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

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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 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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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

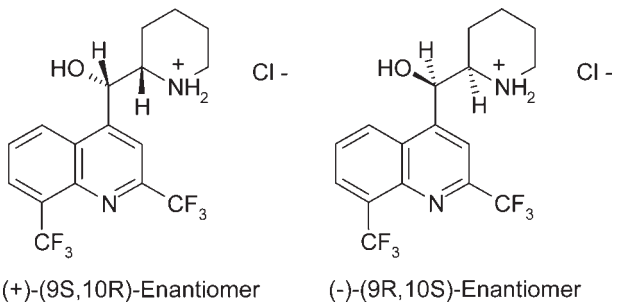

Figure 1. Structure of mefloquine hydrochloride.

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

identified as possible risk factors for increased occurrence of mefloquine-associated neuropsychiatric adverse effects.[51] Patients with active depression or having a recent history of neuropsychiatric events should not use mefloquine hydrochloride for malarial prophylaxis.[29,31] In a recently published Lariam® Medication Guide,[52] approved by the FDA, it was reported that some people who took Lariam® suddenly developed serious mental problems, including severe anxiety, paranoia, hallucinations, depression, and thoughts about suicide. These serious side-effects can persist after Lariam® treatment/prophylaxis is stopped and it was noted that some people who had taken Lariam® actually did commit suicide.[52]

Overdosage of mefloquine hydrochloride tablets leads to an increase in the occurrence of adverse reactions.[29,31]

One study in children suggested that mefloquine hydrochloride therapy for *P. falciparum* in children under 5 years of age can be complicated by vomiting.[53] By contrast, a study carried out in children aged between 5 and 10 years indicated that mefloquine is well-tolerated.[54] These conflicting reports suggest that the therapeutic ratio of the drug in children needs to be defined more precisely.

CHEMICAL PROPERTIES

Solubility

The solubility of mefloquine hydrochloride is reported to range from *very slightly soluble*[55] to *slightly soluble*[56] in water at room temperature. To investigate the solubility properties of mefloquine hydrochloride according to the Biopharmaceutics Classification System (BCS), additional solubility determinations in water and aqueous buffer media were performed.[a] The solubility data were obtained at 37°C using a standard shake-flask method. The results are shown in Table 1 and demonstrate that mefloquine hydrochloride meets the dose/solubility (D/S) criterion of $\leq$250 mL at 37°C in water and acetate buffer, pH 4.5, but not at other pH values tested within the range 1.0–7.5.

Polymorphism

Five polymorphic forms of mefloquine hydrochloride are documented in the literature: the hydrated α- and δ-forms, the β- and γ-polymorphs and the acetone solvate ε-form.[57] There are no references in the literature discussing whether the polymorphic forms affect the physicochemical properties, the bioavailability (BA), or the clinical efficacy of mefloquine. However, Weidekamm et al.[58] hypothesized that the different crystal modifications of mefloquine in the German product Lariam® (predominant form ε) and the Swiss product Mephaquin® (predominant form γ) may account for the different dissolution behavior of the two products (no further supporting information was provided).

Table 1. Solubility of Mefloquine Hydrochloride at 37°C in Different Media and Their Corresponding Dose/Solubility (D/S) Ratios Based on 250 mg Tablet Strength*

Medium	pH	Solubility (mg/mL)	D/S[a] (mL)
Water	6.5	1.806	152
SGF_{sp}[b]	1.0	0.334	823
SGF_{sp}	1.2	0.536	513
Acetate buffer	4.5	1.950	141
SIF_{sp}	6.8	0.412	667
SIF_{sp}[c]	7.5	0.303	908

SGF_{sp}, simulated gastric fluid without pepsin; SIF_{sp}, simulated intestinal fluid without pancreatin.

*Maximum available strength on the WHO Model List of Essential Medicines.[61]

[a]Criterion for highly soluble: $D/S \leq 250$ mL.

[b]Same composition as SGFsp with pH adjusted to 1.0.

[c]Same composition as SIFsp with pH adjusted to 7.5.

Partition Coefficient

The calculated log$P$ of mefloquine free base was reported to be 3.4,[59] while the experimental log$P$ was found to be 3.9.[60]

pK_a

Mefloquine is a weak base with a pK_a of approximately 8.6.[26,56]

Dosage Form Strengths

The WHO Model List of Essential Medicines (EML)[61] describes tablets containing the equivalent of 250 mg mefloquine free base as the hydrochloride. Single API dosage forms with a Marketing Authorization (MA) in Switzerland (CH), Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Sweden (SE), and the United Kingdom (UK) also contain the equivalent of 250 mg of the free base as hydrochloride.[31,62–72]

By contrast, in the United States (US), the only marketed strength is 250 mg mefloquine hydrochloride, which is equivalent to 228 mg of the free base.[73] Notably, the recommended dosing schedule for malarial prophylaxis and treatment is not significantly different from that of the products containing the equivalent of 250 mg free base. The US innovator product was withdrawn from the market in August

[a]Studies performed at the Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany, using Mefloquine hydrochloride ≥98% pure, lot 060099U00, from Roche Diagnostics GmbH, Mannheim, Germany. No information was available on the polymorphic form.

2009 without giving reasons.[74] The US multisource products are still available as of this writing.[73]

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

Since intravenous (i.v.) formulations of mefloquine hydrochloride cause severe venous irritation at the injection site, there is no i.v. dosage form of mefloquine hydrochloride available on the market.[75–77] Therefore, it has not been possible to determine the absolute oral BA of mefloquine hydrochloride.[29,31,76]

The pharmacokinetic properties of mefloquine have been studied by Desjardins et al.[75] using single oral doses of 250, 500, 1000, and 1500 mg. The results of this study indicate a linear correlation between dose and plasma drug level over this range. However, the number of enrolled subjects was quite low (4 patients per dose) and a wide individual variation in C_{max} and AUC values was observed.[75] Hence, no conclusions on the linearity of the pharmacokinetics can be reached.

Looareesuwan et al.[76] studied the BA of a mefloquine hydrochloride tablet formulation (250 mg base) relative to a deuterium labeled mefloquine hydrochloride solution (250 mg base) and reported the relative BA to be $87 \pm 10\%$ in Thai patients with acute malarial infection and $89 \pm 11\%$ in healthy Swiss Caucasians. However, the pharmacokinetic parameters differed significantly between the two groups. The T_{max} observed after tablet administration in Thai patients with acute *P. falciparum* malaria was 31 ± 13 h in contrast to 16.7 ± 12.5 h in the Swiss healthy volunteers.[76] The C_{max} values were 1004 ± 276 ng/ml in the Thai patients and 319 ± 73 ng/ml in the healthy Caucasian volunteers.[76] These differences were postulated to have resulted from (i) the difference in the dose on a mg/kg basis, and (ii) the difference in health status between the two groups of study population.[76]

Beside subject group, food intake can also influence the BA of mefloquine hydrochloride. Food increases the BA of mefloquine hydrochloride by up to about 40%.[29] Crevoisier et al.[32] reported that the C_{max} and the AUC values were 73% and 40% higher under postprandial (10 min after standardized high-fat breakfast) than under fasting conditions. Hence, postprandial administration is preferred and should be advised in the product leaflet.

Permeability

No well-defined information about human permeability of mefloquine hydrochloride is available in the literature. With respect to Caco-2 cell data, Pham et al.[78] studied the interactions of mefloquine hydrochloride with *P*-glycoprotein (*P*-gp) presented in Caco-2 cells. The results demonstrated that mefloquine hydrochloride can penetrate into Caco-2 cells (however no permeability coefficient was reported) and is both a substrate and an effective inhibitor of *P*-gp.[78] Wu and Benet[79] classified mefloquine to Class II (poorly soluble, extensively metabolized) of the Biopharmaceutics Drug Disposition Classification System (BDDCS), based on their observation that there is a relationship between extensive metabolism and high API permeability.[79] However, the degree of correlation between these two parameters is still subject to debate.

Distribution, Metabolism, Elimination

Mefloquine hydrochloride is very extensively distributed into the body tissues. The apparent volume of distribution is about 20 L/kg.[29,31] The concentration of mefloquine in the infected erythrocytes can be as much as twofold higher than its concentration in plasma.[29,31,80] Plasma protein binding is approximately 98% in both healthy volunteers and patients.[29–31,33,77]

The WHO reported that the elimination half-life of mefloquine hydrochloride lies in the range 10–40 days.[30] Similarly, elimination half-lives of mefloquine hydrochloride reported in the literature vary considerably. For instance, in different studies mean terminal elimination half-lives of 13.9 days (range: 6.5–22.7 days)[75] and 20.1 days (range: 14.1–24.0 days)[81] were reported as well as a mean elimination half-life of 21 days (range: 15–33 days).[31] From the study of Looareesuwan et al.,[76] it is interesting to note that the elimination half-life of mefloquine is significantly shorter in Thai patients than in Swiss healthy volunteers (10.3 ± 2.5 days vs. 16.7 ± 1.9 days, respectively). The authors discussed potential reasons for this phenomenon, including the smaller volume of distribution in the Thais due to lower body fat.[76]

Metabolism of mefloquine takes place mainly in the liver, with a clearance of approximately 30 mL/min.[29–31] It is noteworthy that in the study of Looareesuwan et al.[76] the mean oral clearance was approximately 1.7 times lower in the group of Thai patients than in the group of healthy Swiss (17.5 ± 4.4 mL h^{-1} kg^{-1} vs. 28.8 ± 3.5 mL h^{-1} kg^{-1}), possibly due to an impairment of the drug clearance mechanisms caused by the malarial infection and differences in the enterohepatic cycling between the different groups. In any case, the results from the healthy Swiss group in this study are in agreement with those reported previously by Desjardins et al.[75] and Schwartz et al.[82] The main metabolite of mefloquine is 2-8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, which is ineffective against *P. falciparum*.[29,31] In healthy volunteers, the excretion of this metabolite and unchanged mefloquine in the urine reached only 4% and 9% of the administered

dose, respectively.[29,31] The drug is mainly eliminated in the feces.[30]

DOSAGE FORM PERFORMANCE

Bioequivalence

Several studies have demonstrated that the European mefloquine products Lariam® and Mephaquin® are not bioequivalent.[58,83] Weidekamm et al.[58] performed pharmacokinetic studies of Lariam® and Mephaquin® tablets in 18 healthy volunteers. Statistical evaluation of the pharmacokinetic parameters demonstrated that these two products are not bioequivalent and differences in clinical responses cannot be excluded.[58] Moreover, a study in 19 Thai patients with acute uncomplicated *P. falciparum* malaria showed significantly different pharmacokinetics and BA metrics after taking Lariam® (10 patients) or Mephaquin® tablets (9 patients) in combination with dihydroartemisinin.[83] The details of both studies are given in Table 2. Interestingly, the manufacturers report similar relative BA of the tablet versus an oral solution for Mephaquin® and Lariam® (>85% and $87 \pm 11\%$, respectively) in their product information.[29,31] However, the composition(s) of the oral solutions used were not described.

Excipients

Dissolution studies with pure mefloquine hydrochloride powder showed dissolution profiles which differed significantly from those obtained with the drug products Lariam® and Mephaquin® (Fig. 2). However, there have been no studies of chemical or physical interactions of mefloquine hydrochloride with excipients in the literature. The discrepancy in BA metrics between Lariam® and Mephaquin® in a head to head comparison suggests that formulation (including choice of excipients, API polymorph, and/or particle size) and/or manufacturing process can influence the BA of mefloquine hydrochloride. Table 3 shows the excipients present in the IR solid oral drug products containing mefloquine hydrochloride as a single API, with an MA in CH, DE, DK, FI, FR, NL, NO, SE, UK, and the US.[63–72,84]

Dissolution

No compendial methods for dissolution testing of mefloquine hydrochloride tablets are available in the current pharmacopeias.[55,85–87]

For a biowaiver-based approval, the drug and drug products would have to fulfill the solubility, permeability, and dissolution criteria described by the relevant regulatory authority. To explore the dissolution behavior, BCS-conform dissolution tests of the two innovator mefloquine hydrochloride tablets Lariam® (DE) and Mephaquin® (CH) have been performed using three standard buffers: SGF_{sp}—pH 1.2, acetate buffer—pH 4.5, SIF_{sp}—pH 6.8.[b] The dissolution profiles of the two products and of the pure substance are shown in Figure 2. Neither product fulfills the WHO,[2] FDA,[3] or EMA[4] criteria for either *very rapidly dissolving* or *rapidly dissolving* drug products, so from a dissolution standpoint a biowaiver-based approval would not be possible using either of these products as a reference. Interestingly, the dissolution profiles of Lariam® and Mephaquin® do not meet the f_2 similarity criterion[88] in any of the three BCS-conform dissolution tests.[2,3]

DISCUSSION

Solubility

The solubility studies of mefloquine hydrochloride published in the literature were not performed under the conditions specified for BCS classification. Results from additional, BCS-conforming solubility measurements indicate that the D/S ratios for the maximum available dosage strength (274.09–275 mg mefloquine hydrochloride) lie between 141 and 908 mL over the pH range 1.0–7.5. The highest solubility of mefloquine hydrochloride was measured at pH 4.5. At lower pH conditions, a common-ion effect, owing to the high concentration of chloride ions in the media, was observed. According to the WHO[2] biowaiver criteria the D/S ratios in three aqueous media (pH 1.2–6.8) at 37°C must be $\leq$250 mL. Similar criteria are stipulated by the FDA[3] and EMA.[4] Therefore, mefloquine hydrochloride fails to meet the criterion for *highly soluble*.

Permeability and Absorption

Neither human nor cell culture permeability data for mefloquine hydrochloride have been reported in the literature. Additionally, absolute BA of mefloquine hydrochloride has not been determined since there is no i.v. dosage form available. Therefore, its permeability cannot be unequivocally classified.

BCS Classification

Kasim et al.[89] ranked mefloquine hydrochloride as a BCS Class I drug based on solubility data in water and the calculated partition coefficients. By contrast Lindenberg et al.[90] classified mefloquine hydrochloride as BCS Class II/IV (borderline), because of the low solubility in the gastrointestinal pH range and the lack of reliable permeability data. Wu and Benet[79] classified mefloquine hydrochloride as Class II using the BDDCS approach.

[b]Studies performed at the Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany, with Lariam, Roche, Germany, Lot B114312 and Mephaquin, Mepha Pharma AG, Switzerland, Lot 0752105.

Table 2. Summary of *In Vivo* Bioequivalence Studies of Lariam® Versus Mephaquin®

Refs.	Dose	Subjects	Composition	Prandial	Study Design	Pharmacokinetic Parameters	Bioequivalence Criteria, Statistics	Results	*In Vitro* Tests
Na-Bangchang[83]	750 and 500 mg given at 24 and 30 h after an initial dose of 300 mg dihydro-artemisin	19 (9 received Mephaquin® and 10 received Lariam®) male Thai patients with acute uncomplicated falciparum malaria. Age: 16–42 yo. Body weight: 45–58 kg	Not reported	No food was allowed until 2 h after drug intake	Randomized, one-way. Blood samples taken in the range of 0.5 h and 42 days after first mefloquine intake	AUC, C_{max}, T_{max}, $t_{½}$, MRT, calculated by both noncompartmental and compartmental methods	90% confidence interval, Kruskal–Wallace test, Mann–Whitney *U*-test	Lack of bioequivalence of Mephaquin® with Lariam®	No
Weidekamm[58]	750 mg (3 tablets)	9 male and 9 female healthy Caucasian volunteers. Age: 21–39 yo. Body weight: 44–82 kg. Height: 156–184 cm	Lariam®: crystal modifications of mefloquine predominantly form γ. Mephaquin®: crystal modification of mefloquine predominantly form ε. Excipients not reported	Overnight fasted (low-fat breakfast 2 h and standardized lunch 4 h after drug intake)	Open-label, randomized, two-way, cross-over/ washout 3 months. Blood samples taken in the range of 0.5 h and 56 days after drug intake	AUC, C_{max}, T_{max}, calculation by standard non-compartmental methods	90% confidence interval, Schuirmann's two one-sided *t*-tests, ANOVA	Not bioequivalent	Paddle, 50 rpm, gastric juice pH 1.2, 37°C. Dissolution rate of Mephaquin® was much slower than that of Lariam® (30 min: 34 vs. 80%, 1 h: 48 vs. 91%, 4 h: 75 vs. 97%).

yo, years old.

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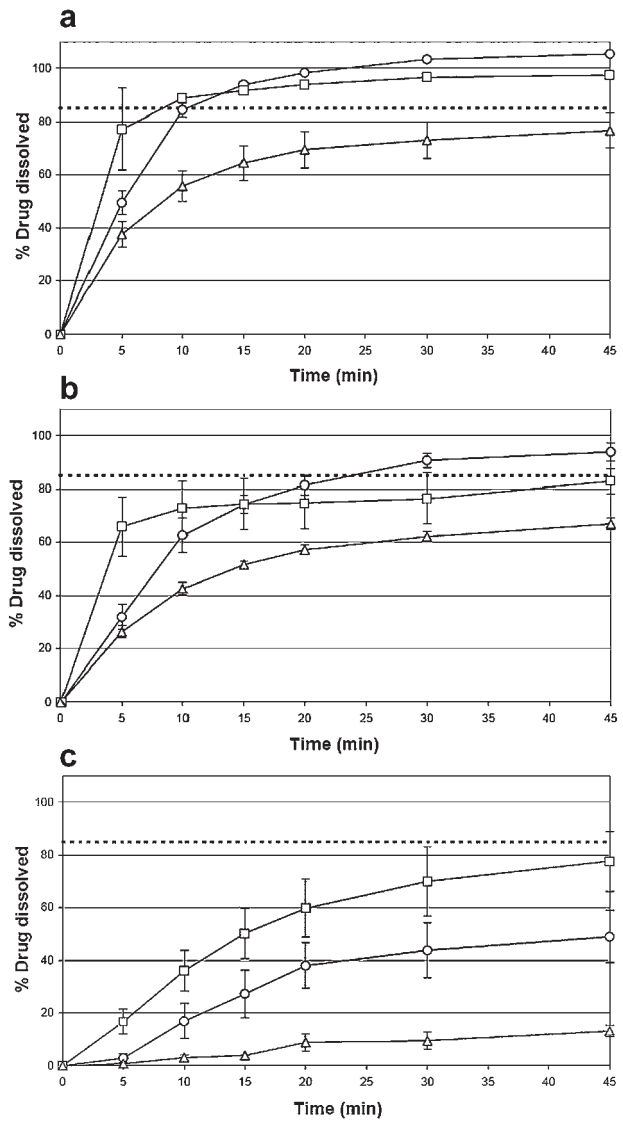

Figure 2. Dissolution profiles of mefloquine hydrochloride tablets in three standard buffers using paddle apparatus at 75 rpm. Top: Lariam®, Middle: Mephaquin®, Bottom: Mefloquine hydrochloride drug substance. The data represent mean ± SD of the percentage of mefloquine dissolved at each sampling time point: ○, simulated gastric fluid without pepsin (SGF_{sp}); □, acetate buffer; Δ, simulated intestinal fluid without pancreatin (SIF_{sp}). The horizontal dotted lines mark the 85% dissolution cut-off criterion, which has to be met for the biowaiver procedure in 15 min (*very rapidly dissolving*) or 30 min (*rapidly dissolving*).

Our analysis indicates that owing to the failure to meet the *highly soluble* criterion and lack of permeability information, mefloquine hydrochloride would have to be assigned to BCS Class II or IV. As its D/S ratio is greater than 250 mL at pH 6.8, and 7.5, it cannot qualify for a dissolution-based biowaiver approval according to the WHO[2] Guidance and no other guidances permit dissolution-based biowaiver approval for any drug products containing BCS Class II compounds. Furthermore, no guidances permit consideration of BCS Class IV APIs for dissolution-based biowaiver approval.

Surrogate Techniques for *In Vivo* Bioequivalence Testing

Dissolution testing under BCS conditions (WHO[2] method, Fig. 2) show the same trend as the *in vivo* pharmacokinetic data (Tab. 2)[58,83]: Lariam® showed a faster dissolution rate than Mephaquin® commensurate with its higher C_{max} and AUC values *in vivo*. However, the BCS methods would have to be validated with further products using an *in vitro–in vivo* correlation before it could be recommended as a surrogate technique for *in vivo* BE studies. Such a test would of course only address bioinequivalence caused by different *in vivo* disintegration and/or *in vivo* dissolution characteristics, noting that BE problems caused by excipient/mefloquine interactions with respect to motility and permeability cannot be addressed with dissolution testing.

Risks of Bioinequivalence Caused by Excipients and/or Manufacturing Parameters

The dissolution profile comparison as well as the pharmacokinetic profile comparison of Lariam® versus Mephaquin® showed significant dissimilarities. These differences could be caused by the different API properties (particle size, polymorph), different excipients used (Tab. 3), or different manufacturing processes. Due to the low solubility of the API, excipients such as surfactants and disintegrants are especially likely to influence the BA of mefloquine hydrochloride. In this study, the fastest dissolution rate and highest BA was achieved by the Lariam® formulation, which contains the surfactant Poloxamer 331, followed by Mephaquin® containing the surfactant sodium lauryl sulfate (SDS), while the pure mefloquine hydrochloride powder dissolved slowest. Thus, a lack of BE between mefloquine hydrochloride products arising from the use of different excipients, or variations in the amount of excipient used, seems likely.

Patient's Risks Associated With Bioinequivalence

Many studies investigating the treatment of malaria with mefloquine hydrochloride have shown that the drug is safe, generally well-tolerated and highly effective against *P. falciparum*.[77,91,92] Additionally, malarial prophylaxis with weekly mefloquine hydrochloride is also relatively well-tolerated and the patients normally show good responses.[34] Additionally the Pan American Health Organization (PAHO)[93] has classified mefloquine as a drug with low health risks.

Sub-bioequivalent BA of mefloquine hydrochloride could lead to sub-therapeutic blood levels resulting in ineffective malarial treatment/prophylaxis.

Table 3. Excipients Present in Mefloquine HCl IR Solid Oral Drug Products With a Marketing Authorization (MA) in Switzerland (CH), Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Sweden (SE), United Kingdom (UK), and the United States (US), and the Minimal and Maximal Amount of That Excipient Present Pro Dosage Unit in Solid Oral Drug Products With a MA in the US

Excipient	Drug Products Containing That Excipient With a MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With a MA in the US (mg)
Ammonium calcium alginate	DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 10)	10.7
Cellulose	CH (11); DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 10, 12, 13)	4.6–1385[a]
Croscarmellose sodium	CH (11)	2–180
Crospovidone	DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 10, 12, 13)	4.4–792[a]
Hydroxypropylcellulose	US (12)	4–132
Hypromellose	CH (11)	0.8–537
Lactose	CH (11); DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 10, 12, 13)	23–1020[a]
Macrogol	CH (11)	0.12–961[a]
Magnesium stearate	CH (11); DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 10, 12, 13)	0.15–401[a]
Poloxamer	DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 10, 13)	3.2–107
Povidone	US (10)	0.17–80
Silica	CH (11); US (10, 13)	0.65–99
Sodium laurilsulfate	CH (11)	0.65–52
Starch	DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 10, 13)	0.44–1135[a]
Starch, pregelatinized	CH (11); US (12, 13)	6.6–600
Talc	CH (11); DE (1); DK (2); FI (3); FR (4); NL (5); NO (6); SE (7); UK (8); US (9, 12, 13)	0.25–220[a]

1. Lariam® Tabletten (Mono). 2. Lariam, tabletter. 3. LARIAM® 250 mg tabletti. 4. LARIAM 250 mg cp séc. 5. Lariam, tabletten 250 mg. 6. Lariam® 250 mg tabletter. 7. Lariam 250 mg tabletter. 8. Lariam 250mg tablets. 9. LARIAM (mefloquine hydrochloride) tablet [Roche Pharmaceuticals]. 10. Mefloquine hydrochloride (mefloquine hydrochloride) tablet [Roxane Laboratories, Inc.]. 11. Mephaquin® [Mepha Pharma AG]. 12. Mefloquine HCl (Mefloquine Hydrochloride) tablet [Sandoz Inc.]. 13. Mefloquine hydrochloride (mefloquine hydrochloride) tablet [Barr Laboratories, Inc.].

[a]The upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

Furthermore, the risk of development of resistant strains may be increased. On the other hand, a supra-bioequivalent BA may increase the incidence and/or severity of adverse effects of mefloquine hydrochloride, which in turn could adversely affect overall health status and patient compliance.[39] Croft and Garner[94] reported that the withdrawal rates of the patients, presumably from intolerability of the adverse events, were high in many studies and impaired the effectiveness of mefloquine prophylaxis.

Two branded products, Lariam® and Mephaquin®, are available on the market. The C_{max} values of subjects who have taken Lariam® differ significantly from those who have received Mephaquin®: C_{max} in the Thai patients (dose 1250 mg) was reported to be 2850–4240 ng/mL (Lariam®) versus 1720–3130 ng/mL (Mephaquin®)[83] and in the healthy Caucasian volunteers (dose 750 mg) 807–1229 ng/mL (Lariam®) versus 450–862 ng/mL (Mephaquin®).[58] Two clinical studies have indicated that the minimum inhibitory concentration for mefloquine is 600[29] and 620 ng/ml,[31] respectively. Focusing on the study from Na-Bangchang et al.,[83] all patients reached plasma levels greater than 600 ng/mL. Nonetheless, four patients of the Mephaquin® group had reappearance of parasitaemia between days 14 and 28. From this study, it can be concluded that Mephaquin® lacks BE to Lariam® and, furthermore, there is some evidence that the two products are not therapeutically equivalent.[83] In the study by Weidekamm et al.[58] the volunteers of the Lariam® group, but not all those of the Mephaquin® group, reached the minimum inhibitory plasma concentration, underscoring the possibility of clinical consequences caused by the lack of BE between the two branded products.[58]

Another point to consider is the difference in tablet strength between the EU and in the US, without adjustments in the dosing schedule. This difference would increase the risk of bioinequivalence on an international level but it is not relevant *per se* to the assessment of BE in a given regulatory jurisdiction. Summarizing, it seems likely that mefloquine products with poor dissolution characteristics or which fail to demonstrate BE in pharmacokinetic studies would be associated with an increased risk of prophylaxis or therapy failure.

CONCLUSIONS

Due to the lack of reliable permeability data and the failure to meet the *highly soluble* criterion, mefloquine hydrochloride cannot yet be assigned conclusively to a BCS Class: it could belong to either BCS Class II or IV. Therefore, a biowaiver currently is not justified for new multisource products or for the reapproval of existing drug products after extensive variations in the formulation and/or manufacturing process, that is, SUPAC level 3[88] or EU type II variations.[95] Small changes may be acceptable based on dissolution testing as described by these regulatory documents.

However, in the future, a biowaiver for new multisource mefloquine HCl drug products may become possible. The long elimination half-life makes its plasma profile rather insensitive to small differences in dissolution behavior among formulations, mefloquine does not appear to be a narrow therapeutic index drug and simple *in vitro* dissolution testing was in some cases successful in discriminating between products being bioinequivalent. So, if further data confirm a good *in vitro*/*in vivo* correlation, a biowaiver might be feasible in the future for new multisource drug products and major formulation changes.

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