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

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Received 18 February 2010; revised 23 April 2010; accepted 27 April 2010

Published online 2 July 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22249

ABSTRACT: Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release solid oral dosage forms containing mefloquine hydrochloride as the only active pharmaceutical ingredient (API) are reviewed. The solubility and permeability data of mefloquine hydrochloride as well as its therapeutic use and therapeutic index, its pharmacokinetic properties, data related to the possibility of excipient interactions and reported BE/bioavailability studies were taken into consideration. Mefloquine hydrochloride is not a *highly soluble* API. Since no data on permeability are available, it cannot be classified according to the Biopharmaceutics Classification System with certainty. Additionally, several studies in the literature failed to demonstrate BE of existing products. For these reasons, the biowaiver cannot be justified for the approval of new multisource drug products containing mefloquine hydrochloride. However, scale-up and postapproval changes (HHS-FDA SUPAC) levels 1 and 2 and most EU type I variations may be approvable without *in vivo* BE, using the dissolution tests described in these regulatory documents. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:11–21, 2011

Keywords: absorption; bioavailability; bioequivalence; Biopharmaceutics Classification System (BCS); mefloquine hydrochloride; permeability; solubility

INTRODUCTION

A biowaiver monograph of mefloquine hydrochloride 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 mefloquine hydrochloride, 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 mefloquine hydrochloride 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] 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

This article reflects the scientific opinion of the authors and not necessarily the policies of regulating agencies, the International Pharmaceutical Federation (FIP), and the World Health Organization (WHO).

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Journal of Pharmaceutical Sciences, Vol. 100, 11–21 (2011)

is advisable or not. This systematic approach to recommend or advise 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 guidances on the role of the biowaiver in establishing BE, for example, WHO,[2] the U.S. Food and Drug Administration (FDA)[3] and/or the European Medicines Agency (EMA)[4] Guidances, but also aim to serve as a critical evaluation of these regulatory documents. Biowaiver monographs have already been published for a variety of APIs.[1,5–23] They are available online at the website of the International Pharmaceutical Federation (FIP).[24]

GENERAL CHARACTERISTICS

Name

Mefloquine[25] (INN); mefloquine hydrochloride (INNM). Mefloquine hydrochloride is a 4-quinolinemethanol derivative with the chemical name of DL-*erythro*-α-2-piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol-hydrochloride.[25] Its two enantiomers are (9R,10S)-(+)-α-piperidyl-2,8-bis(trifluoromethyl)-4-quinoline-methanol-hydrochloride and (9S,10R)-(−)-α-piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol-hydrochloride. According to IUPAC nomenclature it is termed (R,S)-*erythro*-α-(2-piperidyl)-2,8-bis(trifluor-methyl)-4-chinolinmethanol-hydrochloride.[26] The structure of mefloquine hydrochloride is shown in Figure 1. The molecular formula of mefloquine hydrochloride is $C_{17}H_{16}F_6N_2O \times HCl$,[27] its molecular weight is 414.77 g/mol[27] and its melting point is 259–260°C.[28]

Therapeutic Indication

Mefloquine hydrochloride is an orally administered, first-line agent for prophylaxis, treatment, and emergency treatment of malarial infections.[29–31] It is effective for all intraerythrocytic asexual forms of malaria parasites in human, including multi-drug resistant *Plasmodium (P.) falciparum*.[29,31–33] Weekly mefloquine hydrochloride prophylaxis is a highly effective regimen to prevent malaria and is advisable

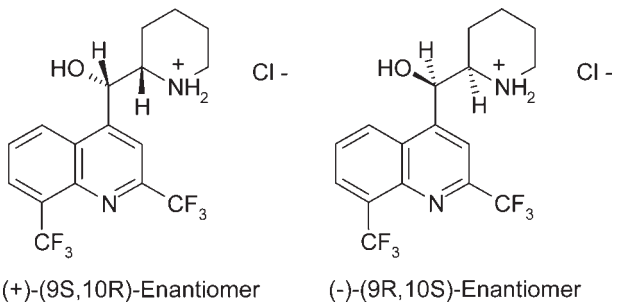

Figure 1. Structure of mefloquine hydrochloride.

when traveling to regions presenting a high risk of infection with strains of *P. falciparum*, which are resistant to other anti-malarials.[29,31,34] Furthermore, mefloquine hydrochloride is indicated for the treatment of mild-to-moderate acute malarial infections caused by mefloquine-susceptible multi-resistant strains of *P. falciparum* and *P. vivax*.[29,31]

The usual dose of mefloquine hydrochloride for prophylaxis of malaria is 5 mg/kg body weight given once a week.[29,31] The first dose must be taken at least 1 week before arrival in the area where malaria is prevalent and the last dose 4 weeks after leaving the region.[29,31] In certain individuals it may be advisable to start prophylaxis 3 weeks prior to departure to make sure that the drug is well-tolerated.[31] For treatment of malaria the daily therapeutic dose of mefloquine hydrochloride is 20–25 mg/kg body weight, administered as three divided doses.[29,31] Mefloquine hydrochloride can also be used as an emergency medication (i.e., on a "stand-by" basis), when prompt medical care is not available within 24 h of the appearance of symptoms.[29,31] The emergency treatment should be started with an initial dose of 15 mg/kg.[29,31] If it is not possible to obtain medical assistance within 24 h, a second dose, in this case 10 mg/kg, must be taken within 6–8 h.[29,31] Patients with body weight $\geq$60 kg must additionally take a third dose of 20–25 mg/kg 6–8 h after the second dose.[29]

The WHO recommended dose for malaria treatment is 15 or 25 mg mefloquine base/kg, depending on the treatment effectiveness and tolerability of the patients.[30] Prophylaxis is recommended with 5 mg of mefloquine base/kg/week, corresponding to an adult dose of 250 mg of mefloquine base/week.[30]

Therapeutic Index and Toxicity

The most frequently reported adverse effects of mefloquine hydrochloride include nausea, vomiting, diarrhea, abdominal pain, anorexia, dizziness, headache, loss of balance, somnolence and sleep disorders, insomnia, and abnormal dreams.[35–37] These side-effects are usually mild to moderate. Some other low incidence side-effects, including depression, were also reported in the literature.[38,39] Isolated, severe adverse reactions include agranulocytosis,[40] Stevens–Johnson syndrome,[41] cutaneous vasculitis,[42,43] and acute generalized exanthematous pustulosis.[44]

Neurological or psychiatric side-effects have been documented in the literature[37,45–49] with the reported frequency of occurrence of neuropsychiatric events varying between 6.5%[37] and 27.4%.[48] One case of severe neuropsychiatric adverse effects related to mefloquine prophylaxis combined with ethanol ingestion has been reported.[50] Further, low body mass index, female gender, and first-time use all have been