COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Amodiaquine Hydrochloride

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ABSTRACT: The present monograph reviews data relevant to applying the biowaiver procedure for the approval of immediate release (IR) multisource solid dosage forms containing amodiaquine hydrochloride (ADQ) as the single active pharmaceutical ingredient (API). Both biopharmaceutical and clinical data of ADQ were assessed. Solubility studies revealed that ADQ meets the "highly soluble" criteria according to World Health Organization (WHO) and European Medicines Agency (EMA) but fails to comply with the United States Food and Drug Administration (US FDA) specifications. Although metabolism hints at high permeability, available permeability data are too scanty to classify ADQ inequivocably as a Class I drug substance. According to WHO and EMA guidances, ADQ would be conservatively categorized as a Class III drug, whereas according to the US FDA specifications, it would fall into Class IV. ADQ has a wide therapeutic index. Furthermore, no cases of bioinequivalent products have been reported in the open literature. As risks associated with biowaiving appear minimal and requirements for "highly soluble" API are met in the WHO and EMA jurisdictions, the biowaiver procedure can be recommended for bioequivalence (BE) testing of multisource IR products containing ADQ as the only API, provided the test product contains excipients used in ADQ products approved in International Conference of Harmonisation and associated countries, and in similar amounts. Furthermore, both comparator and test should conform to "very rapidly dissolving" product criteria (≥85% dissolution of the API in 15 min at pH 1.2, 4.5, and 6.8) and the labeling should specify that the product not be coadministered with high-fat meals. If the comparator and/or test product fails to meet these criteria, BE needs to be established by pharmacokinetic studies in humans. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: absorption; amodiaquine; bioavailability; bioequivalence; Biopharmaceutics Classification System (BCS); permeability; dissolution; solubility

INTRODUCTION

The feasibility of using surrogate *in vitro* dissolution tests to evaluate bioequivalence (BE) (biowaiver procedure) of multisource amodiaquine hydrochloride (ADQ) solid oral dosage forms is reviewed in this monograph. The assessment is based on the clinical and biopharmaceutical data of ADQ obtained from open scientific literature and supported by experimental data generated by performing additional

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solubility and dissolution studies. Furthermore, the risks (of an incorrect biowaiver decision and its probable consequences to the individual patient and/or public health) associated with using the biowaiver procedure to evaluate the BE of ADQ multisource and reformulated products are evaluated. This assessment refers to drug products containing ADQ as the only active pharmaceutical ingredient (API) and not to combination drug products.

The purpose and scope of the biowaiver monograph series have been previously discussed.[1] The prerequisites for a biowaiver and the approach to the risk benefit analysis for a given API are based on the guidelines put forth by the World Health Organization (WHO),[2] European Medicine Agency (EMA),[3] and United States Food and Drug Administration (US FDA).[4] Biowaiver monographs of several APIs belonging to various therapeutic classes have already been published. These monographs are also available on the International Pharmaceutical Federation website (URL: http://www.fip.org/www/index.php? id=642).

METHODS

Literature Research

Literature research was performed to collect relevant data pertaining to the API, dosage, indication, toxicity, therapeutic index, safety, solubility, permeability, pharmacokinetics (PK), bioavailability (BA), BE, bioinequivalence, and excipients interaction of ADQ. Information was obtained from general pharmaceutical literature and PubMed Central.

Solubility Class Determination

Solubility studies on ADQ were performed in buffer solutions (pH 1–7.5) and water (pH 6.8) by a modified shake flask method, in triplicate. Three milliliters of medium was added to around 25 mg of the API preweighed into Uniprep® vials (Whatman, Inc, New Jersey, USA) and gently shaken in an orbital shaker for 48 h at 37 ± 0.5°C. Drug content in each sample was determined by measuring its absorbance after suitable dilution at 342 nm against appropriate blanks using ultraviolet (UV) spectrophotometry (U-3000 Spectrometer; Hitachi Ltd., Tokyo, Japan). The drug concentrations were calculated from calibration curves of the reference API in the respective medium.

In Vitro Dissolution Study

Dissolution studies were performed in triplicate on pure ADQ (Lot no.: 038F0993, Sigma–Aldrich Chemie GmbH, Steinheim, Germany) according to the WHO specifications. ADQ, equivalent to 153 mg of amodiaquine base, was accurately weighed into each empty gelatin capsule. Three standard dissolution media, namely simulated gastric fluid without pepsin at pH 1.2 (SGFsp), acetate buffer at pH 4.5, and simulated intestinal fluid without pancreatin at pH 6.8 (SIFsp) were used. The United States Pharmacopoeia (USP) apparatus 2 containing 900 mL medium maintained at 37 ± 0.5°C was used with a paddle rotation speed of 75 rpm. Five milliliter samples were withdrawn manually at 5, 10, 15, 20, 30, 45, and 60 min using glass syringes through stainless steel sampling tubes fitted with cylindrical polyethylene filter sticks and were again filtered through 0.45 μm Whatman filter units (Schleicher & Schuell GmBH, Dassel Germany). The withdrawn samples were replaced by fresh medium maintained at 37 ± 0.5°C. The samples were suitably diluted with the dissolution medium and analyzed for the drug content using UV spectrophotometer by measuring absorbance against suitable blanks.

GENERAL CHARACTERISTICS

Name: Amodiaquine hydrochloride (BANM, rINNM).

4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl) phenol dihydrochloride dihydrate.[5]

4-[(7-Chloro-4-quinolyl)amino]-α-(diethylamino)-o-cresol dihydrochloride dihydrate[6,7]

The compound has a molecular weight of 464.8g/mol and a melting point of 158°C.[5,8,9]

Therapeutic Indication and Dosage

Amodiaquine hydrochloride is a Mannich base 4-aminoquinoline antimalarial recommended in the treatment of uncomplicated malaria caused by *Plasmodium falciparum*.[5,10] After absorption, it is metabolized chiefly to desethylamodiaquine (ADQm), which also shows antimalarial activity. The WHO recommends the use of ADQ together with artesunate for the treatment of uncomplicated *falciparum* malaria, to reduce the risk of drug resistance compared with monotherapy.[10] Doses of ADQ are generally expressed in terms of its free base. Two hundred milligrams of ADQ is equivalent to 153 mg of amodiaquine base. The doses specified in this manuscript refer to the amount of base unless specified otherwise.

The Summary of Product Characteristics (SmPC) of ADQ tablets (150 mg; Guilin Pharmaceutical Company Ltd., Shanghai, China) recommends a total dose of 35 mg/kg of amodiaquine base administered

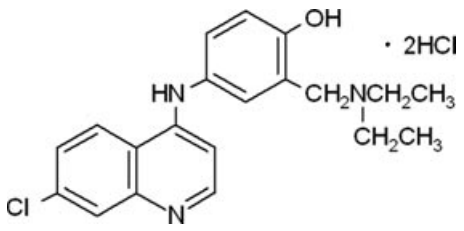

Figure 1. Structure of amodiaquine dihydrochloride.[6]

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