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.

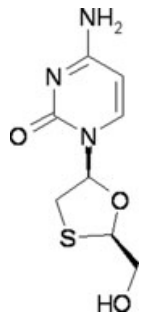

Figure 1. Structure of lamivudine.

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;