Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Stavudine

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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 stavudine (d4T) are reviewed. According to Biopharmaceutics Classification System (BCS), d4T can be assigned to BCS class I. No problems with BE of IR d4T formulations containing different excipients and produced by different manufacturing methods have been reported and, hence, the risk of bioinequivalence caused by these factors appears to be low. Furthermore, d4T has a wide therapeutic index. It is concluded that a biowaiver is appropriate for IR solid oral dosage forms containing d4T as the single active pharmaceutical ingredient (API) provided that (a) the test product contains only excipients present in the IR d4T drug products that have been approved in a number of countries for the same dosage form, and (b) both test product and its comparator are either "very rapidly dissolving" or "rapidly dissolving" with similarity of dissolution profiles demonstrated at pH 1.2, 4.5, and 6.8. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:10–16, 2012

Keywords: stavudine; absorption; Biopharmaceutics Classification System (BCS); permeability; regulatory science; solubility

INTRODUCTION

A biowaiver monograph based on literature data is presented on stavudine (d4T) with respect to its biopharmaceutical properties and the risk of waiving *in vivo* bioequivalence (BE) testing in the approval of new IR solid oral dosage forms containing d4T ("biowaiving"), including both reformulated products and new multisource drug products. This evaluation refers to drug products containing d4T as the only active pharmaceutical ingredient (API) and not any combination products. The purpose and scope of this series of monographs have been previously discussed.[1] Summarizing in few words, the aim is to 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 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 advise against a biowaiver decisions is referred to in a recently published World Health Organization (WHO) guideline.[2] These monographs do

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not intend to simply apply the guidance of WHO,[2] the US Food and Drug Administration (FDA),[3] and/or the European Medicine Agency (EMA),[4] but also aim at a critical evaluation of these and the regulatory documents of other countries. Biowaiver monographs have been already published for several APIs, also available online at www.fip.org/bcs.[5]

EXPERIMENTAL

Literature data were obtained from Web of Science, PubMed, and Micromedex databases up to December 2009. The keywords used for searching were d4T, intestine absorption, linear absorption, absolute bioavailability, bioequivalence, log *p*, solubility, permeability, and lipophilicity. Information was also obtained from regulatory documents published by WHO,[2] FDA,[3] and EMA.[4]

GENERAL CHARACTERISTICS

The structure of d4T,[6,7] as per International Nonproprietary Names, is shown in Figure 1.

Therapeutic Indication and Dose

Stavudine is a pyrimidine nucleoside antiretroviral agent with *in vitro* activity against human immunodeficiency virus (HIV) similar to zidovudine[8–10] and is applied for the treatment of HIV-1 infection as either monotherapy or in combination with other antivirals.[11] d4T inhibits HIV reverse transcriptase by competing with the natural substrate deoxythymidine triphosphate and its incorporation into viral DNA, causing termination of DNA elongation.[11] The phase I study reported by Browne et al.[12] started at 4 mg/(kg day) and the dose was escalated until a daily dose of 12 mg/(kg day) was reached. Little additional antiretroviral activity was gained by this dose escalation, but toxicity increased greatly. On a dosing schedule of every 12 h, activity was maintained and toxicity was lessened at doses as low as 0.5 mg/(kg day). Suboptimal antiviral effects were evident at doses of 0.25 mg/(kg day).[12,13] The recommended dose based on body weight is 40 mg twice daily for patients weighing at least 60 kg and 30 mg twice daily for patients weighing less than 60 kg. The recommended dose for newborns up to 13 days old is 0.5 mg/(kg dose), given every 12 h. The recommended dose for pediatric patients at least 14 days old and weighing less than 30 kg is 1 mg/(kg dose), given every 12 h. Pediatric patients weighing 30 kg or more should receive the recommended adult dosage.[11]

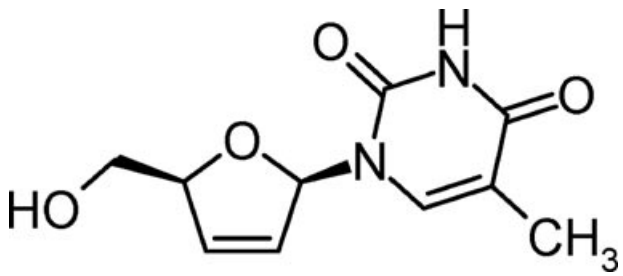

Figure 1. Structure of stavudine.

Therapeutic Index and Toxicity

Both preclinical and clinical studies have shown d4T to be less cytotoxic than zidovudine.[14,15] In clinical studies, d4T has shown to exert a significant antiviral effect with acceptable safety. The principal toxic effect is symptomatic peripheral sensory neuropathy, which is dose related.[12,16–19] Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in feet or hands.[11] d4T-related peripheral neuropathy can be resolved by prompt withdrawal of the therapy. In some cases, symptoms may worsen temporarily following the discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half of the dose.[11] Patients with preexisting liver dysfunction have an increased frequency of liver function abnormalities including severe and potentially fatal hepatic adverse events, and should be monitored according to standard practice.[11] d4T levels used in treatment are generally 100-fold below those that are cytotoxic.[20] Experience with adults treated with 12–24 times the recommended daily dosage revealed no acute toxicity. Complications arising with chronic overdosage include the aforementioned peripheral sensory neuropathy and hepatic toxicity.[11]

CHEMICAL PROPERTIES

Solubility

The solubility in water was reported as 83 mg/mL at 23°C.[11] The pH–solubility profile of d4T at 37.0 ± 0.5°C was determined in 0.01 N HCl (78 mg/mL), pH 4.5 (101 mg/mL), and pH 6.8 (76 mg/mL);[21] no information about polymorphic form was reported.

Polymorphism

Polymorphic forms I, II, and III have been identified. Forms I and II are anhydrous; form III is hydrated and is pseudopolymorphic with forms I and II. The solubility of form II (106.8 mg/mL) in water at 25°C is higher than that of form I (88.8 mg/mL),[22] but polymorph dependent bioavailability (BA) has not been reported. Form I is the stable polymorph and is commercially available.[23]