects were dismissed (subjects 7, 27, 33 and 36) without impacting the study.

- subject 07 voluntarily withdrew from the study prior to Period 2 check-in for personal reasons;
- subject 27 voluntarily withdrew from the study prior to Period 2 check-in due to adverse events (coughing and feeling warm);
- subject 33 voluntarily withdrew from the study prior to Period 2 check-in due to adverse events (pink eye, mucus discharge and extra tearing in both eyes);
- subject 36 was dismissed from the study at Period 2 check in due to non-compliance (consumed restricted item - grapefruit).

Analytical methods

Lamivudine

Subjects' plasma concentrations of lamivudine were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method which was developed, validated and further re-validated.

Zidovudine

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Subjects' plasma concentrations of zidovudine were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method.

Pharmacokinetic Variables

The relevant bioavailability parameters of lamivudine and zidovudine were estimated.

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

Statistical methods

GLM ANOVA was performed on the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. The ANOVA model included sequence, subject tested within sequence, period and product. Non-transformed T_{max} was evaluated and tested using a non parametric test. The statistical analysis was performed using SAS software.

Bioequivalence criteria:

90% geometric intervals of the ratio (Test/Reference) of least square means from the ln-transformed values for AUC_{0-t}, AUC_{0-inf} and C_{max} should be within 80-125%. T_{max} was tested using a null hypothesis non parametric test.

- Results

The results of Pharmacokinetic parameters are listed in table 1.

Table 1. Lamivudine

Treatment	Test (CV %)	Reference (CV %.)	*Ratio of geometric means (%) (90% CI)	Intra-subject CV (%)
AUC_{0-t} **hr.ng/ml**	6866.45 (22)	6876.66 (18)	99.11 [95.63-102.72]%	12 %
$AUC_{0-\infty}$ **hr.ng/ml**	7026.10 (21)	7025.40 (18)	99.44 [96.13-102.86]%	11 %
C_{max} **ng/ml**	1846.81 (31)	1721.07 (28)	105.99 [100.51-111.76]%	17 %
t_{max} **h**	1.09 (47)	1.16 (53)		

$AUC_{0-\infty}$ 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
**log-transformed values*

Table 2. Zidovudine

Treatment	Test (CV %)	Reference (CV %.)	*Ratio of geometric means (%) (90% CI)	Intra-subject CV (%)
AUC_{0-t} **hr.ng/ml**	2754.32 (34)	2763.89 (33)	100.05 [96.59-103.63]%	11 %
$AUC_{0-\infty}$	2789.06	2796.98	100.10	11 %

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hr.ng/ml	(34)	(33)	[96.66-103.66]%	
C_{max} **ng/ml**	2554.28 (40)	2494.98 (42)	105.13 [95.63-115.57]%	31 %
t_{max} **h**	0.59 (31)	0.56 (43)		

$AUC_{0-\infty}$ 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
**log-transformed values*

- Safety data

No serious adverse events were reported during the conduct of this study. None of the adverse event had a significant impact on the safety of the subjects or on the integrity of the study results.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and the CHMP endorsed that no such studies are required for this application.

2.4.4. Post marketing experience

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

2.4.5. Discussion and Conclusion on Clinical aspects

Lamivudine/Zidovudine TEVA is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

The efficacy and safety of lamivudine/zidovudine are well characterized. This generic application contains a clinical overview of the efficacy and safety of lamivudine/zidovudine (based on PUBMED search, extended to other sources of medicinal databases) and is considered sufficient.

To support the marketing authorisation of Lamivudine/Zidovudine TEVA, the Applicant has conducted a single dose (1 x 150/300mg), randomized, two-sequence, two-period, two-treatment, cross-over, bioequivalence study under fasting conditions.

Classical inclusion and exclusion criteria were followed. Sixty-two subjects were dosed in period 1 and 58 subjects were dosed in period 2. Fifty-eight completed the study. They received either one Lamivudine/Zidovudine 150/300 mg tablet or one Combivir 150/300 mg tablet with 240 ml of room temperature potable water. The design of the study is considered adequate. The sampling period of 36 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 t½ of 5 hours. Blood samples 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.

Analytical methods were well validated. The statistical methods have been adequately described and are acceptable and there are no major protocol deviations. Blood collection times were sufficient.

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Moreover during evaluation the Applicant submitted additional clarifications on the analytical part of the dossier:

- The potency of the Test product and the Reference product in the bio-study: the assay content of the test and reference batch did not differ by more than 5%, which was considered acceptable.
- The Applicant indicated that 51 samples for lamivudine and 9 samples for zidovudine were reanalyzed in accordance with the relevant SOP. The reason for reanalysis, the original value, the repeated value, the accepted value as well as the criteria of acceptance were deemed acceptable.

The CIs of the ratio Test/reference of AUC_{0-t} and AUC_{0-inf} parameters fell within the normal 80-125% acceptance range. Thus based on these parameters, the bioequivalence is considered demonstrated.

2.5. Pharmacovigilance

PSUR

The PSUR submission schedule should follow the PSUR schedule for the reference medicinal 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 additional risk minimization activities have been identified.

Routine pharmacovigilance activities according to volume 9A/ICH will be undertaken whilst the product is on the market, including careful review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports. Specific risk minimisation activities are not envisaged as the safety aspects of the product are well characterised and therefore a Risk Minimisation Plan is not required.

As the application is for a generic product of a reference medicinal product with a well-known safety profile, the Applicant did not consider necessary to establish a risk management plan containing other measures than routine pharmacovigilance. The CHMP agrees.

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2.6. User consultation

The user testing of the package leaflet was performed. The criterion for a successful Readability Test was fulfilled. The user testing of the package leaflet is judged acceptable by the CHMP.

2.7. Benefit/risk 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 and zidovudine 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 and zidovudine for the treatment of HIV 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 was 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/zidovudine AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were within the 80-125% range. Since the applicable criteria related to the manufacturing of the product as well as the pharmacokinetic properties are fulfilled, the bioequivalence can be considered demonstrated.

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/Zidovudine Teva as an antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) is favourable and therefore recommended the granting of the marketing authorisation.

Medicinal product no longer authorised