Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Levofloxacin

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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 levofloxacin as the only active pharmaceutical ingredient (API) are reviewed. According to the current Biopharmaceutics Classification System, levofloxacin can be assigned to Class I. No problems with BE of IR levofloxacin 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. In addition, levofloxacin has a wide therapeutic index. On the basis of this evidence, a biowaiver is recommended for IR solid oral dosage forms containing levofloxacin as the single API provided that (a) the test product contains only excipients present in IR levofloxacin drug products that have been approved in International Conference on Harmonization (ICH) or associated countries and which have the same dosage form; (b) both the test and comparator dosage form are "very rapidly dissolving" or "rapidly dissolving" with similarity of the dissolution profiles demonstrated at pH 1.2, 4.5, and 6.8; and (c) if the test product contains polysorbates, it should be both qualitatively and quantitatively identical to its comparator in terms of polysorbate content. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:1628–1636, 2011

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

INTRODUCTION

A biowaiver monograph based on literature data is presented on levofloxacin, with respect to its biopharmaceutical properties and the risk of waiving *in vivo* bioequivalence (BE) testing in the approval of new immediate release (IR) solid oral dosage forms containing levofloxacin, including both reformulated products and new multisource drug products. This evaluation refers to drug products containing

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levofloxacin as the only active pharmaceutical ingredient (API) and not to combination products. The purpose and scope of this series of monographs have been previously discussed.[1] Summarized 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 the 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 decision is referred to in the recently published World Health Organization (WHO) guideline.[2] These monographs do not intend to simply apply the WHO,[2] United States Food and Drug Administration (FDA),[3] and/or European Medicine Agency (EMA) Guidance,[4] but aim also as a critical evaluation of these and other countries' regulatory documents. Biowaiver monographs have already been 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 levofloxacin, intestine absorption, linear absorption, absolute bioavailability (BA), BE, log *P*, solubility, permeability, and lipophilicity. Information was also obtained from regulatory documents published by the WHO,[2] the FDA,[3] and the EMA.[4]

GENERAL CHARACTERISTICS

Levofloxacinum/Levofloxacin (INN),[6] (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.[6,7] The molecule exists as a zwitterion at the pH conditions in the small intestine. The commercially available drug substance is the hemihydrate with the empirical formula $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2}H_2O$ and containing 97.6% levofloxacin by mass.[8] Its structure is shown in Figure 1.

Stereochemistry

Levofloxacin is the S-(-) isomer of the racemic drug substance ofloxacin; it is significantly more active against bacterial pathogens than R-(+)-ofloxacin.[6,7]

Therapeutic Indication

Levofloxacin has a broad spectrum of *in vitro* activity against Gram-positive and Gram-negative bacteria.[8,9] In Brazil, its labeled indications include treatment of adults (≥ 18 years old) with mild, moderate, and severe infections caused by susceptible strains such as upper and lower respiratory tract infection, infection of skin and/or subcutaneous tissue, urinary tract infection, acute pyelonephritis, osteomyelitis, related septicemia/bacteremia, intra-abdominal infections, prostatitis, and nosocomial pneumonia.[10] In the United States (US) in addition to the above-mentioned indications, levofloxacin has been approved to treat infection caused by inhaled anthrax (prophylaxis or postexposure).[11] Also, according to the 16th edition of WHO's Essential Medicines List, levofloxacin may be used as an alternative to ofloxacin in the treatment of multidrug resistant tuberculosis.[12]

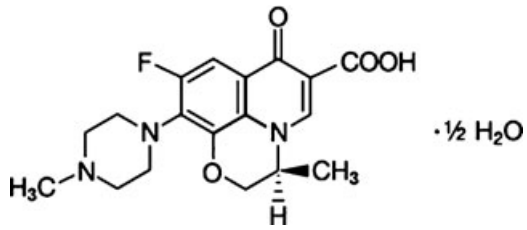

Figure 1. Structure of levofloxacin hemihydrate (Molecular weight = 370.38).

Therapeutic Index and Toxicity

Levofloxacin exhibits a low potential for acute toxicity. The median lethal dose (LD_{50}) values were around 1800 mg/kg for mice, 1500 mg/kg for rats, and more than 250 mg/kg in female monkeys.[13] Generally, its serum and tissue levels do not require routine monitoring.[9–11] Depending on the indication, the dosage regimen can vary from 250 mg daily for 3 days to 500 mg daily for 28 days. Daily doses can be as high as 750 mg.[8–13] The most common adverse reactions (≥ 3%) in humans are nausea, headache, diarrhea, insomnia, constipation, and dizziness.[19] Dysglycemia[20–23] and liver disorders[24,25] in association with levofloxacin have been reported in the literature. Disturbances of blood glucose levels are labeled in the product monograph.[9] As with other quinolones, disturbances of blood glucose, including symptomatic hyper and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended.[8–11] Postmarketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients with 65 years old or older and most were not associated with hypersensitivity.[19,25–29]

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons