COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Lamivudine

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ABSTRACT: Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing lamivudine as the only active pharmaceutical ingredient were reviewed. The solubility and permeability data of lamivudine as well as its therapeutic index, its pharmacokinetic properties, data indicating excipient interactions, and reported BE/bioavailability (BA) studies were taken into consideration. Lamivudine is highly soluble, but its permeability characteristics are not well-defined. Reported BA values in adults ranged from 82% to 88%. Therefore, lamivudine is assigned to the biopharmaceutics classification system (BCS) class III, noting that its permeability characteristics are near the border of BCS class I. Lamivudine is not a narrow therapeutic index drug. Provided that (a) the test product contains only excipients present in lamivudine IR solid oral drug products approved in the International Conference on Harmonization or associated countries in usual amounts and (b) the test product as well as the comparator product fulfills the BCS dissolution criteria for very rapidly dissolving; a biowaiver can be recommended for new lamivudine multisource IR products and major post-approval changes of marketed drug products. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:2054–2063, 2011

Keywords: absorption; bioavailability; bioequivalence; biopharmaceutics classification system (BCS); biowaiver; lamivudine; permeability; solubility

INTRODUCTION

A biowaiver monograph of lamivudine based on literature data together with some additional experimental data is presented. The risks of basing a bioequivalence (BE) assessment on *in vitro* rather than *in vivo* study results for the approval of new immediate release (IR) solid oral dosage forms (so-called "biowaiving") containing lamivudine, including both reformulated products and new multisource drug products, are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing lamivudine as the only active pharmaceutical ingredient (API) and not to combination drug products. The purpose and scope of this series of monographs have been discussed previously.[1] To summarize in few words, the aim is to

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evaluate all pertinent data available from literature sources for a given API to assess the risks associated with a biowaiver. For these purposes, risk is defined as the probability of an incorrect biowaiver decision as well as the consequences of a "false positive" decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver approval is advisable or not. This systematic approach to recommend or advice against a biowaiver decision is referred to in the World Health Organization (WHO) guideline.[2] It is pointed out that these monographs do not simply apply the various guidelines on establishing BE, for example, by the European Medicines Agency (EMA),[3] the Food and Drug Administration (FDA)[4] or the WHO,[2] but also serve as a critical evaluation of these regulatory documents. Monographs for more than 20 APIs are available online at the website of the International Pharmaceutical Federation (FIP).[5]

GENERAL CHARACTERISTICS

Name

Lamivudine (INN)[6] or 3TC is a levorotatory pyrimidinone-1,3-oxathiolane derivative and has the molecular formula $C_8H_{11}N_3O_3S$. According to IUPAC nomenclature it is termed 4-amino-1-pyrimidin-2-one.[7,8] Lamivudine is the (−)-enantiomer of a dideoxy analog of cytidine[9] with a sulfur atom in place of the 3′ carbon of the ribose ring of 2-deoxycytidine.[10] It is therefore also named (−)2′,3′-dideoxy,3′-thiacytidine.[9,11] Alternatively, it can be referred to as (−)-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine[6,11] or 3′-thia-2′,3′-dideoxycytidine.[11]

The chemical structure of lamivudine is shown in Figure 1. Its molecular weight is 229.26 g/mol[7,12] and its melting point is 160°C–162°C.[11]

Therapeutic Indications

Lamivudine is an orally administered nucleoside reverse transcriptase inhibitor (NRTI) used in combination with other antiretroviral agents to treat human immunodeficiency virus (HIV) type 1 infection in patients with acquired immunodeficiency syndrome (AIDS) and as monotherapy in the treatment of hepatitis B virus (HBV) infection. It is a prodrug. The active form is lamivudine triphosphate (3TCTP),[13] which is generated via an intracellular triple phosphorylation process. Lamivudine triphosphate competitively inhibits viral reverse transcriptase by causing termination of DNA replication,[13,14] thus, interrupting HIV replication.

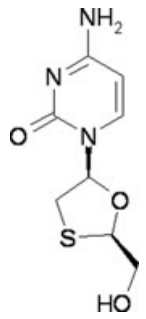

Figure 1. Structure of lamivudine.

THERAPEUTIC INDEX AND TOXICITY

The adverse events of lamivudine reported frequently in the literature include headache, insomnia, nausea, vomiting, diarrhoea, abdominal pain, fever, somnolence, eczema, alopecia, muscle pain, rhabdomyolysis, hepatitis, pancreatitis, peripheral neuropathy, and red cell aplasia, most of which are reported to be mild to moderate.[15–17] However, lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have also been reported.[15–17] On the basis of the information on the product label, the treatment should be suspended immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of lactic acidosis or pancreatitis occur.[15,16] In cases in which acute toxicity arises, lamivudine can be removed from the body by continuous hemodialysis over 24 h.[15,16,18]

Importantly for biowaiver considerations, almost none of the adverse events appear to be dose-related.[19–21] Over the dose range of 0.5 to 20 mg/kg/day, no limiting toxicities were observed.[21] Additionally, dosing regimen appears to have little influence on side effects: Lamivudine's safety profile does not significantly differ between 300 mg once a day and 150 mg given twice a day.[22] Studies in animals that focused on overdosing did not reveal any organ toxicity.[15–17]

Although a minimal cytotoxicity was observed in hemopoietic cell lines and in human peripheral blood lymphocytes during exposure to lamivudine,[23–25] it has been reported that lamivudine is much less toxic than the other NRTIs. Compared with these, lamivudine has only little activity against mammalian DNA polymerase γ and does not interact with mammalian mitochondrial DNA.[25,26] Thus, an induction of clinically important hematological[23] and hepatic adverse events, neuropathy, or myopathy by lamivudine is unlikely.[14,25]

Lamivudine has been reported to compete for the phosphorylation process with some other drugs, for example, cladribine[27] and zalcitabine,[9,19] thereby inhibiting their actions. However, in general, the risk of drug interactions with lamivudine is rather low. Lamivudine is not metabolized by the cytochrome P450 enzymes to any substantial degree;

it has a low metabolic clearance (CL) into a *trans*-sulfoxide metabolite, and exhibits low plasma protein binding.[15,16] Drugs that are primarily eliminated by active renal secretion might possibly interact with lamivudine.[19] For example, cotrimoxazole (combination of trimethoprim and sulfamethoxazole) has been shown to interfere with lamivudine,[14] with the area under the curve (AUC) of lamivudine increasing by about 44% and its renal CL (CL_R) decreasing by about 30%.[19,28] Competition of lamivudine and trimethoprim for the human organic cation transporter (hOCT) is the probable reason for this interaction, decreasing the renal tubular secretion of lamivudine.[28–30] By contrast, the pharmacokinetic parameters of cotrimoxazole are not altered by lamivudine coadministration. Thus, a dose adjustment of lamivudine when starting a course of cotrimoxazole therapy is not considered necessary,[19] unless the patient suffers from renal impairment.[15,16] According to the FDA[31] or Japanese Health Authorities,[32] lamivudine is not a narrow therapeutic index drug.

CHEMICAL PROPERTIES

Polymorphism

Lamivudine may exhibit polymorphism.[8] The API can appear either as acicular or bipyramidal crystals, but only the bipyramidal form is appropriate for the use in tablet manufacturing because of its superior flow properties and stability characteristics.[33,34] No data about potential differences in solubility or BA between the two polymorphic forms could be extracted from the literature.

Solubility

Some information about the solubility of lamivudine is available in the literature. Lamivudine is classified by WHO[8] as "soluble" in water. The Martindale[11] reported its solubility at 20°C as approximately 70 mg/mL. Fernandes et al.[34] obtained equilibrium solubility of lamivudine in water at 15.0°C as 52.8 mg/mL, at 25.0°C as 84.9 mg/mL, and at 35°C as 149.6 mg/mL. Neither of these sources indicates which polymorphic form was studied.

In order to further investigate whether lamivudine fulfils the highly soluble criterion by the EMA,[3] FDA,[4] or WHO,[2] additional solubility determinations in aqueous media were performed.[a] According to the current regulatory guidances, an API is highly soluble if its D/S is 250 mL or less at the pH range of 1.0–6.8,[3] 1.2–6.8,[2] or 1.0–7.5[4] at 37°C. However, the regulatory guidances differ in their definition of D. The FDA regulation defines D as the highest dose strength,[4] whereas the WHO[2] and the EMA[3] regulation defines D as the highest dose recommended by WHO and the highest single dose administered, respectively. However, for lamivudine, 300 mg is both the highest dosage form strength and the maximum daily dose, see below, and that amount dissolved at 37°C in less than 75 mL of solution across the pH 1 to 7.5 range (1.0, 1.2, 4.5, 6.8, 7.5, and in deionized water with a pH 6.5).[b]

Partition Coefficient

In the literature, various values for the log*P* of lamivudine have been reported. Kasim et al.[35] reported a log*P* of 0.06 and a calculated log*P* of −1.46 for lamivudine. In PubChem[7] the log*P* value is given as −0.9 and in Pharm I.S.[36] as −0.81 (calculated value). The DrugBank[12] indicates an experimental log*P* of −1.4 and a predicted log*P* value of −1.28 (using ALOGPS 2.1).

p*K*a

Lamivudine is a weak base with a pK_a of 4.3 (protonation of the NH_2 group).[33,37,38]

Recommended Dose and Dosage Form Strengths

The recommended oral dose of lamivudine for HIV treatment in adults is 300 mg/day, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral drugs.[15,16,39] For infants and children younger than 12 years of age, the recommended oral dose is 4 mg/kg twice daily (maximum 300 mg daily) that is approximately double the recommended dosage for adults on a per kilogram basis. In neonates (<1 month), however, the oral dose should be reduced to 2 mg/kg twice daily because of their immature renal function.[19,39]

Single API dosage forms of lamivudine for HIV treatment with marketing authorizations (MAs) in the European Union (EU),[40] Brazil (BR),[41] Canada (CA),[42] Spain (ES),[43] Hungary (HU),[44] Israel (IL),[45] New Zealand (NZ),[46] South Africa (SA),[47] and the United States (US) [48] are available in two dosage form strengths: 150 mg and 300 mg. The excipients of these products are given in Table 1.

The WHO Model List of Essential Medicines[49] registers lamivudine tablets containing 150 mg of the API, whereas the monograph of lamivudine tablets in the International Pharmacopoeia lists both 150 and 300 mg tablets.[50]

[a] Solubility studies were performed at the Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany, using lamivudine international chemical reference substance, obtained from the WHO Centre for Chem. Ref. Subst., Stockholm, Sweden; SN 2275073, Control No. 105232. No information about the polymorphic form was provided.

[b] Because of the high cost of lamivudine reference substance, rather than measuring an equilibrium solubility value, the ability of the maximum dose to dissolve in less than 250 mL of solution (e.g., D/S < 250 mL) was evaluated.

Table 1. Excipients[a] Present in Lamivudine IR Solid Oral Drug Products with a Marketing Authorization (MA)[b] in the EU,[c] BR, CA, ES,[d] HU,[d] IL, NZ, and the US, and the Minimal and Maximal Amount of that Excipient Present Per Dosage Unit in Solid Oral Drug Products with an MA in the US[e]

Excipient	Drug Products Containing that Excipient with an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with an MA in the US (mg)
Cellulose, microcrystalline	BR (1) CA (2,3) ES (4) EU (5–8) HU (9) IL (10,11) NZ (12,13) US (14,15)	4.6–1385[f]
Magnesium stearate	BR (1) CA (2,3) ES (4) EU (5–8) HU (9) IL (10,11) NZ (12,13) US (14,15)	0.15–401[f]
Sodium starch glycolate	BR (1) CA (2,3) ES (4) EU (5–8) HU (9) IL (10,11) NZ (12,13) US (14,15)	2–876[f]

1. Epivir® 150 mg comprimidos.
2. Pr3TC® lamivudine 150/300 mg tablets.
3. PrHEPTOVIR® lamivudine tablets, 100 mg.
4. Lamivudina NORMON 150/300 mg comprimidos recubiertos con película EFG.
5. Epivir, film-coated tablet, lamivudine 150/300 mg.
6. Lamivudine Teva, film-coated tablet – lamivudine 100 mg.
7. Lamivudine Teva Pharma B.V., film-coated tablet – lamivudine 150/300 mg.
8. Zeffix, film-coated tablet – lamivudine 100 mg.
9. 3TC 150 mg filmtabletta.
10. EPIVIR™ 150/300 MG Tablets.
11. ZEFFIX (lamivudine) Tablets.
12. 3TC™ Tablets (Lamivudine tablets 150mg).
13. ZEFFIX™ (Lamivudine tablets 100mg).
14. EPIVIR (lamivudine 100/150/300 mg) tablet, film coated [GlaxoSmithKline LLC].
15. EPIVIR (lamivudine 150/300 mg) tablet, film coated [State of Florida DOH Central Pharmacy].

[a] Colorants and coating ingredients are not included.
[b] Approval of a drug product by the local regulatory authority. Abbreviations of countries: see text.
[c] Products having an MA granted by the EU are authorized for use in: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxembourg, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, and United Kingdom.
[d] National authorization.
[e] Source of data: FDA. Inactive Ingredients Database. http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm, accessed August 3, 2010.
[f] The upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

PHARMACOKINETIC PROPERTIES

After oral administration, lamivudine demonstrates linear pharmacokinetics for both the AUC and the maximum concentration (C_{max}) over the therapeutic dose range.[17,19,51] Several studies in different populations including single administration as well as multiple administration of lamivudine drug products have confirmed that the pharmacokinetic parameters of lamivudine are not significantly altered by either race or gender.[19] Furthermore, it is reported that pregnancy has only a marginal impact on lamivudine pharmacokinetics.[52]

Absorption and Bioavailability

Literature data for the absolute BA of lamivudine are somewhat variable. This may be due to a high interpatient variation in all pharmacokinetic parameters of lamivudine,[14] and, in fact, some authors regard lamivudine as a highly variable drug.[53] With respect to a phase I study, the absolute BA of lamivudine after oral administration for doses ranging from 0.25 to 8.0 mg/kg (covering the therapeutic dose range) was found to be 82%.[54] Johnson et al.[19] as well as Perry and Faulds[14] confirmed the absolute BA of the drug to be approximately 82% in adults and 68% in children. Studies by Yuen et al.[55] reported the absolute BA of orally administered lamivudine as 86% to 88%.

Administration of lamivudine in combination with food delays its absorption.[17] Although the extent of lamivudine absorption was not significantly affected by administration of a meal, the mean C_{max} values after a single oral administration of 50 mg lamivudine were about 47% lower in the fed state compared with the fasted state (273 ± 56 μg/L vs. 513 ± 215 μg/L) and the time to maximum plasma concentration (T_{max}) was delayed by 2.25 h (3.2 h in the fed state vs. 0.9 h in the fasted state).[9,19] A second study investigating a single oral dose of 150 mg lamivudine, detected a meal-associated reduction of C_{max} by 15% (1312 μg/L in the fed state vs. 1537 μg/L in the fasted state) and a corresponding increase in the median T_{max} from 0.75 h (fasting) to 1.5 h (fed).[19] Nevertheless, the mean oral CL and terminal elimination half-life of lamivudine were not affected by food,[19] and no differences in the safety profile with respect to prandial states can be implied.[22] All in all, the influence of food on lamivudine absorption is not considered to be very relevant to the success of the therapy,[56] and lamivudine can be given with or without food.[15,16,19]

Minuesa et al.[30] reported that all NRTIs are high-affinity inhibitors of the hOCTs type 1–3, which have been associated with antiviral uptake in different tissues and thus with the therapeutic effect of NRTIs. These study results could have implications for clinical practice, especially for the highly active

antiretroviral therapy (HAART), as in HAART, lamivudine is coadministered with abacavir and azidothymidine.[30] However, due to the favorable safety profile of lamivudine it is rather unlikely that this interaction will affect the patient's health.

Orally administered lamivudine is rapidly absorbed across the intestinal wall and penetrates freely the tissues beyond the systemic circulation.[19] The C_{max} is reached within 1.5 h.[19]Administration of 150 mg lamivudine daily led to a mean C_{max} of 3.24 μg/mL in serum and a mean AUC_{0-24} of 46.5 μg·h/mL[57] (both reported as geometric means). In another study, the mean steady-state C_{max} in the plasma was 2.0 μg/mL at a therapeutic dose of 300 mg lamivudine given once daily.[58] When this dose was split up into 150 mg twice daily, the mean steady-state C_{max} in the plasma decreased to 1.2 μg/mL.[19,22,51,58] Another study determined the relative BA of a tablet, Epivir-HBV®, containing 100 mg lamivudine, versus an oral solution;[59] the solution demonstrated a slightly higher C_{max}, but there was no significant difference in $AUC_{0-\infty}$.

Permeability

Generally, there is little information about the permeability of lamivudine in the literature. It seems that the majority of lamivudine is absorbed through passive diffusion.[60] Gastrointestinal permeability studies in rats using ligated loop technique demonstrated a mean percentage disappearance of lamivudine of just 25%–45% in 60 min in each segment studied (stomach, duodenum, jejunum, and ileum).[61]

The biopharmaceutics drug disposition classification system (BDDCS) by Wu and Benet,[62] which categorizes drugs according to their metabolic properties, classifies APIs as low permeable, if they are mainly eliminated as unchanged drug via renal and/or biliary excretion. Therefore, because approximately 70% of the lamivudine dose is excreted unchanged in the urine,[15,16,54] the BDDCS criteria indicate lamivudine to be an API with low permeability.

Distribution, Metabolism, and Elimination

The distribution volume after intravenous administration of lamivudine over the dose range of 0.25 to 8 mg/kg averages 1.3 L/kg,[14–16,54] suggesting that the API distributes at least into the extravascular spaces. The apparent binding of lamivudine to human plasma proteins (particularly albumin) is consistently reported as under 40%.[14–16]

Lamivudine can be secreted in breast milk after oral dosing.[9,15,16] Penetration of lamivudine into the cerebrospinal fluid (CSF) is only low to moderate.[19] Consequently, the application of lamivudine to target HIV in the brain and in the CSF is limited.[38]

The elimination half-life of lamivudine in plasma is rather short (reported in the literature, e.g., as 5–7 h,[15,16,28,55] 3–5 h[37], 4–6 h[63]). However, as a prodrug, lamivudine undergoes intracellular phosphorylation by kinases to form the pharmacologically active moiety 3TCTP,[56] which has an extended intracellular half-life, reported to be as long as 15–19 h[15,16,22] or 10.5–15.5 h.[14]

Both oral CL and elimination half-life were independent of the dose and body weight over an oral dosing range of 0.25 to 10 mg/kg.[9,15,16] Only about 5% to 10% of the API is metabolized to the pharmacologically inactive *trans*-sulfoxide metabolite and excreted via the kidneys.[19] The majority of lamivudine (approximately 70%) is eliminated unchanged in the urine via the organic cationic transport system.[15,16,54] The CL_R after oral administration of 300 mg lamivudine is about 200 ± 55 mL/min,[9] which is greater than the glomerular filtration rate, indicating that lamivudine is eliminated by active renal tubular secretion as well as filtration.[54] As lamivudine is primarily eliminated via the kidneys, its pharmacokinetic parameters are significantly affected in patients with moderate or severe renal impairment and the dosage reduction in these patients is recommended.[19] By contrast, impaired hepatic function has no significant influence on lamivudine efficacy.[64]

DOSAGE FORM PERFORMANCE

Excipients

The only study of interactions between excipients and lamivudine found in the literature was by Ravi et al.,[65] who studied possible solid-state interactions between lamivudine and hydroxypropyl methylcellulose, talc, and magnesium stearate using Fourier transform infrared spectroscopy and differential scanning calorimetry techniques. The authors observed stability of lamivudine in presence of all these excipients.[65] Table 1 shows the excipients present in IR solid oral drug products containing lamivudine as a sole API, with an MA in the EU, BR, CA, ES, HU, IL, NZ, and US. It can be inferred that these drug products successfully passed an *in vivo* BE study. However, because one formulation will most probably be registered in several countries, the products shown in Table 1 will correspond to a far lower number of formulations. Also, it cannot be taken for granted that every drug product has successfully met the *in vivo* BE criteria that are currently in force. Nevertheless, the excipients present in these drug products seem to be safe and not to significantly affect lamivudine absorption when present in amounts usual for IR tablets (Table 1).[66]

Bioequivalence

Several studies investigated the pharmacokinetic parameters of different lamivudine IR drug products. Only one study reported a failure of the test

product (Lamivudine 150 mg, Aspen Pharmacare Holdings Ltd., South Africa) to meet the standard BE criteria versus its comparator (Lamivudine 3TC 150 mg tablets, Glaxo Wellcome, SA) in a randomized, open label, two-period, single dose, crossover study in 24 healthy adult male subjects. The 90% confidence intervals (CIs) fulfilled the BE criteria of 80%–125% for AUC (92%–105%), but not for C_{max} (76%–95%); this failure to meet the lower acceptance limit for the C_{max} values was deemed to be without clinical relevance.[47] If C_{max} is of less importance for the clinical efficacy and safety, widening of the acceptance criteria for C_{max} is acceptable. All other reported studies confirmed BE between the innovator, Epivir®, and the tested generic drug product. As an example, a study by Kano et al.[67] compared the generic FURP-lamivudine 150 mg (Fundação para o Remédio Popular, Brazil) to Epivir® in a single 150 mg oral dose two-way crossover study in 24 healthy volunteers of both sexes. The resulted 90% CIs are 86% to 106% for C_{max}, and 97% to 105% for $AUC_{0-\infty}$, which are both within the 80%–125% BE limits of the comparator.[67] In another published work by Narang et al.,[53] the generic Lamivir® (Cipla Ltd., India) was tested against the comparator in a randomized, two-treatment study involving 24 healthy male subjects; this comparison provided 90% CIs for C_{max} and $AUC_{0-\infty}$ of 89% to 112% and 94% to 107%, respectively, both being entirely within the 80% to 125% BE limits.[53]

It is noted that the narrow 90% CI values observed in all the BE studies would not be consistent with the designation of lamivudine as a highly variable drug.

Dissolution

In the current pharmacopeial guidelines (United States Pharmacopeia,[68] The International Pharmacopoeia,[8] and European Pharmacopoeia[69]) no specific dissolution test conditions are described for lamivudine.

Because lamivudine is highly soluble, biopharmaceutics classification system (BCS)-conformed dissolution conditions can be applied for dissolution testing of lamivudine drug products.[2,3] Three lamivudine drug products (Epivir®, Germany (DE) Aspen™ Lamivudine 150 mg (SA), and 3TC tablets, Switserland (CH)) were subjected to the dissolution testing[c] according to the EMA[3] and WHO,[2] respectively. All tested lamivudine drug products fulfilled the requirements for very rapidly dissolving, that is, 85% of the drug dissolved within 15 min in each required medium (Fig. 2).

DISCUSSION

Solubility

The solubility experiments confirmed D/S ratios for lamivudine of less than 250 mL at 37°C over the full pH range based on highest daily dose strength of 300 mg. The ratios obtained were less than 75 mL over a pH range of 1.0–7.5 at 37°C. Therefore, lamivudine can be classified with certainty as highly soluble according to all regulations.

Permeability

The permeability of lamivudine is described throughout different publications as highly permeable,[2,34] as low permeable,[35,62] or borderline permeable.[70] However, these evaluations are not based exclusively on human *in vivo* data. Thus, because no human mass–balance studies could be identified in the literature, the permeability classification of lamivudine is predicated on its reported BA values of approximately 82%–88% in adults. Hence, the permeability of lamivudine must be regarded as borderline, leading to a conservative assessment of this API as not highly permeable.

BCS and BDDCS Classification

Combining its solubility and the permeability classification, lamivudine is conservatively assigned to BCS class III. The publications of Lindenberg et al.[70] (BCS class I/III, borderline) and Kasim et al.[35] (BCS class III) support this classification. Using the BDDCS approach,[62] lamivudine is also a class III API.

Risks of Bioinequivalence Caused by Excipients and/or Manufacturing Parameters

To date, no studies of excipient interactions or BA problems due to manufacturing variations have been reported. But several studies confirmed BE between the innovator and the generic drug product; in only one study a failure to meet the acceptance limit for the C_{max} was reported. This general meeting of BE criteria suggest that the probability of bioinequivalence by a difference in composition and/or manufacturing parameters versus its comparator is low, and even lower if the test product contains only the excipients listed in Table 1, in usual amounts for each excipient.

Surrogate Techniques for *in Vivo* Bioequivalence Testing

No cases of bioinequivalent lamivudine formulations have been reported in the literature. Because the API is highly soluble, the occurrence of bioinequivalence between different formulations seems to be rather unlikely in absence of excipient effects. In other words,

[c]Studies were performed at the Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany. The dissolution tests were carried out according to the conditions given by the WHO,[2] modifying them slightly by replacing potassium dihydrogen phosphate with sodium dihydrogen phosphate. Lamivudine was quantified using UV spectrophotometry at 270 nm.[34]

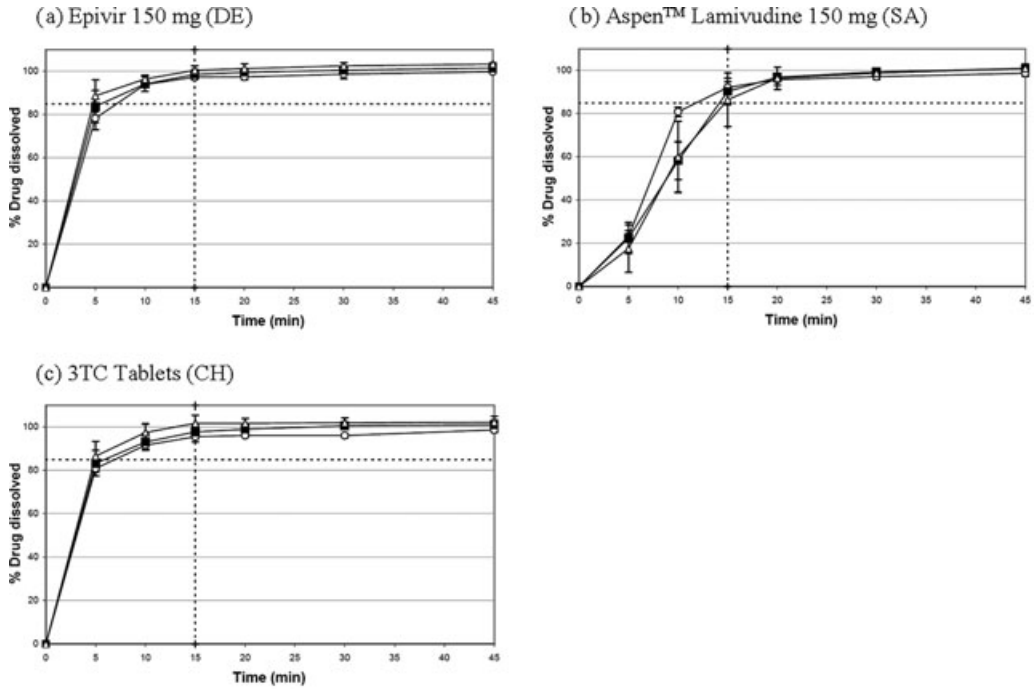

Figure 2. Dissolution of three lamivudine drug products according to EMA[3]/WHO[2]: Paddle apparatus; 75 rpm; 37°C, media: Simulated gastric fluid without pepsin pH 1.2 (○); acetate buffer pH 4.5 (■), and Simulated intestinal fluid without pancreatin pH 6.8 (△). Data points show mean ± SD. The horizontal and vertical dotted lines represent the EMA[3] /WHO[2] criterion of "very rapidly dissolving".

as long as the excipients in the test product do not significantly influence the permeability or the gastrointestinal transit time, comparative dissolution tests can be applied to assess BE of two lamivudine drug products. Despite the differences in excipients of the DE product, which contains a surfactant, and the SA product, which does not, both products were found to be very rapidly dissolving (Fig. 2), meeting the WHO[71] requirements for BE. As a preferred method to compare the performance of two drug products,[72] dissolution can be used to detect differences between products due to inclusion of polymorphs with different solubilities.

Patient's Risks Associated with Bioinequivalence

Though several fatal cases arising from lactic acidosis and severe hepatomegaly have been reported in literature,[9,15,16] these side effects are unrelated to dose. So, there is no direct connection between these toxicities and the possibility of suprabioavailable products. In terms of other toxicities, lamivudine has a wide therapeutic index[73] and a well-established safety profile,[14,21,24,54,64] suggesting that even in case of an incorrect biowaiver decision, a suprabioavailable product is unlikely to result in toxicity.

With respect to therapy failure based on subtherapeutic plasma levels of lamivudine, it should be noted that the current standard of care for HIV/AIDS treatment is based on a triple drug therapy including three APIs belonging to NRTIs, non-NRTIs, and/or protease inhibitors.[74,75] Because the combination of APIs can partially compensate for BA problems with one of the APIs in the regimen, the risk of therapy failure in the event of subtherapeutic plasma concentrations of lamivudine is less critical than for APIs that are used as a single agent.

Taken all together, the patient's potential adverse health outcome associated with bioinequivalence due to approval based upon an errant biowaiver decision is judged to be an acceptable risk.

CONCLUSIONS

From a scientific perspective, a biowaiver is judged acceptable for new single API lamivudine multisource products and also major post-approval changes to marketed products, provided that (a) the test product contains only excipients present in lamivudine IR solid oral drug products approved in the International Conference on Harmonization or associated countries, for instance as shown in Table 1, in usual amounts and (b) the test product as well as the comparator product are very rapidly dissolving, that is, dissolve more than 85% of the labeled amount within 15 min in each of the buffers of pH 1.0–1.2, pH 4.5, and pH 6.8.

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