Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Fluconazole

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ABSTRACT: Literature data pertaining to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing requirements for the approval of immediate release (IR) solid oral dosage forms containing fluconazole as the only active pharmaceutical ingredient (API) are reviewed. The decision is based on solubility, dissolution, permeability, therapeutic index, pharmacokinetic parameters, pharmacodynamic properties, and other relevant data. BE/bioavailability (BA) problems and drug–excipients interaction data were also reviewed and taken into consideration. According to the biopharmaceutics classification system (BCS), fluconazole in polymorphic forms II and III is a BCS class I drug and has a wide therapeutic index. BE of test formulations from many different manufacturers containing different excipients confirmed that the risk of bioinequivalence because of formulation and manufacturing factors is low. It was inferred that risk can be further reduced if *in vitro* studies are performed according to biowaiver guidelines. Thus, it is concluded that a biowaiver can be recommended for fluconazole IR dosage forms if (a) fluconazole is present as polymorphic form II or III or any other form/mixture showing high solubility, (b) the selection of excipients be limited to those found in IR drug products approved in International Conference on Harmonisation (ICH) countries for the same dosage form and used in their usual amounts, and (c) both the test and comparator dosage form are *very rapidly dissolving*, or, *rapidly dissolving* throughout the shelf life with similar dissolution profiles at pH 1.2, 4.5, and 6.8. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3843–3858, 2014

Keywords: fluconazole; bioequivalence; dissolution; biopharmaceutics classification system (BCS); permeability; solubility; biowaiver; therapeutic index; metabolism; elimination

INTRODUCTION

Fluconazole is an orally active bis-triazole derivative used for the prophylaxis and treatment of superficial and systemic fungal infections, mainly candidiasis and cryptococcal meningitis, which are prevalent in immunocompromised patients.[1–3] It is well tolerated in adults and children, including seriously ill patients, and the safety of the drug has been proven in clinical studies.[4–8] Fluconazole has favorable pharmacokinetic (PK) properties: because of its low plasma protein binding, high concentrations of drug can be achieved in the central nervous system, while its long half-life makes once-daily dosing possible.[9] For these reasons, fluconazole is currently recommended as a primary therapeutic drug for the treatment of *Candida albicans* infections, including mucocutaneous candidiasis and genital candidiasis.[10]

In this work, a biowaiver monograph for fluconazole is presented, taking into consideration both its biopharmaceutical and clinical properties. The literature data were reviewed to assess the risks associated with the substitution of *in vivo* testing for biopharmaceutics classification system (BCS)-based biowaiver *in vitro* testing for the approval of new multisource and/or reformulated immediate release (IR) solid oral dosage forms containing fluconazole as the sole active pharmaceutical ingredient (API). Risk for this purpose is defined as the probability of an incorrect biowaiver decision as well as the consequences of such an incorrect decision in terms of public health and the individual patient.

The basis of recommendations to apply the biowaiver procedure or to advise against its use are described in a World Health Organization (WHO) guideline.[11] In addition to the WHO,[11] the United States Food and Drug Administration (US-FDA),[12] the European Medicine Agency (EMA)[13] guidance documents, and regulatory documents of other countries are also taken into consideration. Biowaiver monographs have already been published for over 40 APIs, and these are also available online via www.fip.org/bcs.[14]

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METHODS

Literature Search

Literature data published in PubMed, Micromedex, and Web of Science databases up to September 2013 were accessed by using the following keywords: fluconazole, indication, solubility, polymorphism, intestinal absorption, distribution, metabolism, excretion, dissolution, therapeutic index, linear PK, absolute bioavailability (BA), bioequivalence (BE), log *P*, permeability, mass balance, and radiolabeled studies. Information was also obtained from the WHO,[11] US-FDA,[12] and EMA[13] regulatory guidance documents.

Solubility Studies

Solubility studies of fluconazole (polymorph II) in different pH media were performed at LaGray Chemical Company, Nsawam, Ghana according to WHO guidelines, using a mechanical shaker (IKA-Werke GmbH & Company KG, Janke & Kunkel-Str. 10, Staufen, Germany) maintained at 37 ± 0.5°C. Approximately 0.625 g of fluconaozle was transferred into a 25 mL volumetric flask and brought to volume with the appropriate buffer. The flasks were sonicated for 30 min prior to shaking in a biological shaker for 36 h at 130 rpm. The studies were performed in triplicate and pH was recorded initially and after 36 h of shaking. Each sample was filtered through a 0.45 μm PTFE (Teflon) membrane filter (Sterlitech Corporation, Kent, Washington) and the filtrate was further diluted with mobile phase before HPLC analysis for dissolved fluconazole.[15] The HPLC system [Hitachi HPLC modules (L-2130, L-2200, L-2300, and L-2450) and organizer, with ELITE LaChrom data processing software] consisted of an L1 column (Phenomenex Luna, Madrid Avenue, CA, USA, 5 μm, 25 cm length × 4.6 mm ID) maintained at 30°C. The mobile phase was 20% (v/v) acetonitrile in purified water. The flow rate was 1 mL/min and injection volume was 20 μL. Detection was performed at 260 nm. Concentrations were calculated from peak areas of standard preparations of known concentration.

Dissolution Test of Fluconazole Capsules

Dissolution studies of fluconazole (as polymorph II) capsules in different pH media were also performed at LaGray Chemical Company. Dissolution profiling of fluconazole 150 and 200 mg capsules [Diflucan 150 mg capsules (batch No.: 0734102, manufacturing date: March 2010, expiry date: February 2015) and Diflucan 200 mg capsules (batch No. 0843506, manufacturing date: December 2010, expiry date: November 2015), Pfizer PGM, Amboise, France] was carried out in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8, using a basket apparatus (DISSO 2000; Lab India Instruments Pvt. Ltd, Mumbai, India). The capsules were tested in 900 mL medium (freshly degassed), maintained at 37 ± 0.5°C and stirred at 100 rpm. Samples were withdrawn at predetermined intervals and immediately analyzed using the modified United States Pharmacopoeia (USP) HPLC method for solubility studies.[15]

GENERAL CHARACTERISTICS

Name and Structure

INN: Fluconazole.[16] IUPAC: 2-(2,4-difluorophenyl)-1,3-*bis*-(1*H*-1.2.4-triazol-1-yl)-propan-2-ol.[15,16] Chemically, fluconazole is a triazole derivative as shown in Figure 1 with a molecular formula $C_{13}H_{12}F_2N_6O$ and a molecular weight of 306.27 g/mol.[16]

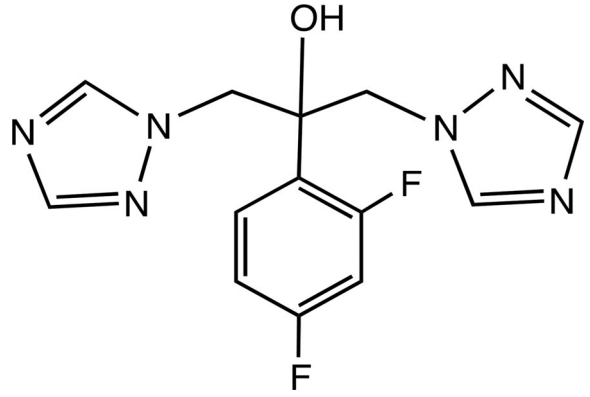

Figure 1. Structure of fluconazole.

Therapeutic Indications and Dose

Fluconazole selectively inhibits fungal cytochrome P450-dependent lanosterol 14-α-demethylase enzyme, and thereby prevents conversion of lanosterol to ergosterol. Ergosterol is an essential component of the fungal cytoplasmic membrane. The interruption in the ergosterol biosynthesis pathway correlates well with the accumulation of 14-α-methyl sterols in fungi and may be responsible for its fungistatic activity.[17]

Fluconazole is indicated for the treatment of genital candidiasis, candida balanitis, acute and recurrent vaginal candidiasis associated with *Candida*, oropharyngeal, and esophageal candidiasis.[10,17,18] Additionally, it is effective for the treatment of urinary tract infections caused by *Candida*, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia.[10,17,18]

Cryptococcal meningitis, commonly seen in AIDS patients, is also treated with fluconazole.[19–21] Fluconazole as a 400 mg once daily dose is indicated as a prophylaxis measure to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation and receiving cytotoxic chemotherapy and/or radiation therapy.[22–24]

Fluconazole is effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age.[10,17,18,25] Based on its efficacy in adults and pediatric clinical study results, fluconazole is also prescribed in children for cryptococcal meningitis, *Candida* esophagitis, or systemic *Candida* infections.[10,17,18,25] Additionally, dose proportionality between children and adults has been established in PK studies in children.[10,17,18,25]

For adults, the recommended dose for vaginal candidiasis is 150 mg as a single oral dose.[10,17,25,26] Oropharyngeal candidiasis and esophageal candidiasis are treated with a loading dose of 200 mg on the first day followed by 100 mg once daily dose in adults, whereas in children, a loading dose of 6 mg/kg on the first day is followed by 3 mg/kg once daily dose.[10,17,25] For cryptococcal meningitis, the recommended dose in adults is 400 mg on the first day followed by 200 mg once daily dose, whereas 12 mg/kg dose on the first day is recommended in children, which has to be followed by 6 mg/kg once a day dosing.[10,17,19–21,25] The recommended dose for the treatment of urinary tract infections and peritonitis is 50–200 mg as a single dose. Relapse of mucosal candidiasis in HIV patients is prevented with a 100–200 mg daily dose.[10,17,25]