

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-799

MEDICAL REVIEW(S)

Team Leader Review of NDA 21-799

APPLICANT: Mutual Pharmaceutical Company
DRUG: Quinine Sulfate (no trade name proposed)
NDA/Indication: Treatment of uncomplicated *Plasmodium falciparum* malaria
SUBMISSION DATE : October 13, 2004
PDUFA GOAL DATE: August 14, 2005
FORMULATION: Capsules, 324 mg (269 mg free base)

RECOMMENDATIONS:

The Review Team finds a favorable risk /benefit profile for quinine sulfate in the treatment of uncomplicated *P. falciparum* malaria and recommends approval of this new drug application (505b2) for this orphan indication. This recommendation is based on the consistent finding of efficacy favoring quinine in a meta-analysis of published randomized clinical trials, and the demonstration of bioequivalence of the applicant's formulation to an approved formulation utilized in the pivotal clinical trials (GPO, Thailand). The conclusions on the safety of quinine for uncomplicated malaria is based on a larger body of evidence including data from published clinical trials, individual case reports, data from pregnancy registries, and information from the FDA and WHO safety databases. In addition to appropriate labeling of the drug's safety risks, the review team recommends a pregnancy category C for the package insert. There were too few patients over 65 in the published clinical trials of malaria to characterize the safe use of quinine for this indication. On the other hand, more adverse events and serious adverse events in the FDA AERS and WHO databases occurred in patients over 50, the majority of whom were treated for nocturnal leg cramps. Additionally, the median age of 11 patients reported to have developed torsade de pointes was 75 years (range 41-93), all reported indications were for leg muscle cramps (n=7). Because the elderly consists of a population for whom quinine's multiple drug -drug interactions would be especially relevant, and in whom off-label use for nocturnal leg cramps is likely considerable, the review team recommends a WARNING statement in the label referring to potential increased risk in the elderly, in patients with underlying QT prolongation, or receiving QT prolonging medications, and in patients with underlying clinical conditions that predispose to QT prolongation. In addition, the team recommends that the label indicate that quinine is not approved for use in prophylaxis and for the treatment of nocturnal leg cramps. Although the review team finds that pediatric dosing of quinine sulfate may be similar to adult dosing based on pharmacokinetic studies in the literature, age-appropriate dosing recommendations are hampered by the lack of a pediatric formulation.

The review teams' proposed risk management plan centers on an educational program consisting of a patient package information sheet, and an educational program for prescribing physicians, including a Dear Doctor letter.

Approval of this NDA assures the availability of quinine sulfate for patients with malaria, an orphan indication in the United States, in the event that enforcement action is taken against quinine sulfate products that are misbranded under section 502 of the Federal Food Drug and Cosmetics Act.

BACKGROUND:

Of the estimated 300 - 500 million cases of clinical malaria that occur worldwide, about 1 million, the majority of whom are children, die each year (<http://www.cdc.gov/ncidod/dpd/parasites/malaria/default.htm>, 8/8/2005). *P. falciparum* infection is mostly inapparent for the majority of the half a billion semi-immunes in malaria endemic areas (<http://www.guardian.co.uk/medicine/story/0,11381,1434273,00.html> 7/29/2005). In the US however, where the *P falciparum* vector has been eradicated, malaria is uncommon, although an increase in recreation and military travel has resulted in more imported cases of malaria over the years. Over a 28 year period from 1966 through 1987, the CDC received a total of 1760 reports of imported malaria of which 3.8% were fatal (Division Director Memorandum, R. Lipicky, M.D. HFD 110, 2/26/1991). More recent estimates indicate approximately 1300 malaria cases in the US in returning non immune civilian and military travelers. Drug development and availability, for a serious infection in a non immune population, has always been a challenge in the US, due in part to the relative infrequency of malaria.

Quinine is a cinchona alkaloid that is a levorotatory isoform of the antiarrhythmic drug quinidine. Both drugs are chemically identical and share the same molecular formula (C₂₀H₂₄N₂O₂). Both drugs are effective blood schizonticides, an activity shared with other available antimalarial agents. While quinidine is approved in the US for the initial treatment of severe and life threatening *P falciparum* malaria, quinine is not. An intravenous formulation of quinine was never manufactured in the US and nor was an NDA ever submitted to the Agency. However, the CDC Drug Service procured stocks of IV quinine and from January 1979 to April 1991, held an IND for the drug as a mechanism to distribute IV quinine in the US. Delays in obtaining intravenous quinine from this central source were temporarily allayed following the approval of IV quinidine for severe malaria in 1991, and the CDC IND was withdrawn (MMWR 1991; 40 (no.RR-4):21-3). However, as newer antiarrhythmics replaced quinidine as the drug of choice, continued availability of quinidine became challenging for the less economically viable indication of malaria. The concerted efforts of the manufacturer, the CDC and the FDA have ensured the continued availability of quinidine in select US hospitals (MMWR1996; 45:494-5). Early and aggressive therapy of *P falciparum* malaria is needed to prevent the development of hyperparasitemia and severe malaria, thereby obviating an urgent need for IV quinidine.

A number of other antimalarial agents are available worldwide for the treatment of malaria. Increasing drug resistance and drug toxicity preclude use of these alternative agents in some patients. Chloroquine and pyrimethamine-sulfadoxine resistance has increased in many parts of the world, and resistance to mefloquine has also emerged in the Thai-Burmese border. The latter agent is associated with neuropsychiatric adverse events whereas halofantrine is associated with cardiotoxicity and is not currently marketed in the US. Although several artemisinin derivatives have shown significant antimalarial activity no commercial sponsor has submitted an NDA for malaria in the US. The availability in the US of several unapproved formulations of oral quinine is largely

due to the commercially viable use in nocturnal leg cramps. The relative bioavailability and purity of these formulations is not assured. The availability in US of an approved formulation of quinine proven safe and effective against *P. falciparum* malaria would fill a gap for an alternative antimalarial agent for returning US travelers.

Quinine use is documented from the 15th century, long before the malarial parasite was identified as the etiological agent for this disease. Despite the worldwide use of quinine and some increase in reported resistance in regions in Southeast Asia and New Guinea (Baird 2005), the drug remains effective in many parts of the world, and continues to be recommended by the WHO and CDC as an important therapeutic agent in the narrow armamentarium for malaria.

Recommendations for the Use of Quinine in Combination Treatment of Uncomplicated <i>P. falciparum</i> Malaria in Published Guidelines		
Reference	Indication for Oral Quinine	Regimen
CDC May 2004	Treatment of uncomplicated malaria in adults (<i>P. falciparum</i> or species not identified and infection acquired in a chloroquine-resistant area or in areas of unknown resistance)	650 mg 3 X daily for 3-7 days in combination with tetracycline, doxycycline, or clindamycin for 7 days
WHO. 2001		Orally, 8 mg base/kg 3X daily for 7 days with tetracycline, doxycycline, or clindamycin OR with sulfa-pyrimethamine for 3 days

The WHO recommendation specifies a 7 day course of quinine in combination, except for combined use with Fansidar, for which a 3 day regimen is specified. The CDC recommends 3-7 days of quinine sulfate therapy, combined with a 7 day regimen of tetracycline, doxycycline or clindamycin. The CDC also recommends quinine sulfate as therapy for chloroquine resistant *P. vivax* and also therapy for pregnant women with uncomplicated *P. falciparum* or *P. vivax*.

However, it is estimated that approx. — capsules of quinine sulfate are sold per year in the US, based on prescription data compiled by the Office of Drug Safety from an IMS database query. Over — of these prescriptions are for indications other than malaria, predominantly for neuromuscular disorders, particularly for muscle cramps. There are no accurate data on over the counter and internet sales for quinine, but it is known that at least 22 manufacturers including 13 distributors continue to market the drug in the US (<http://cpip.gsm.com>, 8/2005). None of these marketed products have a label that accurately depicts the safety profile of quinine.

A total of four quinine sulfate products marketed pre 1938, were approved by the Agency in accord with the Food Drug and Cosmetics Act, based on finding of safety. Three of these formulations were oral (tablets, capsule), and one was topical (vaginal jelly/powder). None of these formulations were approved for malaria and all have been

withdrawn by the Commissioner after the Drug Amendments of 1962, which required evidence of drug effectiveness for the stated indication.

Quinine sulfate tablets for use in nocturnal leg cramps, however, continued to be marketed post 1962. In 1994, in response to a citizen's petition to ban the use of quinine in leg cramps due to the reports of fatal hypersensitivity and thrombocytopenia, the Agency determined that there was a lack of adequate data to establish the safety and efficacy of quinine sulfate use in the treatment and or prevention of nocturnal leg muscle cramps. This conclusion was buttressed by a 1977 Advisory Panel recommendation that the drug not be made available over the counter (Federal Register 11/8/1985 p 46592). In the FR 1994 notice, the Agency further noted that quinine sulfate use has resulted in adverse events ranging from visual and auditory disturbances, to unpredictable serious and fatal hypersensitivity reactions. Based upon the adverse benefit to risk ratio, the Agency concluded that drug products containing quinine cannot be generally recognized as safe for the treatment and prevention of nocturnal leg muscle cramps. Any over the counter drug products that were labeled, presented or promoted for the treatment and or prevention of nocturnal leg muscle cramps were to be regarded as a new drug based on the Federal Food Drug and Cosmetic Act, and that in the absence of an approved new drug application, or abbrev new drug application, marketed quinine products are considered misbranded and subject to regulatory action (21 CFR 310.546 based on 59 FR 43252, published August 22, 1994). The Agency subsequently issued a letter to 44 companies manufacturing quinine stating the illegal status of their products marketed for nocturnal leg cramps. Following distribution of this letter, the labels of unapproved marketed quinine sulfate products were revised by the individual manufacturers to eliminate all reference to nocturnal leg cramps and to reflect an indication of malaria.

On March 20, 1998, the Agency published a Federal Register notice that any drug product containing quinine that is labeled, represented, or promoted for the treatment and/or prevention of malaria is regarded as a new drug within the meaning of section 201(p) of the act, for which an approved application or abbreviated application is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the based on the Federal Food Drug and Cosmetic Act. (21CFR 310.547, based on FR notice 63 FR 13528).

On February 13, 2003 URL/Mutual Pharmaceuticals, Inc. (URL/Mutual) proposed the submission of a new drug application for Quinine Sulfate Tablets, 260 mg and Quinine Sulfate Capsules, 324 mg to the FDA. A meeting to discuss the requirements for submission of a quinine sulfate NDA submitted pursuant to section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act was held on July 15, 2003. The Division agreed to the applicants' proposal to summarize publicly available information for quinine with the following caveats:

- That the search strategy utilized and the criteria for inclusion of studies be described a priori
- That the pivotal studies be clearly identified

- That the numbers of patients in these pivotal studies should be clear
- That the pivotal studies should incorporate an appropriate comparative design and address other efficacy concerns, e.g., immune status of the populations in the studies, the geographic distribution of resistance, and the geographic location of the studies
- That detailed information on recrudescence rates be available
- That the submission provide a discussion, supported by the literature, of the comparative risks and benefits of quinine compared with other drugs, in the indication being sought
- The Division also stated that the applicant provide information regarding quinine's potential to prolong the QT interval and that the applicant should consider the safety of the product for off-label use, particularly for leg cramps, as the Division may determine the need to put wording in the label, possibly even in the WARNINGS section, regarding such off-label use.

At this meeting, the applicant noted that companies currently marketing quinine sulfate without approval should have to pull their products off the market. URL/Mutual noted that this has been the case in the past for marketed but unapproved products when an NDA for the product is approved. The applicant notes that _____

_____ The applicant noted however, that they are not certain how much quinine sulfate is currently sold and that they also not certain how quinine sulfate is used other than for malaria and leg cramps.

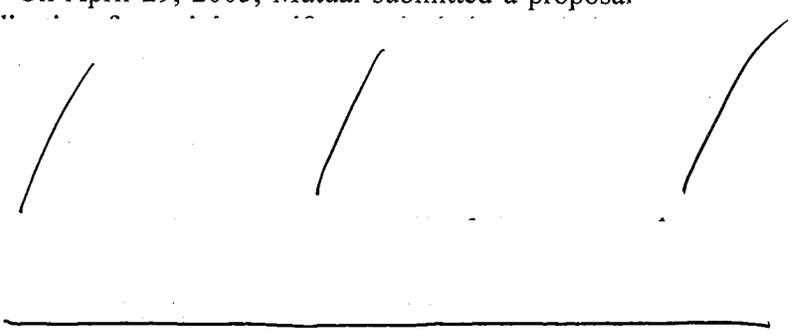
The pharmacokinetic characterization of quinine in this NDA required comparison of the applicant's product with the products used in the pivotal studies supporting the application, formulations supported by WHO or other international organizations, or product that has gone through an approval process. In continuing discussion with the Applicant it was decided that the GPO product formulated in Thailand, approved by the Thai regulatory process and used in several pivotal studies, served as comparator for the applicant's bioequivalence study.

The applicant was encouraged to provide as much information as possible regarding the pharmacokinetics of quinine sulfate in older patients, particularly given the predisposition for Qt prolongation and the frequent use of concomitant medications in the elderly population. _____

_____ At this meeting, the Division concurred with the applicant's seeking an Orphan Drug designation. Additionally, exclusivity was discussed and as reflected in the minutes, an approval for the treatment of malaria, would qualify the applicant to seven years of exclusivity if their quinine sulfate product is the first approved for this indication.

On October 14, 2004, Mutual submitted a new drug application (NDA) 21-799 for quinine sulfate for the treatment of uncomplicated malaria caused by *Plasmodium*

falciparum. On April 29, 2005, Mutual submitted a proposal



Clinical Efficacy:

The Division shared the applicant's optimistic view that the regulatory requirement for labeling of quinine for the indication of 'treatment of uncomplicated *P. falciparum* malaria would be met given the large body of published information on the safety and efficacy of the drug. The applicant performed an extensive search of existing scientific literature databases, identified the published clinical trials that met prespecified criteria for adequate and well-controlled studies and performed a systematic review of the data supporting efficacy and safety of quinine from this published literature (see Dr. Tracy's statistical review for details). The Division required that the applicant pre-specify any planned meta-analysis of the data substantiating the efficacy of quinine monotherapy and in combination for the treatment of *P falciparum* malaria. The Division also noted that for the latter claim, substantiation in adequate and well-controlled studies demonstrating the advantage of combination therapy over monotherapy and the efficacy of quinine in infections where resistance is clearly characterized would be needed to support the claim.

Bioequivalence between the applicant proposed quinine sulfate capsule formulation and the quinine sulfate 300 mg tablet formulation manufactured by the GPO, Bangkok, Thailand, (used in at least 2 of the 9 pivotal trials) was required to bridge the demonstrated efficacy of quinine in the pivotal trials to the applicant's proposed formulation (see Dr. Gerlie Geiser's review for details).

Quinine's efficacy and safety in the treatment of *P falciparum* malaria was established and antedated the science of randomized clinical trials. The published experience on quinine efficacy, while considerable, consists therefore of observational case series that would be considered inadequate based on current clinical trial standards. In the contemporary literature that fulfills the criteria established by the review team, the data originates in settings where reduced quinine efficacy has emerged, the impetus for study being to evaluate more promising therapies against quinine. The information that was reviewed would therefore tend to bias against quinine.

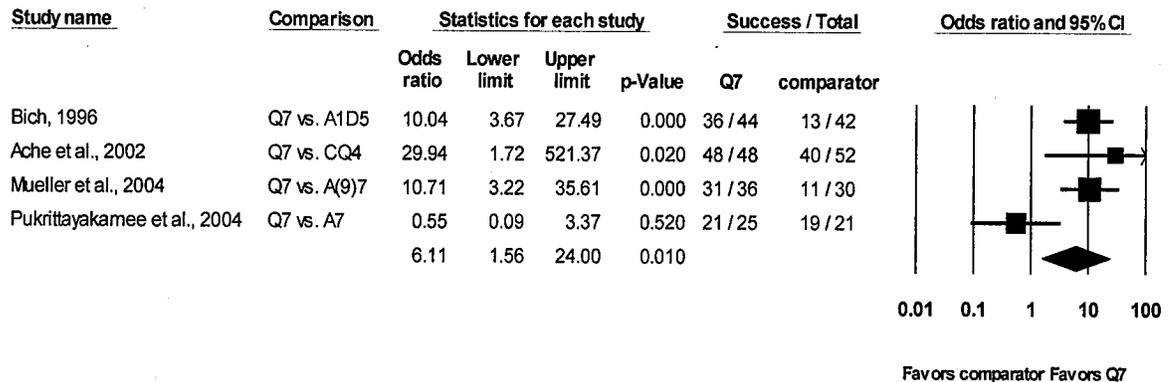
The review team undertook a systematic review of 22 randomized, active-controlled, studies evaluating quinine sulfate efficacy in 1,456 oral quinine treated patients of 2,495 patients enrolled. Eleven studies evaluated quinine monotherapy and 17 evaluated combination therapy. Nine of these studies were of sufficient rigor for inclusion in the meta-analyses performed by the biostatistics review team.

QUININE MONOTHERAPY

Five of 6 studies evaluated the efficacy of 7 day quinine monotherapy at a common 28 day time point. The cure rates in these studies were 82-86% (61-70%) in the evaluable (ITT) populations and one additional study of 48 patients had a cure rate of 100% in both populations.

Figure 1 from Dr. LaRee Tracy’s review depicts the results of a meta analysis performed on four of the above studies. These studies evaluated a 7 day quinine regimen versus a non-quinine comparator in Southeast Asia (2), Africa (1), and South America (1). Quinine efficacy in the evaluable (n=153) and ITT (n=185) populations in these studies ranged from 82% to 100% and 61% to 100% respectively, likely reflecting the range of quinine resistance in the regions tested. Nonetheless the estimated odds ratio suggests that the probability of cure is 6.11 times greater with Q7 versus a non-quinine control, especially against chloroquine regimens CI [1.56, 24.00], 99% CI [1.01, 36.9], p-value=0.010. The estimated odds ratio in the ITT population was 3.31, 95% CI [1.00, 10.97], 99% CI [0.68, 16.00], p-value=0.051 suggesting no difference in overall treatment effect.

Figure 1 Meta-Analysis of 7 day quinine monotherapy regimens vs comparators in Evaluable Patients with Uncomplicated *P. falciparum* malaria



Q = quinine, CQ= chloroquine, D=doxycycline, A= artemisinin derivative including artemisinin-containing tea Mueller et al),

Figure 2 Meta-Analysis of 7 day quinine monotherapy regimens vs comparators in ITT Patients with Uncomplicated *P. falciparum* malaria

**NDA 21-799 Quinine for the treatment of uncomplicated *P falciparum* malaria
Team Leader Review**

Study name	Comparison	Statistics for each study				Success / Total		Odds ratio and 95%CI
		Odds ratio	Lower limit	Upper limit	p-Value	Q7	Comparator	
Bich, 1996	Q7 vs. A1D5	4.816	2.130	10.887	0.000	36 / 59	13 / 53	
Ache et al., 2002	Q7 vs. CQ4	29.938	1.719	521.370	0.020	48 / 48	40 / 52	
Mueller et al., 2004	Q7 vs. A(9)7	4.642	1.860	11.583	0.001	31 / 48	11 / 39	
Pukrittayakamee et al., 2004	Q7 vs. A7	0.491	0.130	1.860	0.295	21 / 30	19 / 23	
		3.307	0.996	10.974	0.051			

Q = quinine, CQ= chloroquine, D=doxycycline, A= artemisinin derivative including artemisinin-containing tea (Mueller et al),

These conclusions are limited by the size of the populations studied and the variety of comparators evaluated (short regimens or nontraditional formulations of artemisinins, chloroquine in areas of chloroquine resistance),

Indirect proof of quinine efficacy as an antimalarial also exists from studies that have evaluated increasing doses or duration of quinine therapy. The following table summarizes the efficacy of quinine monotherapy of varying duration in Africa, from the last 10 years. The efficacy rates between the 1.5 and 3 day quinine regimens compared to the full 7 day course suggests that longer treatment durations are more efficacious, likely due to the provision of adequate therapy to cover multiple replicative cycles of the parasite. One other indirect line of evidence is the enhanced quinine efficacy of intravenous and loading dose therapy in severe malaria, reviewed as supportive evidence of efficacy by Dr. Mary Singer.

Efficacy of Quinine Monotherapy by Duration of Therapy

Studies performed in Africa that utilized various treatment durations of quinine monotherapy	Treatment /Duration	Cure Rate (28 days) in Evaluable Population n/N (%)
Metzger, et al., 1995 (Gabon)	Q 1.5	14/37 (38%)
Kremsner, et al., 1994 (Gabon) (pediatric)	Q3	10/31 (32%)
Mueller, et al., 2004 (Dem. Rep. Congo)	Q7	31/36 (86%)

Despite the voluminous literature documenting quinine efficacy, several factors limit the conclusions derived from a review of the randomized controlled trials of quinine safety and efficacy. These include differences in study design, choice of comparators, evolving resistance patterns, and the difference between the semi-immune populations studied and the intended population of non immune returning travelers. However, the review teams' conclusion of efficacy of quinine monotherapy based on this meta analysis is strengthened by the objective nature of the outcome measure (parasitemia), the longer time course for natural resolution of untreated malaria (reported to be 7 months in Eales DE and Young MD The duration of untreated or inadequately treated *Plasmodium*

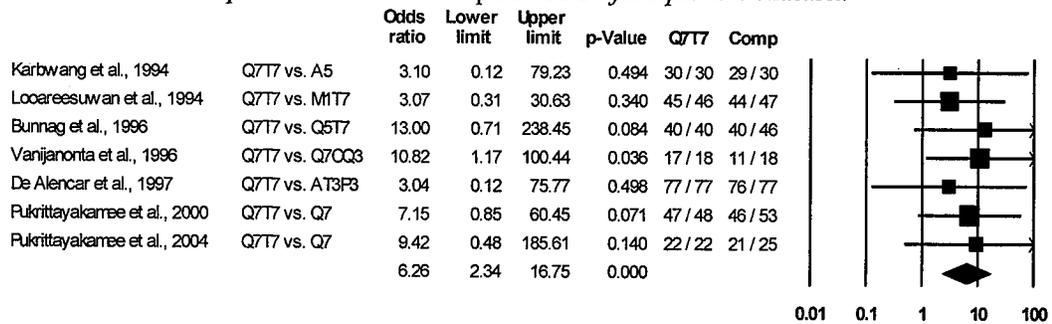
falciparum infections in the human host. 1952. J Natl Mal. Soc 1:327-336.) compared to the 28 day endpoint employed in these studies, and the consistent finding of efficacy favoring quinine in the ITT and evaluable populations analysis. The dose and duration response to quinine also serve as indirect lines of evidence that support the conclusions drawn from the meta analyses.

COMBINATION REGIMENS

In combination with 7 day oral tetracycline:

In seven primary studies, where 325 patients received quinine 10 mg/kg tid in combination with tetracycline for 7 days, the cure rates were 4-100% and 68-95% in the evaluable and ITT populations (one study not reporting ITT rates). The lower cure rates in the ITT population consisted generally of patients lost to follow-up.

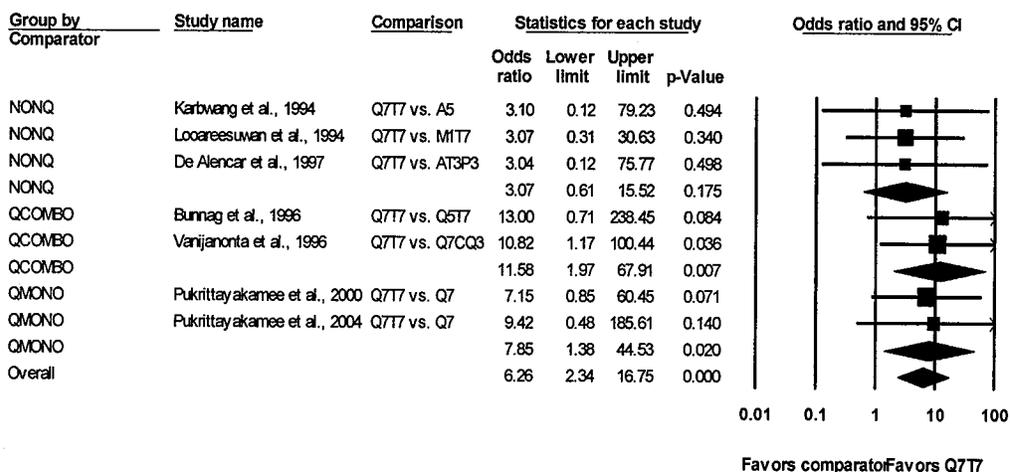
Figure 3 Meta-Analysis of 7 day quinine tetracycline combination regimens vs comparators in evaluable patients with uncomplicated *P. falciparum* malaria



The following forest plot reveals the efficacy analysis of 7 day quinine-tetracycline combination in comparison to various subgroups of quinine containing and non quinine containing treatment regimens. Note that only 2 studies directly compared quinine monotherapy to that of quinine in combination with tetracycline, both 7 day regimens. These studies were robust in design and considered by the review team to comprise the primary evidence of efficacy of quinine in combination therapy. The studies suggest reproducible benefit favoring combination therapy in an adult Thai population, (estimated treatment effect of 7.85 (OR), 95% CI [1.38, 44.52].

Figure 4 Meta-Analysis of 7 day quinine tetracycline combination regimens sub-grouped by comparator type (Evaluable Population)

**NDA 21-799 Quinine for the treatment of uncomplicated *P falciparum* malaria
Team Leader Review**



NONQ = non quinine QCOMBO = quinine in combination QMONO= quinine monotherapy

In evaluating whether a shorter course of combination therapy would have similar efficacy to the 7 day course of quinine monotherapy, Dr. Singer notes that none of the pivotal studies undertook this direct comparison. However, the range of efficacies with the combination short course studies (87% to 94%) were similar to the efficacies reported in the quinine 7 day monotherapy studies in Figure 1 above. Furthermore, the studies by Kremsner and Metzger supports the finding of improved efficacy with quinine in combination therapy over quinine monotherapy, as shown in Figure 4 above. Nonetheless, differences in study populations, differences in parasite susceptibilities in regions where studies were conducted, and differences in chosen comparators and dosage regimens employed, preclude statistically validation of these conclusions.

Cure Rates (28 days) for Quinine Combination Therapy and Antimalarial Drug Comparators (African studies)

Study	Geographical Location	Antimalarial Treatment Regimen	Cure Rate in Evaluable Population n/N (%)
Metzger, et al., 1995	Gabon	Q1.5	14/37 (38)
		Q1.5 + C3	33/36 (92)
		Q1.5 +D3	32/35 (91)
Kremsner, et al., 1994 (pediatric study)	Gabon	Q3	10/31 (32)
		Q3 +C3	30/34 (88)
Ramharter, et al., 2005 (pediatric study)	Gabon	Q3 +C3	45/48 (94)
		Q3 +A3	40/46 (87)

Dr. Tracy discusses the statistical issues in meta analysis that are pertinent to the regulatory standards of efficacy evaluation based on published literature. While these may limit the precision of the treatment effect attributable to quinine therapy, the attempt to precisely estimate treatment effect may in itself prove limiting. Because older studies were not designed and may not present efficacy analyses in a manner that fulfills the regulatory requirement for an adequate and well controlled study, the true efficacy of an old standard drug such as quinine, may be underestimated.

Summary: The review teams finds that in the pivotal trials that fulfilled the applied criteria, 7 days of quinine therapy generally resulted in at least an 80% cure, defined as initial clearing of parasitemia within 7 days without recrudescence by day 28 after treatment initiation, regardless of the country in which malaria was acquired. In areas where multi-drug resistance of *P. falciparum* is known to be present, such as in Southeast Asia, cure rates with 7 days of oral quinine monotherapy were at least 80%; while cure rates for 7-days of oral quinine combined with an antimicrobial agent (tetracycline or clindamycin) were greater than 90%. In areas where multi-drug resistance of the parasite was not as prevalent, cure rates with 7-days of quinine monotherapy ranged from 86 to 100%. *P. falciparum* malaria that is clinically resistant to quinine has been reported in some areas of South America, Southeast Asia, and Bangladesh, and quinine may not be as effective in those areas. It is important to point out that most failures even from areas of resistance consisted generally of RI rather than outright clinical failures, accounted for perhaps by the generally difficult compliance with oral quinine.

Clinical endpoints of fever resolution and survival supported the conclusions derived from the primary surrogate endpoint of parasite clearance at 28 days. Fever resolution generally occurred earlier than the parasite clearance time in the studies evaluating either mono or combination therapy. In more severe malaria which is universally fatal if left untreated, parenteral quinine resulted in survival rates of at least 80% for patients, buttressing the evidence of efficacy of quinine as an efficacious antimalarial agent.

When administered with other antimalarial agents, quinine showed equal or greater compared with monotherapy. The evidence that supports these conclusions is generally reflective of the efficacy of quinine in areas of increased drug resistance, as quinine was the default comparator to a new drug/combination under evaluation to overcome local parasite resistance. There was more limited evidence of quinine efficacy in areas where parasites remain susceptible. Indeed the selection criteria for randomized, controlled studies, likely biased the information to that derived from contemporary studies in the era of drug resistance. Nonetheless, one potential area of concern is that the efficacy of quinine monotherapy in these areas could be an overestimate of drug efficacy in returning travelers, as these studies were generally performed in semi-immune populations. The negotiated label

Published data from randomized, controlled clinical trials for shorter regimens of oral quinine in conjunction with tetracycline, doxycycline, or clindamycin for treatment of uncomplicated *P. falciparum* malaria is limited, and these shorter course combination regimens may not be as effective as the longer regimens. A definite trend to earlier fever resolution was evident from the studies evaluated by Dr. Singer, which when coupled with the frequent adverse events with oral quinine, explains the impetus for more abbreviated therapy. However, the 28 days parasitological outcomes were inconsistent, particularly when the second antimalarial combined with quinine was a short acting agent, indicating perhaps that sustained antimalarial activity (when infection is not uniform in phase) is needed to achieve consistent cures.

The approval of antimalarial agents based on published literature finds regulatory precedence in the approval of quinidine gluconate for severe *P falciparum* malaria (NDA 7529 for IV Quinidine Gluconate , S010). In 1991, quinidine gluconate was labeled for use as an antimalarial following review of two pivotal studies (Miller et al 1989; NEJM 321:65-70, Phillips et al 1985; NEJM 312:1273-8). The other drugs approved for the treatment of *P falciparum* malaria reviewed in the Division were based on more substantial prospectively collected data reviewed by the Agency in more traditional NDA submissions. These generally had more generous success rates (~90-97%) that reported in the pivotal studies for malaria. However, these differences may be more apparent than real, as the studies for these other agents are more recent and generally adhered to the basic tenets of advance clinical trials.

CLINICAL SAFETY

A broader database provided data for Dr. Mary Singer's safety review of this NDA. To augment the safety data from the published randomized controlled trials of efficacy, the applicant performed an additional search for contemporary (1993 to 2004) articles describing the safety of oral and parenteral quinine. Safety data from the following additional sources was also submitted with the NDA:

- safety data from 50 healthy volunteers in the single-dose bioequivalence study
- postmarketing adverse events reported to FDA (obtained through FOIA)
- postmarketing adverse events reported to WHO
- labeling for quinine products marketed worldwide (France, Germany, Canada, Australia, Denmark, Taiwan, Thailand)

The review team performed also performed directed searches for individual adverse events of interest. To complement the Review Team's risk –benefit assessment of quinine

for the uncomplicated malaria indication, the Division pursued consultations with several offices in the FDA. The division consulted with

the Office of Drug Safety for a more robust search of postmarketing safety data
the Pregnancy and Labeling team for safety information from pregnancy registries and databases,

DDMAC and DMETS regarding the proposed package insert and patient package insert, and

DSRCS for quinine utilization data as a means of measuring the impact of quinine approval and labeling on drug utilization

Further, a meeting was held with the ODS in attendance to describe the risk management strategy adopted by the Division in conjunction with drug approval.

The drug adverse event profile of quinine is well recognized, and has been the subject of several published reviews. Dr. Singer's review describes these individual adverse events, as do the ODS and Pregnancy and Labeling team consults, and the reader is referred to these for greater detail. The review finds that the commonly noted adverse events are well described and include cinchonism, tinnitus, headache, dizziness, and gastrointestinal intolerance (nausea, vomiting, abdominal pain, or diarrhea). The relative frequency of specific adverse events was difficult to quantitate from the available studies, due to methodologic differences in data gathering or in data reporting. The more common treatment limiting adverse events were cinchonism and vomiting. The more serious adverse events were often described as occurring rarely, but have been seen at therapeutic doses for malaria. These include thrombocytopenia, deafness, glaucomatous hepatitis, skin rash, acute interstitial nephritis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome (TTP-HUS), disseminated intravascular coagulopathy (DIC), and blindness. Some of these events were fatal. The published literature, and the FDA and WHO postmarketing safety databases revealed similar adverse event profiles. For details regarding these well known events, the reader is referred to Dr. Mary Singer's review.

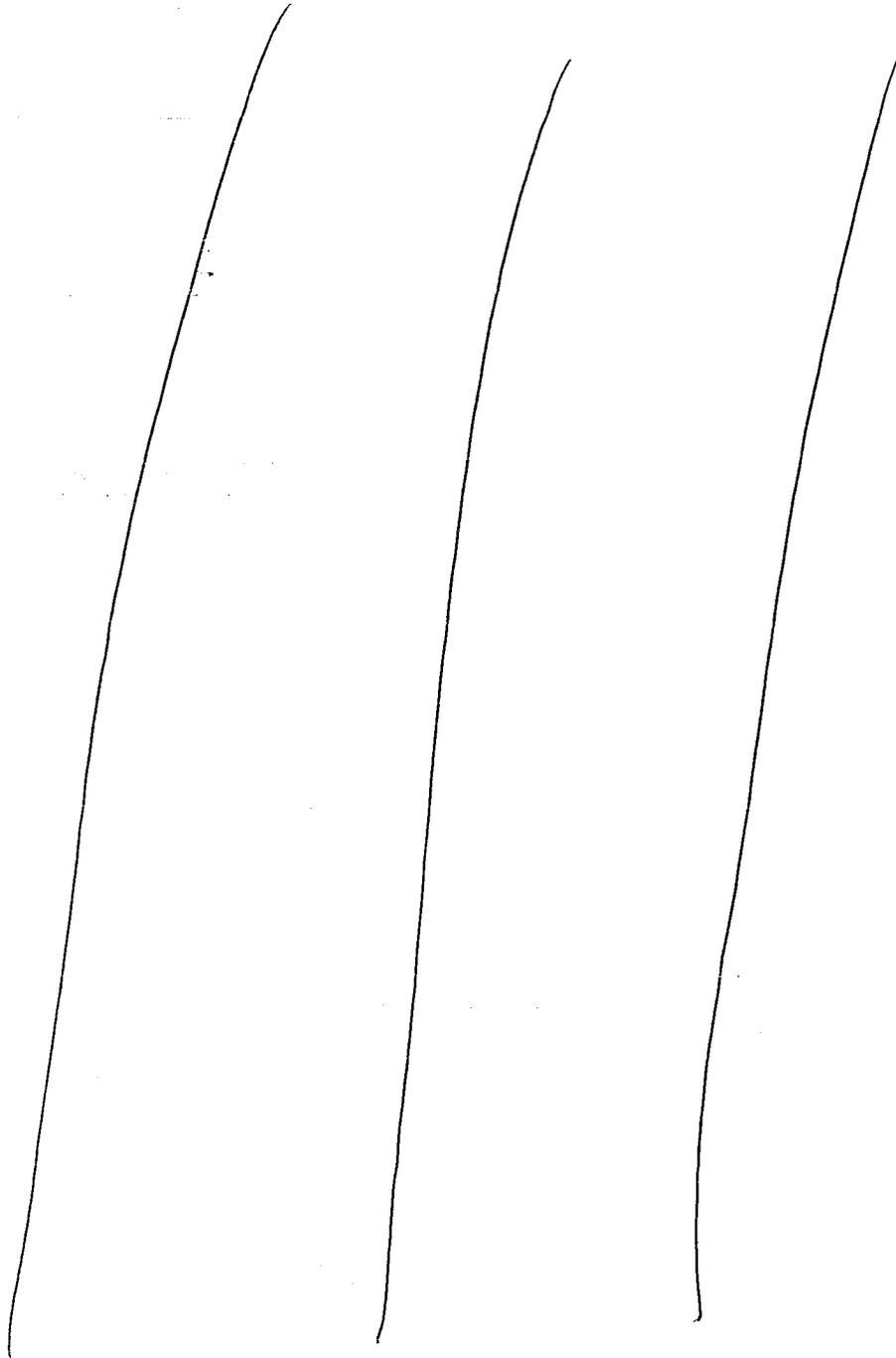
This NDA submission does provide updated safety information in the following areas which are given prominence in the negotiated label, and are briefly summarized below:

- a) a summary of safety in pregnancy and lactation
- b) detailed analysis of the drug-drug interactions of quinine
- c) a summary of the adverse events for quinine in the FDA's passive reporting system (AERS)
- d) a summary of the clinical experience on the cardiac safety of quinine

SAFETY IN PREGNANCY AND LACTATION

Quinine is a teratogen in animals, the NOAEL ranging from 0.8X (dog) to 2X (monkey) the estimated human dose. The Pregnancy and Lactation Team, OND, HFD 020, conducted a review of the 2 studies in pregnancy submitted with the NDA, relevant articles identified through a directed literature search, the proposed label and current treatment guidelines, as the basis for their recommendation of a pregnancy category C label for quinine. The reader is referred to Dr. Gerard Nahum's review for details. The

salient findings from this review is summarized in their labeling recommendations, reproduced below:



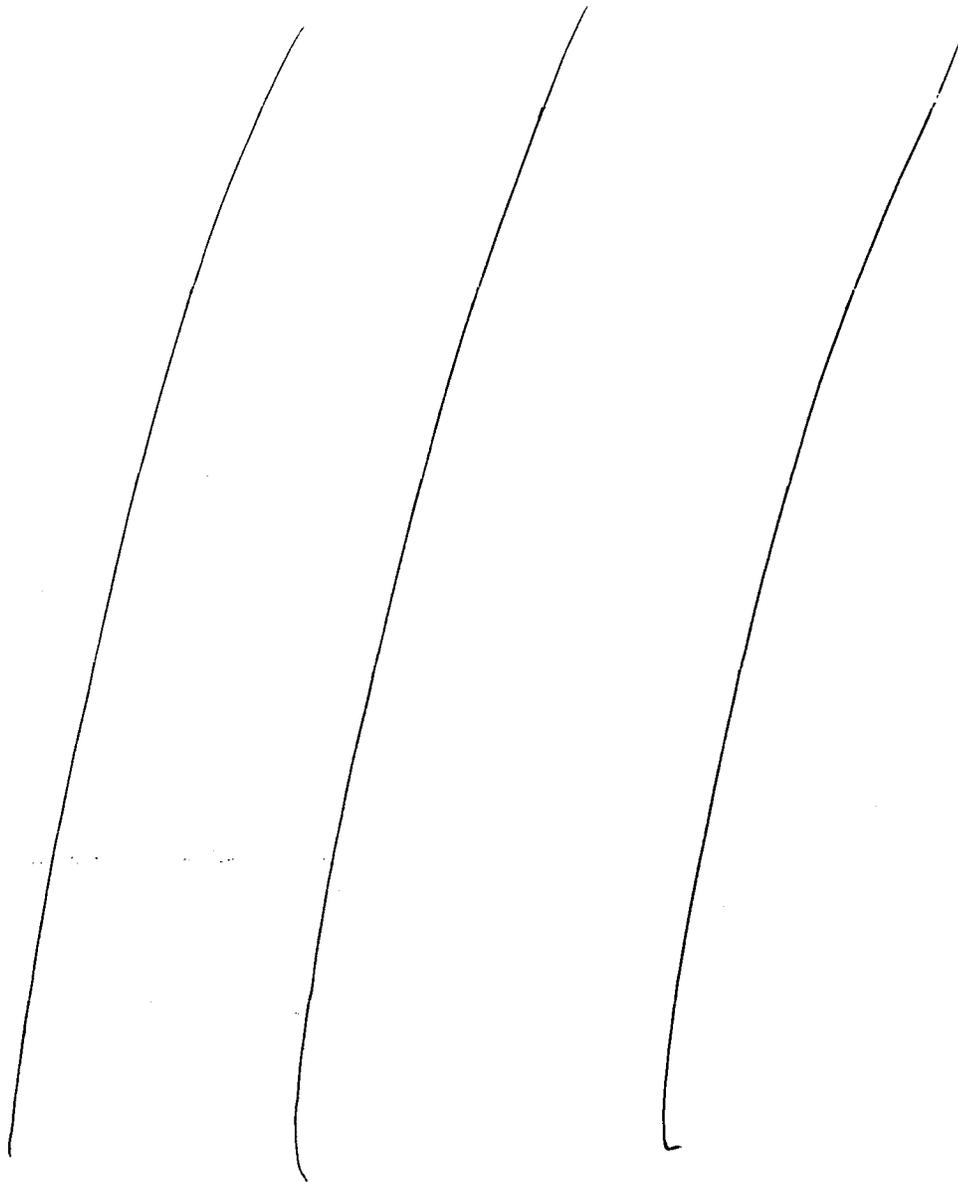
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PHARMACOKINETIC CONSIDERATIONS/ DRUG-DRUG INTERACTIONS:

The reader is referred to Dr. Gerlie Gieser's Clinical Pharmacology and Biopharmaceutics review for detail. Dosing recommendations for quinine target plasma concentrations of 8 – 20 mcg/mL. Plasma concentrations are 1.4- 2-fold higher in malaria patients as compared to healthy subjects, owing to reduced drug clearance and distribution. Concentrations usually decrease as the patient recovers. Dosage adjustment are unnecessary despite slight variations in pharmacokinetics due to age, gender, race, body weight, concurrent diabetes, pregnancy, and smoking..

Following are labeled PK and drug-drug interaction findings of note.

[Redacted]



PASSIVE SAFETY REPORTS IN AERS DATABASE

The Office of Drug Safety conducted a review of 642 adverse event reports listing quinine as suspect drug, from its Adverse Events Reporting system up to March 31, 2005 in response to a request from the review team. The reader is referred to Dr. Farinas and Ahmad's consultative review for details. Of these, 63 (9.8%) were fatal cardiac events

(11 torsade de pointes, 7 chest pain, 6 arrhythmia, 5 palpitations, 5 tachycardia, 4 CHF, 4 syncope, 3 ventricular tachycardia, and 2 each of "abnormal" heart arrest and atrial fibrillation, 1 bradycardia and the rest unspecified).

More adverse events occurred in patients over 50 (351/642, 55%), the majority of whom were treated for nocturnal leg cramps. The average age of patients in whom an adverse event was reported was 56 years, (median 59 y, range 20 month to 101 years). The most frequent indication (97/213, 46%) reported was for nocturnal leg cramps.

The majority of the reported events were serious (537/642, 83.6%). The average age of patients in whom a serious adverse event was reported was 56 years. About half of serious events (228/537, 43%) occurred in patients treated for nocturnal leg cramps.

Additionally, the median age of 11 patients reported to have developed torsade de pointes was 75 years (range 41-93), all reported indications were for leg muscle cramps (n=7). One of these events was fatal.

CARDIOVASCULAR SAFETY

The main cardiac effect of concern for quinine is the potential for fatal arrhythmias due to its QT prolonging potential. Quinine is an optical isomer of quinidine, an antiarrhythmics drug that blocks sodium and potassium currents. Both drugs also produces alpha-adrenergic receptor blockade and vagal inhibition; IV quinidine is associated with marked hypotension and vagal inhibition. Quinine's cardiovascular effects, like quinidine, include intraventricular conduction delay resulting in QT prolongation, α -adrenergic receptor blockade and vagal inhibition. Quinine also is known to result in hypotension through a direct relaxing or depressive effect on blood vessel wall smooth muscle and/or an α -adrenergic antagonizing effect. The factors that increase susceptibility to this effect are not known.

The evidence for cardiac safety of quinine is summarized below

PRECLINICAL

In vitro: At concentrations as low as 0.78 $\mu\text{g/mL}$, quinine is an open-state blocker of Na^+ channels (resulting in an increased threshold for excitability and decreased automaticity) and blocks the rapid component of the K^+ channel delayed rectifier (I_{kr}) (resulting in prolonged action potentials in most cardiac cells). At higher concentrations, quinine blocks the slow component of delayed rectifier, inward rectifier, transient outward current, and L-type Ca^{2+} current.

Preclinical data indicates that quinine is generally less potent in its CV adverse events than quinidine. The median inhibitory concentration (IC_{50}) values determined with voltage-clamp pulses to 0 mV in the HERG channel and delayed rectifier current assays, were 3.6 $\mu\text{g/mL}$ and 44.6 $\mu\text{g/mL}$ for quinidine and quinine, respectively. Thus quinine is considered to be 10 fold less potent than quinidine, on a mg per mg basis on the HERG channel. In rat ventricular myocytes, however, quinine and quinidine were equipotent, have been shown to reduce, but not block, K^+ (I_{to}) and Ca^{2+} (I_{ca}) currents in rat ventricular cardiomyocytes; both at 15.66 $\mu\text{g/mL}$) (Michel *et al.*, 2002). In the rat aorta studies however, quinidine was 3-5 times more potent than quinine in inhibition of KCl^- and

norepinephrine -induced contractions (del Pozo *et al.*, 1996). These differences are attributed stereoselectivity of the cardiac tissue.

In vivo: Qt prolongation from quinine was not adequately studied in animals. Please see Dr. Steve Kunder's review of the preclinical safety of quinine for additional detail.

CLINICAL

In vitro The potential interaction of quinine with mefloquine, halofantrine, and other drugs known to prolong QTc intervals was evaluated in studies with human liver microsomes and showed that quinine can inhibit the metabolism of mefloquine and halofantrine. Clinical studies have demonstrated increased QTc intervals in patients who received concomitant quinine and mefloquine. No such data exists for concomitant quinine and halofantrine therapy.

Cardiac Safety from single dose PK studies (RA3-085 and R04-0376)

Two studies on healthy normal volunteers with no attendant comorbidities, limited to 12 subjects per dose, evaluated single doses of 2 dose strengths (324 and 640 mg) of quinine. These studies find a mean 10 msec increase of QTc postbaseline for the 324 mg dose and a 12 msec increase for the 640 mg dose. While a temporal relationship was observed between mean plasma quinine concentrations and mean QTc change from baseline, maximum QTc change occurring at Tmax of plasma quinine (2-4 hours post-dose), linear regression analysis indicates a small relationship between QTc change from baseline and plasma quinine concentration, more prominent in females than in males. Linear regression analysis of QTc change from baseline as a function of plasma quinine concentration showed a fasted y intercept of $0.0036x - 0.0432$ ($R^2 = 0.066$) for the entire population, Corresponding values in females were $y=0.0038x+2.65$ ($R^2= 0.083$) and $y=0.0025 - 1.6288$ ($R^2 = 0.034$) in males. Intersubject variability was a mean of 20 msec. In study R04-0376, 7 of 24 subjects had a maximum QTc interval of >450 msec (maximum 470 msec); 5 of the 7 were female, no arrhythmias or cardiac adverse events were noted. . Please see Dr. Gerlie Gieser's review for additional detail.

Cardiac Safety from Randomized Studies of Oral Quinine Monotherapy

None of the randomized clinical trials of oral quinine monotherapy for uncomplicated malaria evaluated ECGs. Similarly, no significant cardiac events were reported..

Cardiac Safety from Randomized Studies of Oral Quinine in Combination

One study of quinine combination therapy for uncomplicated falciparum malaria, systematically evaluated ECGs at baseline and 48 hours post-treatment (Vanijanonta, et al., 1996). The median QTc prolongation in 25 patients who received chloroquine + quinine was 11% (range -17% to +21%) compared to 7% (range -5% to +24%) of 25 patients in the quinine + tetracycline group. No significant cardiac adverse events were noted.

Cardiac Safety from Randomized Studies of IV Quinine

Electrocardiographic changes were evaluated in 7 studies of parenteral quinine for treatment of severe malaria; of whom only two report the objective findings in the body of the text. One study that reported 500 msec prolongations in 45% of patients (n=60), and a QT increase over baseline of at least 25% in 9% of patients (n=12), concludes that "there were no significant ECG abnormalities"(Tran et al). The second, a comparative

study in children who received intravenous quinine or intramuscular artemether for cerebral malaria was not included by applicant's table below (Murphy, et al., 1996). This study describes an unusual baseline rate of QTc prolongation in 32% of patients in both treatment groups. Treatment resulted in greater QTC prolongation in 61% of artemether, and in 40% of quinine treated patients. A QTc prolongation > 25% from baseline was reported in 20/82 (24.4%), and 5/80 (6.3%) of artemether and quinine recipients. No significant cardiac adverse events were noted.

Dr. Singer summarizes the significant QTC prolongations reported as adverse events from these studies in the following two tables taken from her review:

	Mutual pharmacokinetic studies (healthy subjects)	RCT with oral quinine (patients with uncomplicated malaria)	RCT with parenteral quinine (patients with severe malaria)
QTc prolongation > 500 msec	n/N (%)	n/N (%)	n/N (%)
	0	NR	60/822 (7.3)

The comparative incidence significant QTc prolongation in the pooled studies of patients treated with parenteral quinine or comparator is shown in the following table.

	Quinine N=822	Comparator** N=830
	n (%)	n (%)
QTc prolongation > 500 msec	60 (7.3)	38 (4.6)

Cardiac Safety from Additional Non Randomized Safety Studies

A number of studies have evaluated ECG changes, including QTc prolongation and other cardiovascular effects with quinine. QTc interval prolongation occurred in both healthy subjects and in adults and children with malaria who received either oral or intravenous quinine; however, no serious cardiac arrhythmias were reported. Eleven studies in which systematic ECG monitoring was performed were summarized by the applicant in the following tables.

ECG Data in Healthy Subjects Exposed to Quinine

A single dose of IV quinine (300 mg) over a 4 hour period in 12 healthy Caucasian volunteers resulted in no QTc prolongation (Claessen, et al., 1998).

A single infusion of quinine (10 mg/kg) over a 1 hour period in 8 healthy Thai subjects resulted in mean QTc interval prolongation of 82 msec (increase from mean of 417± 14 milliseconds to 499 ± 31milliseconds). By comparison, the same dose of quinidine 9 quinidine (10 mg/kg) over 1 hour) in the same subjects resulted in a mean change in QTc of 157 msec (increased from mean of 407± 20 milliseconds to 557± 70 milliseconds). (Karbawang, et al., 1993).

A single bolus intravenous dose of quinine (5 mg/kg), in 7 healthy adults resulted in QTc prolongation in all subjects, with a maximum QTc of 415 msec from a baseline of approximately 405. The increase corresponded to the distribution phase of quinine (White, et al., 1983b).

No significant cardiac adverse events were noted in the 27 healthy subjects evaluated in these studies. The study comparing single doses of quinidine (mean QTc increase 157

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msec) vs quinine (mean QTc increase of 82 msec) confirms that quinidine has more potent Qt prolonging potential than quinine.

Reported Electrocardiographic Changes in Healthy Subjects receiving IV quinine

Citation	Population*	Dose	Findings	Note
Karbwang et al 1993(Thailand)	8 healthy subjects Age= 19-27 y	Rapid IV infusion (1 hour): 10 mg/kg as a single dose	8/8 had QTc Inc Mean 82msec (417-499 msec) max 1.5- 2h.	No clinical aes
Claessen et al 1998 (The Netherlands)	12 healthy subjects mean Age = 24 years	4 hour IV infusion: 300 mg as a single dose	No changes in QTc	No clinical aes
White et al. 1983 (Thailand) EKG measured q 2minutes to 18 minutes	7 healthy subjects Age = 18-35 y	Rapid small dose: single 5 mg/kg dose over 5 minutes	Absolute QTc increase NOT described "more variable" max at 1-4 min "Figure 1, it appears that the mean QTc not >415 msec"	Mean QRS interval (baseline 87 m sec to 96msec) 1 - 4 min

ECG Data in Patients with Malaria

Nine studies in patients with malaria evaluated ECG on treatment with quinine. Of these seven describe the effect of the QTc interval in the body of the text, whereas 2 (Bethel et al, 1996 and Davies et al, 2000), do not. Although QTc interval prolongation was noted in 6 of these 7 studies (Touze, et al., 2002, Karbwang, et al, 1997; Classen, et al., 1998; Mehta, et al., 1994; White, et al., 1983; and Fulkerson, et al. 1970), no serious cardiac arrhythmias were reported.

Electrocardiographic Changes In Malaria Patients receiving oral or IV to oral quinine

Citation	Population*	Dose	Findings	Limitation
Oral quinine				
Touze et al., 2002 (France) 12-lead ECG: baseline, 9 & 24h post 1st dose. Continuous ECG and holter	15 patients Age= 31 y	Orally, 25 mg/kg/day in 3 divided doses for 5 days	Maximum QTc dispersion 65 msec, vs .100msec w/ halofantrine No arrhythmia. No clinical aes.	No measurements beyond the first day
IV and IV to oral quinine				
White et al., 1983a, (Thailand) Sequential ECG: Baseline & qh x 8 In 10 w/ severe malaria, ECG at start and end of infusion	18 patients (severe) Age = 23 y 13 patient (un- complicated) Age= 26 y	4 hours IV loading dose: 10 mg/kg followed by 4 hours IV or oral quinine 10 mg/kg q 8 h	Quinine=Mean (± SD) QTcprolongation 41 ± 29 msec (10%). Max 70 msec Quinidine =123 ±126 milliseconds, or 24 ± 8% No arrhythmias were noted.	QRS prolonged (11/18)
Claessen et al., 1998 sequentially over 3-days	10 patients uncomplicated Age = 34 y	4 hour IV infusion: 600 mg 3 x day for 3 days	Mean (± SD) QTc increased (baseline 390 ± 40msec to 470 ± 40msec post) 80msec increase (20±11%)	Relation to infusion not noted
Mehta et al., 1994, (India) Sequential ECG: Baseline & q 12 h for the first 72 h	12 patients with loading doses and 11 age /sex matched patients w/o loading Age= NR	4 hours IV loading dose: 20 mg/kg IV maintenance dose: 10 mg/kg q 8 h X 7 days shifted to po control group had no loading doses	QTc prolonged 15% of baseline and persisted to Day 6. No arrhythmias No clinical aes.	Prolongation in msec not described, but occurred in 4/12 or 33% no description in group with no loading dose
Fulkerson, 1970, (U.S.) 12-lead ECG Baseline & daily (IV) and 6h postdose for oral	US servicemen 7 patients 12 non-malaria patients	? hr IV infusion: 1300 mg q 16 hours x 10 days Oral: 650mg q 8h x 10 days (two groups of 6 with each group receiving a different oral formulation of quinine	18/19 had ECG Δ QTc prolongation max 6h postdose Multifocal pvc's rate related in 1/7 IV & 1/12 oral patients (6h post)	Maximal QTc increase not noted.
Karbwang et al. 1997 (Thailand) ECG 2h post dose QD on IV	19 patients Age = 15-65y	? hr IV loading dose: 20 mg/kg ? hr IV maintenance dose: 10 mg/kg to oral quinine q 8h x 7 days	QTc prolongation "common" No arrhythmias No clinical aes.	Prolongation not reported No ECG data on oral quinine
Bregani et al., 2003 (Tanzania)	10 children Age = mean 38 months,	4 hour IV loading dose: 20 mg/kg 4 hour IV maintenance dose: 10	No prolongation No arrhythmias No clinical	Holter, Not 12 lead ECGS,

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Continuous in 1 st 24 hours	median 18 months	mg/kg q 8h	aes.	1 st 24 h only
Bethell et al., 1996 (Vietnam) ECG monitoring in 1 st 24 hours	53 severe malaria patients (11 adults, 42 children) Age = 6 y (median)	total dose in 24-hour ECG monitoring period: IV or IM, 30 to 40 mg/kg	No discussion of QTc prolongation No arrhythmias No clinical aes.	Not 12 lead ECG
Davis et al., 1990 (Thailand) baseline & q 5 min for the 1 st infusion then 35, 40, 60, 90 min post maintenance	16 patients Age = 26 y	30 minute infusion IV loading dose: 7 mg/kg IV maintenance dose: 4 hour IV infusion maintenance: 10 mg/kg to oral q 8h x7 days	"Changes in ECG indices were similar to those reported in other studies"	ECG evaluated only first 2 doses

Two of these studies were comparative:

In quinine-treated patients (pooled patients with cerebral malaria and uncomplicated *P. falciparum* malaria), the maximum QTc prolongation was 41 ± 29 milliseconds, or $10.3 \pm 7.7\%$ of pretreatment values; while in quinidine-treated patients, maximum QTc prolongation was 123 ± 126 milliseconds, or $24 \pm 8\%$ of baseline values, confirming that quinidine has a greater potential to cause QTc prolongation than quinine (White, et al., 1983a).

In a 60 African patients with *P. falciparum* malaria randomized to various antimalarial therapies, QTc dispersion increased in quinine treated patients (25 mg/kg daily in 3 doses), but no value exceeded 65 msec. In comparison, 5 of 15 patients who received halofantrine (1500 mg daily in 3 doses) had QTc dispersion values of > 100 msec. (Touze, et al., 2002).

These studies confirm the QTc prolonging potential of quinine, but indicate that this may be less than that observed with either halofantrine or quinidine. Mild to moderate (up to 20% of baseline) QTc prolongation is noted in the patient population studied in these clinical trials, which consisted of younger children and adults in the developing world. It is unclear if this magnitude of QTc prolongation would be as benign in a population of older patients on multiple interacting medications.

Cardiac Adverse Events Reported in the Published Literature

The applicant summarized several case reports of serious or fatal cardiac arrhythmias in patients who received quinine, as shown in the table below.

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Published Case Reports of Serious Quinine-Associated Cardiotoxicity

Author, Year(Country)	N	Adverse Event	Dosage Regimen / Route / Indication
Bonington <i>et al.</i> , 1996 (U.K.)	1	Ventricular fibrillation / death	Intravenous loading dose of 1.4 grams of quinine (20 mg/kg) infused over 4 hours, followed 8 hours later by an i.v. dose of quinine 600 mg for treatment of <i>P. falciparum</i> malaria
Tigga <i>et al.</i> , 2001 (India)	2	Tachycardia, irregular rhythm, unifocal premature ventricular contractions, nodal escape beats following the PVCs, and U waves	Intravenously, 600 mg i.v. over 4 hours for treatment of <i>P. falciparum</i> malaria
Kochar <i>et al.</i> , 1998 (India)	1	Prolonged QTc interval and multiple ventricular premature beats, followed by ventricular fibrillation	Intravenously, 7 mg/kg loading dose, followed by 600 mg over 3 to 4 hours 3 times a day for treatment of <i>P. falciparum</i> malaria
Weinke <i>et al.</i> , 1993 (Germany)	3	Arrhythmia (not otherwise specified)	"Usual doses" of quinine, often initiated intravenously and later switched to oral drug for treatment of <i>P. falciparum</i> malaria
Martin <i>et al.</i> , 1997 (U.S.)	1	Torsades de pointes	A single 260-mg dose of oral quinine sulfate for leg cramps concurrently with astemizole 10 mg (Hismanal [®])

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These include a 71 year-old female missionary from Zambia with baseline QTc prolongation, who received intravenous quinine for *P. falciparum* malaria (20 mg/kg loading dose administered over 4 hours; followed by 600 mg administered every 8 hours for two doses) (Bonington, 1996). The review team proposes that quinine be contraindicated in patients with prolonged QT interval .

Two cases of cardiac arrhythmias in young men with *P. falciparum* malaria treated with standard doses (10 mg/kg every 8 hours) of intravenous quinine are reported by Tigga, et al. (2001) and are attributed to an idiosyncratic response to quinine as QTc intervals were not prolonged in either patient.

The one case of QTc prolongation with a clear drug relationship to quinine (Kochar, et al.,1998) was a 46 year-old Indian female with no history of cardiovascular or peripheral vascular disease who developed bilateral gangrene of the feet with *P. falciparum* malaria. She received intravenous quinine (7 mg/kg loading dose, then 600 mg three times daily), administered over 3-4 hours for each dose. Her baseline ECG was normal, had recurrent syncopal attacks at which time, on treatment ECG showed a prolonged QTc interval (not quantified) with concurrent multiple ventricular premature beats followed by ventricular fibrillation requiring cardioversion, and infusion of potassium and magnesium. The QTc prolongation and ventricular arrhythmias resolved after 48 hours of quinine discontinuation. The patient recovered and was discharged from the hospital. The review team proposes a WARNING statement in the final product labeling regarding QT prolongation and ventricular arrhythmias.

Syncope and torsades de pointes occurred in a 42 year-old female after a single dose of Quinamm® (260 mg quinine sulfate) for severe leg cramps (Martin, et al. 1997). This patient was receiving multiple medications that could have predisposed her to the arrhythmia, including astemizole (10 mg), triamterene plus hydrochlorothiazide, isradipine, oral potassium, alprazolam and fluoxetine. In addition she had decreased serum potassium and magnesium. ECG on hospital admission showed torsades de pointes, with a QT interval of > 680 msec.. The arrhythmia resolved and the QTc interval normalized 3 days post quinine discontinuation. This case illustrates that serious cardiac

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arrhythmias occur in the setting of patients on multiple medications and with underlying concomitant conditions that predispose to torsade de pointes, such as electrolyte abnormalities. The temporal relationship between the torsades de pointes and administration of quinine, suggests a causative role for quinine, particularly in the presence of chronic astemizole use. Torsades de pointes has also been described in association with quinine and astemizole in 2 cases identified in the AERS postmarketing database. The review team recommends a WARNING regarding concurrent therapy with astemizole and other CYP3A4 substrates, class IA and III antiarrhythmic agents, macrolide antibiotics, and the antimalarials halofantrine and mefloquine, all agents known to cause QT prolongation.

Other notable labeling proposals

The Geriatrics section of the label highlights the limited safety information in elderly patients. This is especially relevant given the drug interaction profile of quinine and the frequent comorbidities in elderly patients that may put them at greater risk of quinine's adverse events, especially its moderate QT prolonging potential.

The Indications section of the label specifies that quinine is not approved for prophylaxis of malaria, as no data was submitted to this NDA to support such a claim.

The label also notes that the drug is not for use in patients with nocturnal leg cramps. This statement supports previous Agency determinations as articulated in 21 CFR 310.546 based on 59 FR 43252, published August 22, 1994 and 21CFR 310.547, based on FR notice 63 FR 13528, published March 20, 1998.

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Cc
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CLINICAL REVIEW

Application Type NDA
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Reviewer Name Mary E. Singer, M.D., Ph.D.
Review Completion Date August 12, 2005

Established Name Quinine Sulfate
(Proposed) Trade Name Quinine Sulfate Capsules, 324 mg
Therapeutic Class Antimalarial drug
Applicant Mutual Pharmaceutical Co., Inc.

Priority Designation S

Formulation 324 mg capsules
Dosing Regimen 648 mg orally 3 times daily
Indication Acute, uncomplicated malaria
Intended Population Adults

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Clinical Review
Mary E. Singer, M.D., Ph.D.
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1 EXECUTIVE SUMMARY

Over 500 million persons per year are infected with malaria, and up to 2.7 million people die annually from this disease. Most deaths due to malaria occur in young children or in non-immune individuals infected with the parasite, *Plasmodium falciparum*. Significant morbidity and mortality also occurs in pregnant women with *P. falciparum* malaria. Infection with *P. falciparum* in pregnant women may result in low-birth weights in infants, potentially resulting in increased perinatal mortality. According to the World Health Organization (WHO) (<http://rbm.who.int/wmr2005/index.html>), in 2004 approximately 107 countries or territories had regions at risk for malaria transmission, and over 3.2 billion people were at risk for malaria. Approximately 75% of *P. falciparum* cases worldwide and more than 80% of malaria deaths occur in sub-Saharan Africa. In the U.S., in 2002, the Centers for Disease Control and Prevention (CDC) (<http://www.cdc.gov/malaria/facts.htm>) reported 1337 cases of malaria, and 8 deaths. Most cases of imported malaria in this country occur in returned travelers, who are generally non-immune, and are at risk for severe or complicated malaria.

Quinine is derived from the bark of the cinchona tree and has been used successfully for hundreds of years in the treatment of malaria. Synthetic antimalarial agents, such as chloroquine, sulfadoxine-pyrimethamine, and mefloquine came into wide use after quinine became unavailable during the World Wars. However, resistance of the parasite to chloroquine and sulfadoxine-pyrimethamine are now widespread, and mefloquine resistance is increasing, particularly in Southeast Asia. Resistance of *P. falciparum* to quinine has also been documented in Southeast Asia. Parenteral quinidine (in the U.S.) is currently considered the drug of choice for treatment of severe malaria. Parenteral quinine is not available in the U.S. at this time. For uncomplicated *P. falciparum* malaria, acquired in areas of chloroquine resistance, the CDC recommends oral quinine sulfate in combination with an antimicrobial agent such as tetracycline, doxycycline, or clindamycin for 3 to 7 days in the 2004 treatment guidelines.

This NDA was a 505 (b) 2 submission, and was based on safety and efficacy data from published literature, from 2 bioequivalence studies sponsored by the applicant, and on postmarketing adverse event data reported to the FDA Adverse Event Reporting System (AERS) database and to the WHO database. The applicant searched the worldwide literature from 1951 to 2004, for randomized, controlled studies on the efficacy of quinine sulfate. Approximately 1300 citations were selected for review, and from these references, 21 published, randomized, controlled studies were submitted in support of this application for use of oral quinine sulfate in treatment of uncomplicated *P. falciparum* malaria. The following conclusions were drawn from review of these studies, which are discussed in the Integrated Review of Efficacy (IRE) in section 6 of this review:

In areas where multi-drug resistance of *P. falciparum* is increasing, such as Southeast Asia, cure rates with 7 days of oral quinine monotherapy were at least 80%; while cure rates for 7 days of oral quinine combined with an antimicrobial agent (tetracycline or clindamycin) were greater

than 90%. In areas where multi-drug resistance of *P. falciparum* was not as widespread, cure rates with 7 days of quinine monotherapy ranged from 86 to 100%.

Completion of a 7 day oral quinine treatment regimen may be limited by drug intolerance, and shorter courses (3 days) of quinine combination therapy have been used. However, the published data from randomized, controlled clinical trials for shorter regimens of oral quinine in conjunction with tetracycline, doxycycline, or clindamycin for treatment of uncomplicated *P. falciparum* malaria is limited, and the shorter course combination regimens may not be as effective as the longer treatment regimens.

The safety of quinine sulfate is reviewed in the Integrated Summary of Safety, in section 7 of this review. In brief, quinine has a well-known toxicity profile. The most common adverse events with quinine are a cluster of symptoms, referred to as cinchonism. Symptoms of mild cinchonism include headache, vasodilatation, sweating, nausea, tinnitus, hearing impairment, vertigo or dizziness, and visual disturbances. More severe symptoms of cinchonism are vomiting, diarrhea, abdominal pain, deafness, blindness, and disturbances of cardiac rhythm or conduction. Most symptoms of cinchonism are reversible and resolve with quinine discontinuation.

Quinine, like quinidine, its diastereomer, has antiarrhythmic properties, and can cause QT prolongation, which can increase the risk of potentially fatal cardiac arrhythmias such as torades de pointes and ventricular fibrillation. Other significant safety concerns with quinine are hypersensitivity reactions, and drug interactions. These issues are described in detail in the Integrated Review of Safety (IRS), section 7 of this review. Appropriate Warnings, Precautions, and Contraindications have been proposed for the final product label

1.1 Recommendation on Regulatory Action

Approval is recommended for quinine sulfate 324 mg oral capsules for the treatment of uncomplicated *P. falciparum* malaria.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The applicant has agreed to a risk management plan to be implemented with one year of the NDA approval, as a postmarketing commitment, as outlined below.

1.2.2 Required Phase 4 Commitments

The applicant has agreed to the following phase 4 commitments:

1. Develop a **Risk Management Plan** to be implemented within one year of NDA approval that includes the following elements:

- An educational program directed at physicians and other health care providers regarding the safe and effective use of quinine sulfate for treatment of *Plasmodium falciparum* malaria.
- A written “Dear Doctor” Letter to physicians describing the favorable risk/benefit ratio of oral quinine sulfate for treatment of *P. falciparum* malaria; in contrast with the unfavorable risk/benefit ratio for treatment of nocturnal leg cramps.

2. Post-marketing Surveillance for Adverse Events:

Provide twice-yearly analysis of postmarketing adverse event data, including assessment of possible causal relationship of adverse events to quinine sulfate, analysis of adverse events by age (< 16, 16 to 65 and > 65 years old) and by indication for quinine use. These analyses are requested in addition to the required 15-day reporting for all serious adverse events and the required quarterly updates of post-marketing adverse events associated with oral quinine sulfate.

1.2.3 Other Phase 4 Requests



1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This was a 505(b) 2 submission, and all data supporting the application, including preclinical and clinical data was obtained from published literature. The applicant searched the worldwide literature since 1951, found more than 1300 citations relating to the treatment of malaria with quinine, and from these 21 randomized, controlled published studies from the literature in support of quinine mono- or combination therapy for treatment of uncomplicated *P. falciparum* malaria were identified and submitted for this NDA. Several additional studies were identified in the published literature by the Medical Officer and Statistical Reviewer and were included in this review. The applicant also provided 14 nonrandomized controlled studies which evaluated the efficacy of parenteral quinine (monotherapy) in the treatment of severe malaria. These studies were considered supportive for this NDA, and conclusions from these studies are summarized briefly in this review. Additionally, 12 non-randomized studies of oral quinine for treatment of uncomplicated *P. falciparum* were submitted in support of the application. These latter studies have not been described in detail for this review.

Safety data for quinine sulfate was obtained from the clinical studies of oral and parenteral quinine for treatment of malaria, from case reports in the literature, from reviews of quinine toxicity, and from postmarketing data, described further in section 4.

1.3.2. Efficacy

Quinine, which is a natural product derived from the bark of the cinchona tree, has been used worldwide for centuries as an effective antimalarial agent. When quinine became unavailable during the World Wars I and II, development of synthetic antimalarial agents was rapid, and chloroquine became the drug of choice after WWII. By 1961, quinine use was largely replaced by the use of synthetic antimalarial drugs. With the emergence of chloroquine resistance, as well as resistance to other antimalarial drugs, quinine has again become important in treating malaria, particularly in certain geographical areas such as Southeast Asia, where resistance to multiple antimalarial drugs, including mefloquine, is increasing, and in this country, in non-immune returned travelers from malaria-endemic areas. Most of the published studies on quinine efficacy are fairly recent (since 1974), and largely focus on comparing new antimalarial agents to quinine. Quinine-resistant *P. falciparum* malaria has been described recently, mainly in Southeast Asia, but also in some localized areas of South America and Bangladesh.

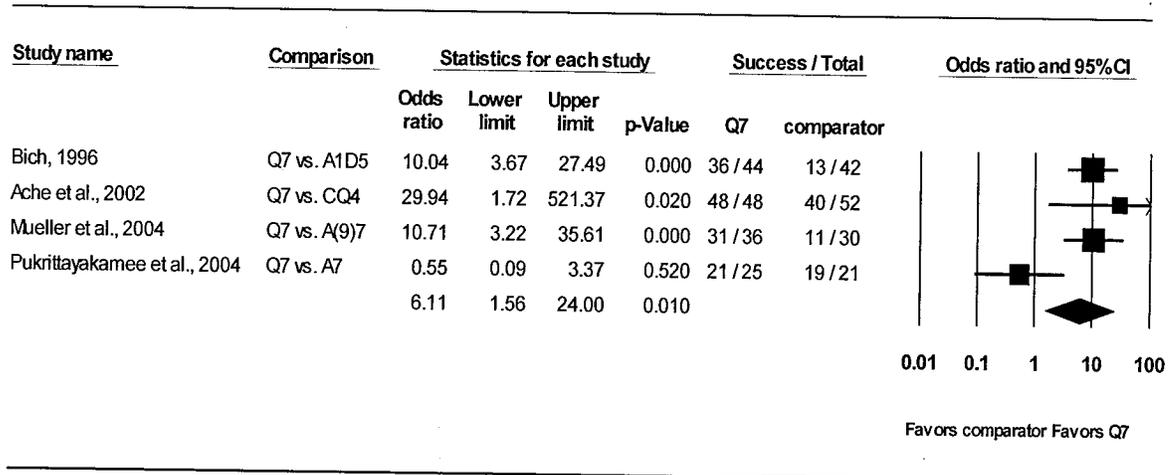
The studies submitted for this NDA were all conducted in malaria-endemic areas, mainly in semi-immune individuals. Nevertheless, demonstration of efficacy in those populations would generally be expected to translate to treatment of non-immune individuals who have returned from malarious areas of the world. Studies on the efficacy of oral quinine monotherapy and quinine combination regimens for treatment of uncomplicated malaria were provided in support of this application, and are summarized in this review. Studies on the efficacy of parenteral quinine for treatment of severe *P. falciparum* were submitted in support of this application, and were reviewed briefly.

Quinine Monotherapy

In this review, cure rates are defined as disappearance of parasitemia by day 7 without recrudescence by 28 days post treatment initiation. This endpoint is basically the same as the endpoint, "Adequate Clinical and Parasitological Response" recommended by the World Health Organization (WHO) in their classification of outcomes for treatment of malaria (WHO, 2003). Cure rates for oral quinine monotherapy differ somewhat by geographical region. In 4 studies conducted in Southeast Asia in the mid 1990's, cure rates for 7 days of oral quinine ranged from 82-87% in the evaluable populations. Treatment failures in the evaluable population were due to parasite recrudescence. In one study performed in South America in the late 1990's, cure rates were 100%, and in one study in Africa early this century, 86%. Shorter courses (1.5 or 3 days) of oral quinine monotherapy in two studies in Africa resulted in unacceptable cure rates of 38%, and 32%, respectively.

A meta-analysis was performed by the Statistical Reviewer, Ms. LaRee Tracy, using cure rates in the evaluable population in 4 studies which evaluated quinine monotherapy (10 mg/kg 3 times daily for 7 days) vs. a non-quinine comparator. These 4 studies were chosen by similarity in study design, and the dose and duration of quinine therapy. The odds ratio was 6.11 overall in favor of quinine, suggesting the probably of cure was approximately 6 times greater with quinine than with a non-quinine antimalarial regimen. This analysis is shown in Figure 1 below.

Figure 1. Meta-Analysis of Quinine Monotherapy vs. non-Quinine Comparator in Evaluable Population (Statistical Reviewer's Analysis)



Quinine Combination Therapy

Two studies conducted in Thailand directly compared 7-day oral quinine monotherapy to 7-days of quinine in combination with either tetracycline or clindamycin (Pukritayakamee, et al., 2004; Pukritayakamee, et al., 2000). Although not statistically significant when corrected for multiple comparisons, higher cure rates were observed with 7-days of quinine plus tetracycline or clindamycin than with quinine alone, as shown in Table 1 below. Several other studies in Thailand also demonstrated cure rates ranging from 94-100% for 7-day courses of quinine in combination with tetracycline (Table 1 below). Thus, in Southeast Asia, the efficacy of a 7-day regimen of quinine in combination with an antimicrobial agent appears higher than that of 7 days of quinine alone.

Three studies in Gabon evaluated short courses of quinine in combination with antimicrobial agents. Metzger, et al (1995) reported cure rates of 92 % and 91%, respectively for treatment groups who received 3 doses of quinine (12 mg/kg) plus clindamycin or doxycycline, in comparison to 3 doses of quinine (12 mg/kg) alone, which resulted in cure rates of only 38%. In two pediatric studies, cure rates of 94% were reported with a 3-day regimen of quinine plus clindamycin (Ramharter, et al., 2005); and 88% cure was reported in patients who received a 3 day course of quinine plus clindamycin in comparison to 3 days of quinine alone, which resulted in a 32% cure rate (Kremsner, et al., 1994). There were no African studies which evaluated 7 days of quinine monotherapy in comparison to 7 days of quinine combination therapy. Additionally, there were no studies in Africa which directly compared 7-day quinine regimens

with shorter-course quinine regimens; however, cure rates reported in the Thai studies, with 7-day quinine combination regimens, were somewhat higher (94-100%) than with the 3-day quinine combination regimens reported in Gabon. These data are summarized in Table 1 below.

One study in Brazil (De Alencar, et al., 1997) reported a 100% 28-day cure rate with a 7-day regimen of quinine plus tetracycline; while another study in Venezuela (Ache, et al., 2002) reported 100% cure rates with quinine alone. None of the studies conducted in South America directly compared quinine monotherapy and combination therapy. Additionally, few studies outside of Africa evaluated short-course quinine combination therapy. In Brazil, Kremsner, et al., (1988) evaluated a 3-day quinine-clindamycin regimen in comparison to 3 days quinine plus 2 days sulfadoxine-pyrimethamine, and reported 90% cure rates with the former, and 30% with the latter regimen in evaluable populations. This is in contrast to an earlier Brazilian study (De Souza, et al, 1985) in which cure rates with 3 days quinine and single dose sulfadoxine-pyrimethamine were 92%. Duarte, et al., 1996 reported cure rates of 77% in the intent to treat population with a 3 day combination regimen of quinine plus tetracycline. In this study, only 1/88 patients failed due to parasite recrudescence, while the other the failures were due to patient loss to follow-up. The efficacy of quinine monotherapy in comparison to quinine combination therapy is summarized by geographic location in the following table.

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Table 1 Summary of Efficacy of Oral Quinine Monotherapy vs. Quinine Combination Therapy by Geographical Region (Evaluable Population)

Study and Region	Geographic Location	Dates	Quinine Monotherapy (duration-days)	Efficacy* quinine monotherapy n/N (% cure)	Quinine Combination Therapy (duration-days)	Efficacy* of quinine combination n/N (% cure)
Southeast Asia						
Pukrittayakamee, et al 2004	Thailand	--	Q7	21/25 (84)	QT7	21/22 (100)
Pukrittayakamee, et al., 2000	Thailand	1995-1997	Q7	46/53 (87)	QT7	47/48 (98)
Bunnag, et al., 1996	Thailand	1990-1992	--	--	QC7 Q5T7	60/60 (100) 40/46 (87)
Vanijanonta, et al., 1996	Thailand	1993-1994	--	--	Q7T7 Q7T7	40/40 (100) 17/18 (94)
Loaresuwan, et al., 1994	Thailand	1991	--	--	QT7	45/46 (98)
Karbwang, et al., 1994	Thailand	--	--	--	QT7	30/30 (100)
Bich, et al., 1996	Vietnam	1993-	Q7	36/44 (82)	--	--
South America						
Ache, et al., 2002	Venezuela	1999-2000	Q7	48/48 (100)	--	--
Duarte, et al., 1996	Brazil	1992-1993	--	--	Q3T7	68/88(77) (ITT)
De Alencar, et al., 1997	Brazil	1995-1996	--	--	QT7	77/77 (100)
Kremsner, et al., 1988	Brazil	1987	--	--	Q3SP2 Q3C3 Q3SP1	9/30 (30) 36/40 (90) 46/50 (92)
De Souza, et al., 1985	Brazil	--	--	--	--	--
Africa						
Mueller, et al., 2004	Congo	2001	Q7	31/36 (86)	--	--
Metzger, et al., 1995	Gabon	1993-1994	Q1.5	14/37 (38)	Q1.5C3	33/36 (92)
Ramhartner, et al., 2005	Gabon	2003-	--	--	Q1.5 D3 QC3	32/35 (91) 45/48 (94)

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 Mary E. Singer, M.D., Ph.D.
 NDA 21-799
 Quinine Sulfate Capsules USP, 324 mg

(pediatric)	2004				
Kremsner, et al., 1994 (pediatric)	1992	Gabon	Q3	10/31 (32)	Q3C3
					30/34 (88)

*efficacy = 28 day cure rate in evaluable population

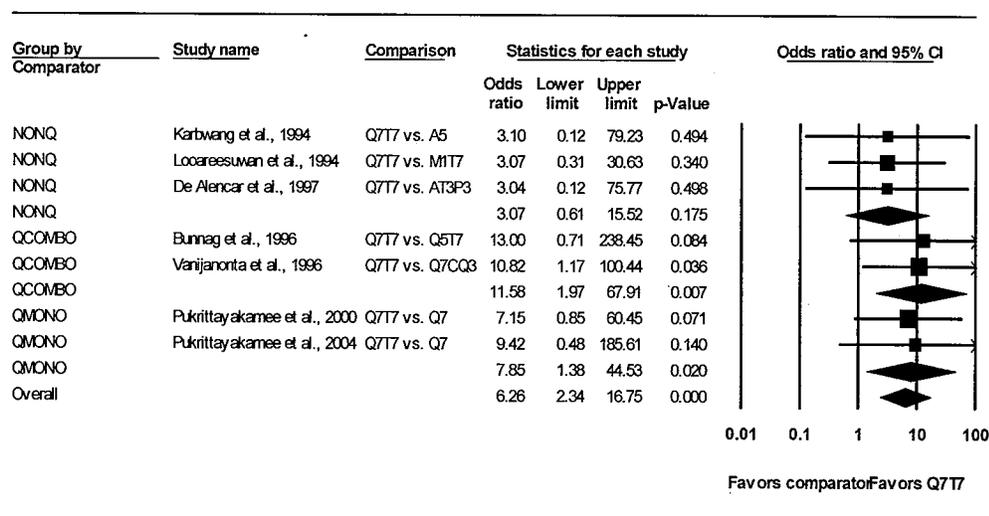
Q= quinine; SP= sulfadoxine-pyrimethamine; D= doxycycline; T= tetracycline; C= clindamycin

Medical Officer Comments: Some of the studies submitted by the applicant were not used for this comparative analysis due to differences in study design, patient population, or problems with randomization. Overall, these studies show that quinine monotherapy is effective for the treatment of *P. falciparum* malaria in > 80% patients regardless of geographical region. These data also suggest that quinine combination therapy (7-days) may be more effective than quinine monotherapy (7 days) in areas of multidrug-parasite resistance, such as Southeast Asia. In areas where multidrug resistance is not as widespread, namely, Africa and South America, the efficacy of quinine monotherapy ranged from 86 to 100%. Shorter course (3-day) regimens of quinine monotherapy were not effective in the treatment of this infection; and shorter course (3-day) quinine combination therapy, although better than quinine alone, may not be as effective as 7 days regimens.

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In a meta-analysis performed by the Statistical reviewer, which evaluated the efficacy of the Q7T7 (7 days oral quinine plus 7 days oral tetracycline) regimen versus comparator regimen in 7 studies, the odds ratio was 6.26 overall in favor of the Q7T7 regimen (p-value = 0.00). These 7 studies were chosen by similarity of study design, and in the dose and duration of quinine therapy. When the 2 studies which compared quinine monotherapy directly to quinine combination therapy were analyzed as a subgroup, the odds ratio was 7.85 in favor of the combination regimen. This result was statistically significant (p-value = 0.02). When the quinine-tetracycline regimen was compared to a non-quinine comparator in 3 of these studies, the odds ratio was 3.07 in favor of the quinine combination regimen. However, this result was not statistically significant (p-value = 0.175). This analysis is shown in figure 2 below.

Figure 2. Meta-Analysis of Quinine plus Tetracycline (7 day) Combination Regimen vs. Comparator (with sub-grouped by non-quinine comparator, another quinine combination regimen, or quinine monotherapy) (Statistical Reviewer's Analysis)



Quinine Monotherapy vs. Other Antimalarial Agents

Quinine monotherapy was compared to other antimalarial agents in a number of the randomized, controlled studies submitted for review. These data are summarized in the following table which shows studies which compared quinine monotherapy to another antimalarial agent. In comparison to other antimalarial agents, in one South American study (Ache, et al., 2002) cure rates were higher with quinine monotherapy than with chloroquine or sulfadoxine-pyrimethamine. Similarly, in a study performed in Bangladesh (Rahman, et al., 2001), oral quinine monotherapy cure rates were higher than those observed with chloroquine or mefloquine due to recrudescence indicating some high level resistance (RIII). In a Thai study (Pukrittayakamee, et al., 2004), cure rates for oral quinine were similar to those seen with 7 days of oral artesunate.; while quinine was significantly better than artemisinin tea in an African study (Mueller, et al., 2004) Artemisinin derivatives such as artesunate are not currently licensed for marketing in the U.S. Studies which did not use a 7-day course of quinine for comparison to monotherapy with another antimalarial agent, or have a 28 day parasitological endpoint, were not included in this analysis.

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Table 2: Efficacy of Quinine Monotherapy in comparison to other Non-Quinine Comparator (Evaluable Population)

Study	Location	Dates	Quinine Monotherapy (duration)	Efficacy* Quinine Monotherapy n/N (% cure)	Other Antimalarial Drug (duration-days)	Efficacy* of other Antimalarial Drug n/N (%)
Pukrittayakamee, et al., 2004	Thailand	Not available	Q7	21/25 (84)	A7	19/21 (90)
Bich, et al., 1996	Vietnam	1993-	Q7	36/44 (82)	A1D3	13/42 (31)
Rahman, et al., 2001	Bangladesh	1996-1997	Q7	40/49 (82)	CQ	34/149 (23)
Ache, et al., 2002	Venezuela	1999-2000	Q7	48/48 (100)	M1	51/70 (73)
					CQ3	0/12 (0)
					CQ4	40/52 (77)
					SP1	41/53 (77)
Mueller, et al., 2004	Democratic Republic of Congo	2001	Q7	31/36 (86)	Artemisin tea (5g)7	12/32 (38)
				--	Artemisin tea (9g)7	11/30 (37)

Efficacy = Cure rate, defined as initial clearance of parasitemia without recrudescence by day 28 in evaluable population. Q= quinine; A= artesunate or artemisinin; CQ= chloroquine; M= mefloquine; SP= sulfadoxine-pyrimethamine; D = doxycycline

Medical Officer Comments: *These studies show that quinine monotherapy was as effective as or better than the antimalarial drugs used as comparator in several different geographical locations. The cure rates of 82-86% for oral quinine monotherapy in the evaluable population are due to recrudescence. Patients lost to follow-up were not included in the evaluable population. Except in the study performed in Bangladesh (Rahman, et al., 2001, in which 3 quinine-treated patients had a high level of resistance as indicated by RIII recrudescence (no response to therapy), all recrudescence infections in the other studies were RI or RII (recrudescence by day 28 of follow-up) with quinine monotherapy. In contrast, for chloroquine-treated patients in the same study, 59/149 (39.5%) had RIII recrudescence; while 32/149 (21%) had RI and 21% RII recrudescence. Currently quinine has a niche in treatment of malaria for use in areas of chloroquine resistance, or in areas of multidrug (chloroquine, mefloquine and sulfadoxine-pyrimethamine) resistance, or in patients who do not tolerate other antimalarial agents. These data would support this clinical practice.*

Quinine Combination Therapy vs Other Antimalarial Agents

The efficacy of quinine in conjunction with antimicrobial agents which have some antimalarial activity, tetracycline, doxycycline, clindamycin and sulfadoxine-pyrimethamine was compared to that of other antimalarial drugs given as monotherapy or in combination. These data are summarized in the table below. Cure rates at 28 days in published studies are presented by geographical region in the following table. In Thailand, cure rates were similar for a 7-day course of quinine plus tetracycline to a 5 day course of artesunate (Karbwang, et al., 1994), a 7-day course of artesunate plus tetracycline (Pukrittayakamee, et al., 2004), or single dose mefloquine plus 7 days tetracycline (Looaresuwan, et al., 1994). In Brazil, a 7-day course of quinine plus tetracycline had similar cure rates to a 3 day course of atovaquone plus proguanil (De Alencar, et al., 1997). Additionally, a regimen of quinine for 3 days plus tetracycline for 7 days was similar in efficacy to a 7-day course of artesunate plus tetracycline (Duarte, et al., 1996). In Africa, a recent pediatric study which evaluated short courses (3 days) of quinine combined with clindamycin to a short course (3 days) of artesunate plus clindamycin, showed similar cure rates in the two treatment arms (Ramharter, et al., 2005); while the short course (3 days) of quinine plus clindamycin resulted in higher cure rates than chloroquine alone or chloroquine plus clindamycin (Kremsner, et al., 1994). These data are summarized in Table 3 below.

In the meta-analysis performed by the Statistical Reviewer, in which a subset of 3 studies which evaluated Q7T7 vs a non-quinine comparator were analyzed, the odds ratio was 3.07 in favor of the Q7T7 regimen, as shown in Figure 2 above.

Table 3: Efficacy of Quinine Combination Therapy in comparison with other Antimalarial Regiments in Treatment of Uncomplicated *P. falciparum* Malaria

Study (by geographical region)	Study Location (Dates)	Quinine Combination (duration-days)	Cure Rates at 28 days in Evaluable Population n/N (%)	Non-Quinine Comparator (duration-days)	% Cure at 28 days in Evaluable Population n/N (%)
Southeast Asia:					
Pukritayakamee, et al., 2004	Thailand (dates not provided)	Q7T7	22/22 (100)	A7T7	19/21 (90)
Pukrittayakamee, et al., 2000	Thailand (1995-1997)	Q7C7	60/60 (100)	None	--
		Q7T7	47/48 (98)	None	--
Bunnag, et al., 1996	Thailand (1990-1992)	Q5T7	40/46 (87)	None	
		Q7T7	40/40 (100)	None	--
Vaninjanonta, et al., 1996	Thailand (dates not provided)	Q7T7	17/18 (94)	None	--
		Q7CQ3	11/18 (61)	None	
Bich, et al., 1996	Vietnam (1993-unknown)	A1Q3	23/32 (72)	A1D3	13/42 (31)

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 Quinine Sulfate Capsules USP, 324 mg

Looaresuwan, et al., 1994	Thailand (1991)	Q7T7	45/46 (98)	M1T7	44/47 (94)
Karbwang, et al., 1994	Thailand (dates not provided)	Q7T7	30/30 (100)	A5	29/31 (97)
Asia					
Rahman, et al., 2001	Bangladesh (1996-1997)	Q3SP	96/145 (66)	CQ3	34/149 (23)
				M1	51/70 (73)
South America					
Duarte, et al., 1996	Brazil (1992-1993)	Q3T7	68/88 (77)*	A7T7	70/88 (79)*
De Alencar, et al., 1997	Brazil (1995-1996)	Q7T7	77/77 (100)	AT3+P3	76/77 (99)
Kremsner, et al., 1988	Brazil (1987)	Q3C3	36/40 (90)	AM3	1/25 (4)
		Q3SP2	9/30 (30)	--	--
De Souza, et al., 1985	Brazil (dates not provided)	Q3SP1	46/50 (92)	M1	49/49 (100)
Africa					
Metzger, et al., 1995	Gabon (1993-1994)	Q1.5 C3	33/36 (92)	None	--
		Q1.5 D3	32/35 (91)	--	--
Ramharter, et al., 2005 (pediatric study)	Gabon (2003-2004)	Q3C3	45/48 (94)	A3C3	40/46 (87)
Kremsner, et al., 1994 (pediatric study)	Gabon (1992)	Q3C3	30/34 (88)	CQ	3/32 (9)
				CQC3	23/33 (70)

*ITT population

Q= quinine; A= artesunate; T= tetracycline; C= clindamycin; CQ= chloroquine; AT+P= atovaquone+proguanil; AM= amodiaquine; M=mefloquine

Medical Officer Comments: *In the evaluable population, all treatment failures were due to recrudescence. Patients lost to follow-up were not included in the evaluable population. Except for the study performed in Bangladesh (Rahman, et al., 2001), all quinine treatment failures were due to RI recrudescence. In that study, 12/145 (8.2%) of patients had RIII recrudescence, and 5/145 (3.4%) RII recrudescence. These data may indicate the presence of high-level quinine-resistance in Bangladesh. As noted previously, a high level (39.5%) of RIII recrudescence in chloroquine-treated patients was also reported in the same study.*

In the 4 studies which compared 7 days of quinine in combination with tetracycline (Pukrittayakamee, et al., 2004; Looaresuwan, et al., 1994; Karbwang, et al., 1994; and De Alencar, et al., 1997), cure rates were similar for the quinine combination and comparator (artesunate-tetracycline, mefloquine-tetracycline, artesunate alone, or atovaquone-proguanil). Cure rates were lower with chloroquine than with quinine-based therapy, as expected, because of extensive parasite resistance to chloroquine, except in areas of Central America west of the Panama Canal and some parts of the Middle East.

Additionally, because of widespread P. falciparum resistance to sulfadoxine-pyrimethamine, short courses of quinine in combination with sulfadoxine-pyrimethamine are not expected to be more effective than a short course of quinine alone, and thus may not be a useful comparator.

1.3.3 Safety

For this review, information on adverse events associated with quinine use was derived from published clinical studies, case reports, postmarketing reports of adverse events submitted to the FDA AERS database, and to the WHO database, as well as from reviews of quinine toxicity. Most of the clinical studies provided in support of this application did not report adverse events systematically. Additionally, there may have been publication bias in adverse event reporting in those studies which did so. Methods for adverse event monitoring were reported in only a few studies. The safety data available is such that a reliable estimate of adverse event incidence cannot be made. Nevertheless, an attempt was made in this review to identify common and less-common adverse events for the purpose of product labeling.

Important safety issues with quinine sulfate include hypersensitivity reactions, QT prolongation, and the potential for serious cardiac arrhythmias, hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, exacerbation of muscle weakness in patients with myasthenia gravis, optic neuritis, blindness, deafness, hypoglycemia, and multiple drug interactions. These safety issues are discussed in the IRS (section 7) of this review.

In the proposed product label, Contraindications to use of quinine sulfate include use in patients with prolonged QT interval, with G-6-PD deficiency, with optic neuritis, with myasthenia gravis, and with known hypersensitivity to quinine or related drugs. Warnings in the proposed label for quinine sulfate include use of quinine sulfate for treatment or prevention of nocturnal leg cramps, a Warning regarding the potential for QT prolongation and ventricular arrhythmias, Warnings about patients with G-6-PD deficiency, and myasthenia gravis, and regarding concomitant use of neuromuscular blocking agents, rifampin, class IA and III antiarrhythmic agents, astemizole, cisapride, erythromycin, and other medications known to cause QT prolongation. Specific Precautions in the in proposed label include information regarding hypersensitivity reactions, atrial fibrillation and flutter, concomitant use of digoxin, hypoglycemia, and drug interactions.

1.3.4 Dosing Regimen and Administration

The dose of oral quinine sulfate proposed by the applicant is 648 mg (salt) 3 times daily. This dose would be approximately equivalent to 9-10 mg salt/kg 3 times daily for a 60 to 70 kg person. Most of the published studies which evaluated the efficacy and safety of oral quinine therapy used doses of 10 mg/kg 3 times daily or 600-650 mg (salt) 3 times daily. No dose-ranging clinical studies were identified in the literature to evaluate the optimal dose of quinine for treatment of uncomplicated malaria. Across published studies, the maximal total plasma concentration of quinine after a single dose of 500 mg quinine base ranged from 2.4 to 5.6 mg/L; while in the bioequivalence studies sponsored by the applicant, the mean peak plasma concentration of quinine after a single 648 mg capsule of quinine sulfate was 3.2 mg/L.

The therapeutic range for unbound quinine has not been determined precisely, but is thought to lie between 0.8 and 2 mg/L, corresponding to total plasma quinine concentrations of approximately 8 to 20 mg/L (White, 1996). As reviewed by Dr. Gieser, Clinical Pharmacology, simulations of pharmacokinetic data in healthy subjects showed that with a dose of 648 mg every 8 hours, total quinine concentrations of approximately 8 mg/L could be achieved within 3 days of therapy. Somewhat higher levels of total plasma quinine (estimated range of 9-16 mg/L) are attained rapidly (within 24 hours) in patients with malaria because of a reduction in quinine clearance, particularly in the acute phase of the infection. Quinine has a narrow therapeutic index, and levels within the therapeutic range cause cinchonism, and possibly more serious toxicities. As reviewed by Jaeger, et al., (1987), in the setting of chronic quinine administration or with quinine overdose, toxic effects of quinine have been reported at plasma quinine concentrations ≥ 10 mg/L for blindness, and > 16 mg/L for cardiac arrhythmias. No serious adverse events, including serious cardiac dysrhythmias and blindness were reported in the clinical studies reviewed for this NDA.

The proposed dose of quinine sulfate for treatment of uncomplicated *P. falciparum* malaria (648 mg 3 time daily) is appropriate based on clinical data showing efficacy with this (or similar) regimen(s) in published studies, and on years of clinical experience with this medication.

_____ . Data from the submitted studies suggests that a 7 day course of quinine, whether alone, or in combination with antimicrobial agents may constitute optimal therapy. _____

_____ I we have proposed changes in the Dosage and Administration section of the label to read as follows:

“For treatment of uncomplicated *P. falciparum* malaria in adults, the dosage is 648 mg (two capsules) every 8 hours for 7 days. (See Clinical Studies.)”

Medical Officer Comments: The CDC recommends quinine sulfate 10 mg (salt) /kg 3 times a day in combination with an antimicrobial drug for 3-7 days for treatment of uncomplicated P. falciparum malaria acquired from areas of chloroquine resistance or unknown resistance (CDC 2004 Guidelines for Treatment of Malaria in the United States). A 7 day course of therapy is recommended for patients who acquired P. falciparum malaria in Southeast Asia. The WHO recommends quinine sulfate 8 mg (base)/kg 3 times daily as monotherapy for 7 days for P. falciparum acquired from areas where the parasite is quinine-sensitive, and the same quinine sulfate dose in combination with an antimicrobial agent for 7 days in areas of decreased susceptibility to quinine (WHO 2000). Data supporting courses of quinine shorter than 7 days are limited; however, it is acknowledged that many patients cannot tolerate quinine for more than a few days due to symptoms of cinchonism, and studies comparing short-course quinine in combination with an antimicrobial or other antimalarial agents to 7-day regimens, are needed.

1.3.5 Drug-Drug Interactions

Quinine is metabolized by the cytochrome P450 system in the liver, mainly via CYP3A4, and to a less extent CYP 2C19. Thus, drugs that affect the activity of CYP3A4 may alter plasma quinine concentrations. Additionally, *in vitro* and *in vivo* evidence collectively suggests that quinine has the potential to influence the metabolism of other drugs that are substrates of CYP3A4 and CYP2D6. See Pharmacology Review by Dr. Gerlie Gieser for further details.

Drugs known to interfere with quinine sulfate absorption include antacids containing aluminum or magnesium. Drugs known to increase quinine exposure include cimetidine, ketoconazole, tetracycline, troleandomycin, a macrolide antibiotic, and the urinary alkalizers, acetazolamide, and sodium bicarbonate; while rifampin, a potent CYP3A4 inducer, is known to decrease quinine exposure. Quinine sulfate is known to increase levels of carbamazepine, and phenobarbital, astemizole, cisapride, digoxin, and desipramine. We have proposed changes to the proposed label, expanding the section on drug interactions to describe these interactions or potential interactions in detail.

Important pharmacodynamic interactions with quinine have also been reported. Quinine, like its diastereomer, quinidine, has antiarrhythmic properties, and has been shown to prolong the QT interval when administered orally or parenterally, in healthy individuals and in those with underlying diseases. Clinical (pharmacokinetic) studies have demonstrated increased QT intervals in patients who received concomitant quinine and mefloquine. Additionally, *in vitro* studies have demonstrated that quinine inhibits the metabolism of halofantrine via cytochrome P450 CYP 3A4. Therefore, quinine could potentiate the cardiotoxic effects of halofantrine, including QT prolongation and potentially fatal cardiac arrhythmias such as torsades de pointes and ventricular fibrillation. We have proposed a WARNING in the final product label regarding concomitant use of mefloquine or halofantrine with quinine sulfate.

Although not specifically studied, quinine use should also be avoided with concomitant class I antiarrhythmic agents, such as quinidine or procainamide, and III antiarrhythmic agents, such as amiodarone and sotalol), and with any medication known to cause QT prolongation. Case reports in the published literature and from the AERS database describe QT prolongation and torsades de pointes associated with quinine with concomitant astemizole. Additionally, an AERS report described a fatal case of torsades de pointes in an elderly woman receiving erythromycin and dopamine in addition to quinine. As noted above, there is a pharmacokinetic interaction between quinine and astemizole, resulting in increased plasma levels of astemizole. Similar interactions of quinine with other drugs known to cause QT prolongation, such as cisapride, terfenadine, and others could potentially result in serious or potentially fatal ventricular dysrhythmias. We have proposed a statement in the PRECAUTIONS section of the final product label regarding concomitant use of quinine sulfate with drugs known to cause QT prolongation.

Rifampin may increase metabolism of quinine, thereby reducing the quinine concentration in plasma. Because of concern about potential treatment failures, a Warning was proposed for the final product regarding the concomitant use of quinine sulfate and rifampin.

Quinine has effects on skeletal muscle, namely, neuromuscular blocking activity, and could potentiate the activity of neuromuscular blocking agents, such as tubocurarine, succinylcholine, pancuronium, and others. We have proposed a Warning in the final product labeling regarding concomitant administration of drugs with neuromuscular blocking activity and quinine sulfate.

Special Populations

Pregnancy

P. falciparum malaria can cause substantial morbidity and mortality in pregnant women and the fetus. Infection in non-immune pregnant women can result in spontaneous abortion or fetal loss, with a maternal mortality of approximately 10%, as reviewed by Phillips-Howard and Wood (1996). The applicant submitted one randomized, controlled, open-label study which compared efficacy of quinine monotherapy to a combination of mefloquine plus artesunate in Thai women in the second or third trimester of pregnancy (McGready, et al 2000). Cure was assessed at day 63 of follow-up, rather than the 28 day endpoint used in most of the other studies. Cure rates were 98% for the mefloquine-artesunate group (N=65 evaluable patients), and 67% for the quinine treatment group (N=41 evaluable patients). Patients were followed until delivery, and of 92 births, there were no stillbirths, congenital abnormalities, or differences in mean birthweight or estimated gestational age between treatment groups. There were no serious adverse events reported in the study, but the incidence of tinnitus and dizziness were higher in the quinine treatment group. The efficacy of quinine monotherapy in this study would be unacceptable for treatment of pregnant women with malaria. This is probably due to two factors, namely, the 63 day rather than 28 day endpoint used in this study could result in lower efficacy due to late recrudescence or reinfection, although the latter, as confirmed by polymerase chain reaction (PCR) was reported only in 2 patients. Secondly, the study was performed in an area of Thailand, known to have increased quinine (and mefloquine) resistance of *P. falciparum*.

A second randomized, controlled study performed in Thailand was identified in the published literature, which compared oral quinine sulfate to oral artesunate plus mefloquine (Bounyasong, 2001). In this study, pregnant women (at least 28 weeks gestational age) were treated with oral quinine 10 mg/kg q8h for 7 days (N=29), or 5 days oral artesunate plus 25 mg/kg mefloquine on day 6 (N=28). None of the evaluable patients had recrudescence within 28 days. Fever and parasite clearance times were significantly shorter in the mefloquine+artesunate group, and neonatal birthweight, Apgar score at 1 minute were significantly lower in the quinine treatment group. There was no difference between treatment groups in the incidence of intrauterine growth retardation, or the gestational age at birth, and no congenital abnormalities were reported in either group. Adverse events were more frequent in the quinine treatment group. Those events more common in women treated with quinine than those treated with mefloquine+artesunate were nausea, vomiting, vertigo, tinnitus, and hypoglycemia. Additionally, the mean hematocrit at the end of treatment was significantly lower in patients who received quinine than the comparator regimen.

A third randomized, controlled study performed in Thailand was found in the published literature, comparing a 7 day course of oral quinine sulfate plus clindamycin (N=65) to a 7 day course of oral artesunate (N=64) in pregnant women with uncomplicated *P. falciparum* malaria

(McGready, et al., 2001). In this study, cure rates were 100% at follow-up (day 42 after treatment initiation) for both treatment regimens. There was no difference in the adverse event profile, except for more tinnitus reported in patients who received quinine. Additionally, there was no significant difference in pregnancy outcomes (mean birthweight, proportion of low birthweight, and estimated gestational age) between the two treatment groups. One stillbirth was reported in each treatment group, but neither was attributed to the study drug. Additionally, one congenital abnormality (midline epidermoid cyst) was reported in one infant of a mother who received quinine treatment.

Safety issues with quinine in pregnancy include hypoglycemia, caused by increased insulin secretion by pancreatic beta cells. Pregnant women, many of whom have altered glucose homeostasis, appear to be particularly vulnerable to quinine's effect on insulin production. Earlier literature suggested that quinine was associated with increased stillbirths, spontaneous abortion, intrauterine growth retardation, low-birthweight, or congenital abnormalities (mainly deafness and optic nerve hypoplasia). Additionally, as described by the Pharmacology/Toxicology reviewer, Dr. Steven Kunder, teratogenic effects have been reported in several animal species (rabbits, guinea pigs, and chinchillas), but not in others (mice, rats, dogs, and monkeys). However, as reviewed by Dr. Gerard Nahum, Medical Officer, of the Pregnancy and Lactation Team, recent epidemiological studies did not show any increased increased of these events in women who had received quinine at some time during pregnancy.

The applicant proposed a pregnancy category — in the quinine sulfate label. After consultation with the Pregnancy and Lactation Team, we have proposed that quinine sulfate receive a pregnancy category C based on our risk/benefit assessment. The risks associated with quinine treatment appear relatively low in comparison to the risk of significant morbidity and mortality associated with *P. falciparum* malaria in pregnant women and the fetus. Additionally, in areas of multidrug parasite resistance, there may be few treatment options available for pregnant women. The CDC has recommended the use of oral quinine sulfate plus clindamycin for treatment of uncomplicated chloroquine-resistant *P. falciparum* malaria in pregnant women (CDC 2004 Guidelines for Treatment of Malaria in the U.S.).

The following statement regarding the use of quinine in pregnancy was proposed for the final product labeling under Precautions/Pregnancy:

“Quinine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The risks and benefits of alternative treatments should be considered. If quinine sulfate is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazards to the fetus.”

Quinine crosses the placenta and gives measureable blood levels in the fetus. In 8 women who delivered live infants 1 to 6 days after starting quinine therapy, placental cord plasma quinine concentrations were between 1.0 and 4.6 mg/l (mean 2.4 mg/l) and the mean (\pm SD) ratio of cord plasma to maternal plasma quinine concentrations was 0.32 ± 0.14 . Quinine levels in the fetus may not be therapeutic. If congenital malaria is suspected after delivery, the infant should be

evaluated and treated appropriately. This information will be stated in the Precautions/Pregnancy section of the proposed label.

At doses several times the proposed dose for treatment of malaria, quinine may stimulate the pregnant uterus. However, there is no evidence that quinine causes uterine contractions at the doses used for treatment of malaria. This is stated in the proposed label in the Precautions/Labor and Delivery section.

Quinine is also secreted in the breast milk of women. There is limited information on the safety of quinine in breastfed infants. In one pharmacokinetic study, quinine levels in breast milk were approximately 30% of the maternal plasma concentration; and it was estimated that infants received 1.5 to 3 mg per day of quinine via breast milk. No quinine-associated toxicities were reported in the 25 infants in this study. This information is stated in the proposed label in the Precautions/Nursing Mothers section.

Pediatrics

P. falciparum malaria causes substantial morbidity and mortality in children, particularly those who are non-immune, i.e. younger children, and those who do not live in hyperendemic areas. Many of the studies submitted for this NDA which evaluated oral quinine sulfate for the treatment of uncomplicated *P. falciparum* malaria included pediatric patients; however efficacy and safety results in these studies were not reported separately for children and adults. Some of the supportive studies on treatment of severe malaria with parenteral quinine were pediatric studies, and review of the literature identified several randomized, controlled pediatric studies which evaluated oral quinine for treatment of uncomplicated *P. falciparum* malaria, and are included in this review.

The safety and efficacy of oral quinine sulfate for treatment of uncomplicated *P. falciparum* malaria in children ≥ 16 years of age can be extrapolated from adult data. However, although the dosing of quinine sulfate may be similar to adult dosing based on pharmacokinetic studies in the literature, the current formulation of quinine sulfate (capsules for oral administration) may not be appropriate for young children, and a new age-appropriate quinine sulfate formulation may be required.

2 INTRODUCTION AND BACKGROUND

Quinine has been used worldwide as an antimalarial drug for hundreds of years, and has been marketed in the U.S. since prior to 1938. Until 1994 quinine was used extensively for treatment of nocturnal leg cramps. At that time, the FDA issued a final rule in the Federal Register of 22 August, 1994 (59 FR 4324) stating that quinine was not safe and effective for treatment or prevention of leg cramps, and prohibited its marketing for that indication. Until 1998, quinine was available as an over the counter product. At that time, a final rule was issued (63 FR 13526) restricting the availability of quinine to prescription for the treatment of malaria.

Quinine sulfate is available in this country from a number of different manufacturers, as tablets or capsules in several different strengths. This is the first quinine sulfate product for malaria submitted for NDA review. Quinine sulfate remains effective for treatment of *P. falciparum* malaria in most parts of the world. There are several geographical regions; however, with increasing parasite resistance to quinine, namely, certain areas in Thailand, and some localized areas in South America and Bangladesh. This is a 505(b) 2 application, and review of the efficacy of quinine sulfate was solely from published randomized, controlled studies. A number of these studies were performed in areas of multi-drug (chloroquine, sulfadoxine-pyrimethamine, and mefloquine) parasite resistance, and in areas of documented quinine resistance. The applicant also submitted 2 pharmacokinetic studies in healthy volunteers, which established bioequivalence of this product to an approved quinine sulfate tablet from Thailand. Additional safety data from these studies and from postmarketing adverse event data was also reviewed.

2.1 Product Information

Description

Quinine sulfate is an antimalarial drug derived by purification of quinine derived from the cinchona tree. The chemical name is cinchonan-9-ol, 6'-methoxy- (8 α , 9R)-sulfate (2:1) (salt) dehydrate. Quinine sulfate is a white, crystalline, odorless powder that darkens on light exposure. The powder has a bitter taste. Quinine sulfate will be supplied by Mutual Pharmaceutical Company as capsules for oral administration, each containing 324 mg quinine sulfate, USP, the equivalent of 269 mg quinine free base. Inactive ingredients in the capsules include corn starch, magnesium stearate, and talc.

Established Name and Trade Name

Quinine sulfate is the established name of the product; and no trade name has been proposed.

Chemical Class

Quinine sulfate is not a new molecular entity, new salt or ester, new dosage form, or new combination product. For many years, quinine sulfate has been available from a number of manufacturers in the U.S. as 200 mg, 300 mg, or 325 mg tablets, and 260 mg, 324 mg, or 325 mg capsules for oral administration. Mutual Pharmaceutical Company has supplied quinine sulfate, and has marketed quinine sulfate capsules and tablets for over 15 years.

Pharmacological Class

Quinine belongs to the class of quinoline antimalarial agents. Mefloquine, primaquine, and halofantrine belong to the same pharmacological class.

Proposed Indication

The applicant has proposed that quinine sulfate is indicated for the treatment of uncomplicated *P. falciparum* malaria.

Dosing Regimen

The proposed dosing regimen of quinine for treatment of uncomplicated *P. falciparum* malaria is 648 mg, i.e. (2) 324 mg capsules of quinine sulfate 3 times daily.

We have proposed a 7-day dosing regimen of 648 mg oral quinine sulfate every 8 hours for the treatment of uncomplicated *P. falciparum* malaria in adults.

There is some evidence from the literature that a 7-day regimen of quinine sulfate plus either tetracycline or clindamycin is more effective than quinine monotherapy in Southeast Asia. Only limited data from the literature supports shorter course (up to 3 days) quinine combination therapy in other geographical areas. Information regarding the efficacy of quinine mono- and combination therapy is proposed for the Clinical Studies section of the final product label

2.2 Currently Available Treatment for Indications

The antimalarial drugs currently approved for treatment and marketed in the U.S. are chloroquine (Aralen®), sulfadoxine-pyrimethamine (Fansidar®), mefloquine (Lariam®), atovaquone-proguanil, (Malarone®), primaquine phosphate and quinine sulfate. Halofantrine (Halfan®) is also FDA-approved, but not currently available in the U.S. The use of chloroquine for treatment of *P. falciparum* malaria is limited to areas of where the parasite is susceptible, namely Central America west of the Panama Canal, the Dominican Republic, Haiti, Mexico, and some areas in the Middle East. The use of sulfadoxine-pyrimethamine (Fansidar®) has been used for malaria self-treatment, but its use is also limited to malaria acquired in areas where the parasite is sensitive.

Mefloquine can still be used in most geographical regions for treatment of uncomplicated *P. falciparum* malaria, except in certain areas of Thailand, particularly the Thai-Myanmar and Thai-Cambodia border, and some local areas in South America. Mefloquine, however, is indicated for the treatment of mild to moderate acute malaria caused by *P. falciparum*, and is not available as an intravenous preparation for severe *P. falciparum* malaria in the U.S. The use of mefloquine is also limited to individuals without a neuropsychiatric history due to neuropsychiatric adverse events associated with its use.

The use of halofantrine in this country has been limited by its known cardiotoxicity related to QT prolongation, and reports of death in young people without a cardiac history. Quinine sulfate oral tablets or capsules have been available in this country since prior to the Food, Drug, and Cosmetic Act of 1938, and until 1998, was available for over-the-counter use. Quinine sulfate has been available by prescription only for the treatment of malaria since 1998. Parenteral quinine sulfate for treatment of severe *P. falciparum* malaria is not available in the U.S.; however, parenteral quinidine, the diastereomer of quinine has been approved for treatment of severe malaria caused by *P. falciparum*.

Antimalarial agents approved for malaria prophylaxis include chloroquine, mefloquine, atovaquone-proguanil, and doxycycline. The latter is an antimicrobial agent with antimalarial activity.

Quinine sulfate is an important drug for treatment of uncomplicated *P. falciparum* malaria, particularly in parts of the world with increasing multi-drug resistance, including mefloquine resistance. In these regions, quinine is generally used in combination with an antimicrobial agent such as tetracycline or clindamycin in case of quinine resistance, and/or to prevent development of quinine resistance. Quinine sulfate is also important for treatment of malaria in the U.S., mostly in returned travelers. Because these individuals are generally non-immune to *Plasmodium* sp., and are at risk for development of severe or complicated malaria if not recognized and treated rapidly with an effective drug, and because the drug-resistance of the acquired parasite is not generally known, the Centers for Disease Control and Prevention (CDC) has recommended the use of oral quinine sulfate in combination with doxycycline, tetracycline, or clindamycin for *P. falciparum* malaria acquired in areas of chloroquine resistance or unknown resistance (CDC 2004 Guidelines for Treatment of Malaria in the U.S.).

2.3 Availability of Proposed Active Ingredient in the United States

Quinine sulfate for oral administration is currently available as 200 mg, 300 mg, or 325 mg tablets, and 260 mg, 324 mg, or 325 mg capsules for oral administration from a number of different manufacturers in the U.S. None of these products currently has an approved label. The DSPIDP consulted ODS (DSRCS) for information regarding quinine sulfate utilization and indications for use in this country. Mr. Michael Evans analyzed data from the National Prescription Audit (NPA) database, and in 2004, an overall total of _____ prescriptions for quinine sulfate were estimated from many different suppliers. In January to June, 2005, an estimated _____ quinine sulfate prescriptions were recorded. Mr. Evans also provided information from The National Disease and Therapeutic Index (NDTI) database, which was queried to assess the proportion of quinine sulfate prescribed for malaria or other indications. These data are collected by a panel of approximately 3,000 office-based physicians in the U.S. For two consecutive days per quarter, the physicians complete and submit a survey of their practice patterns to IMS health. These data are then projected to the national level for an estimate of use. In Mr. Evan's review of the NDTI database for 2004, it was estimated that _____ of quinine sulfate prescriptions were for the diagnosis, "Symptoms related to limbs", and _____ were for the diagnosis of "Abnormal movement disorders." In that year, none of quinine sulfate prescribed by the physicians surveyed was for the diagnosis of malaria.

Medical Officer Comments: We interpreted this information as reflecting the current medical practice in the U.S., i.e. most quinine sulfate is currently prescribed for treatment of nocturnal leg cramps or for similar indications such as muscle cramps, leg pain, and for restless leg syndrome. Because the vast majority of patients with malaria are hospitalized in this country, it is not surprising that the limited number of office-based physicians surveyed for this database prescribed little or no quinine sulfate for malaria.

2.4 Important Issues with Pharmacologically Related Products

Quinine and quinidine, its diastereomer, and other cinchona alkaloids may cause a symptom complex called ‘cinchonism’, which is very common in its mildest form. The signs and symptoms of cinchonism are discussed in the Integrated Review of Safety (IRS), section 7. Quinidine has cross-reactivity with quinine, and patients who experienced hypersensitivity with quinidine should not receive quinine. Additionally, quinine and quinidine both have antiarrhythmic properties, affecting cardiac rhythm and conduction, and causing QT prolongation. Quinidine is reportedly 4 to 10-fold more potent than quinine with regard to its effects on membrane repolarization and prolonging conduction time. The potential cardiotoxic effects of quinine are further described in the IRS, section 7.

Mefloquine is a closely-related synthetic quinoline antimalarial agent. Mefloquine inhibits has also been associated with QT prolongation when used concurrently with quinine or halofantrine. Mefloquine also has cross-reactivity with quinine, and patients who experienced hypersensitivity reactions to mefloquine should not receive quinine. Mefloquine has also been associated with a number of neurological and psychiatric adverse events, such as headache, seizures, nightmares, disorientation. In one case report the use of quinine with mefloquine resulted in increased seizures in a patient with a seizure disorder at baseline (Miyashita, et al., 1994). Although quinine has been associated with dizziness and dysphoria, reports of neurological events such as seizures, ataxia, and coma have been described only in the setting of quinine overdose.

Halfantrine, although approved for treatment of malaria, is currently not available in the U.S. because of safety issues, namely significant QTc prolongation and deaths due to torsades de pointes and other serious cardiac arrhythmias.

Quinidine is an antiarrhythmic agent available in the U.S. for oral or parenteral administration. Intravenous quinidine is the only parenteral antimalarial agent available in the U.S. for treatment of severe *P. falciparum* malaria. Quinidine is the diastereomer of quinine and both have similar properties with regard to membrane depolarization, and the potential for QTc prolongation. Quinine may have less potential for cardiotoxicity than quinine, as reviewed in the ISS.

2.5 Presubmission Regulatory Activity

Quinine has been marketed in the U.S. since before 1938, when the Federal Food, Drug and Cosmetic Act was enacted. Quinine was available as an OTC medication until 1988, when a final rule (63 FR 13526) made quinine available by prescription only for treatment of malaria. Prior to

that time, another final rule in 1994 (59 FR 43234) banned marketing of quinine for treatment or prevention of nocturnal leg cramps, because it had not been shown to be safe and effective for that indication. Before Mutual Pharmaceutical Company submitted NDA 21-799, no quinine sulfate products for malaria were submitted for NDA review; and there are currently no FDA-approved quinine sulfate products on the U.S. market. Prior to submission of NDA 21-799, the following regulatory activities took place:

A pre-NDA meeting with URL/Mutual Pharmaceutical Company was held on 15 July, 2003. At that time, the requirements for submission of a 505(b) 2 NDA were discussed. Nonclinical and clinical requirements for the NDA were discussed including the need to perform bioequivalence studies with an approved drug from another country, to link Mutual's product with one of proven efficacy for the treatment of malaria. The company stated its intentions not to seek pediatric labeling at this time,

URL/Mutual Pharmaceutical Company inquired as to whether the proposed indication would be eligible for Orphan Drug Designation. The Agency agreed that the treatment of malaria would be an orphan indication in the U.S.

IND 67,012 was submitted January 21, 2004 for a phase 1, 3-way crossover study to establish bioequivalence of Mutual Pharmaceutical's quinine sulfate 325 mg capsule with the 300 mg quinine sulfate tablet manufactured by the Government Pharmaceutical Company (GPO), Thailand.

A pre-NDA meeting with URL/Mutual Pharmaceutical Company of 25 May, 2004 to discuss further the necessary information required for the NDA submission. The Division requested additional published clinical studies as supportive evidence for safety and efficacy of quinine sulfate, as well as additional information regarding the cardiac effects of quinine.

There is currently no FDA Guidance for Industry regarding development of drugs for treatment and/or prevention of malaria, although a draft form is currently in progress.

2.6 Other Relevant Background Information

Quinine sulfate is marketed in many countries worldwide, across Africa, Asia, the South Pacific, the Americas, and Europe. Quinine sulfate and other quinine salts are approved for treatment of malaria in a number of other countries. Additionally, some countries also have treatment of nocturnal leg cramps and treatment of myotonia congenita listed as indications in their approved labels. The applicant provided product labels from 11 foreign countries. These were reviewed for indications, and safety information in the Integrated Review of Safety (IRS) (section 7) of this review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Mutual Pharmaceutical Company has been marketing quinine sulfate capsules for over 15 years. The manufacturing procedures and processes were described in this NDA. The control procedures and methods were revised to comply with FDA and (International Conference on Harmonization) ICH regulatory standards. Quinine sulfate is supplied for oral administration as capsules containing 324 mg quinine sulfate, USP (269 mg quinine base). The labeled storage conditions for the drug product is 25-30° C (77-86°F) with a proposed expiration dating period of 24 months. Capsules will be packaged in _____ bottles which provide light protection. There is no applicable Product Microbiology information for this product. See CMC review by Dr. Gene Holbert for full details.

3.2 Animal Pharmacology/Toxicology

Published data on animal and *in vitro* studies were provided in support of this 505 (b) 2 application and no further preclinical studies were performed as agreed upon with the FDA at the pre-NDA meeting 25 May, 2004. See Dr. Steven Kunder's Pharmacology/Toxicology Review for full details. This section briefly summarizes the nonclinical pharmacology of quinine sulfate.

Absorption, Distribution, Metabolism, and Excretion

Quinine is rapidly absorbed following oral administration. It concentrates in erythrocytes and is distributed to liver, heart, lung, kidneys and muscle in animals. Quinine distribution is increased in *Plasmodium*-infected animals. Distribution to the brain is minimal and is not affected by infection. Placental transfer of quinine was demonstrated in sheep, with fetal exposure < 10% that of maternal exposure. Quinine is metabolized extensively in the liver in all animal species tested. The major metabolite is 3-hydroxyquinine. The isozyme, CYP450 3A is the main enzyme involved in quinine metabolism. The plasma half life of quinine is approximately 1 hour in mice, 13-16 hours in rats, and 7 hours in dogs. Half-life is prolonged in the setting of renal failure. Quinine is excreted in urine and feces. Approximately 10-20% of the drug is excreted unchanged in the first 24 hours.

Repeat-Dose Toxicity of Quinine

Repeat-dose chronic toxicity studies in Leeds rats showed high rates of mortality (25% died within 2 months) and adverse effects on the liver with quinine sulfate in drinking water at estimated doses of 100 mg/kg/day. Histopathological changes in the liver included periportal glycogen depletion, mild periportal fibrosis, small areas of cholangiofibrosis, lipid accumulation in Kupffer cells in large cytoplasmic droplets, binucleate hepatocytes, and increased numbers of lysosomes. No hyperplasia, liver necrosis, or liver tumors were reported. No deaths were observed in the 13-week studies in which Sprague-Dawley rats received up to 200 mg/kg/day quinine hydrochloride.

Cardiovascular Effects of Quinine

Quinine sulfate has similar cardiovascular effects as quinidine, including antiarrhythmic activity, and QT prolongation, but quinine appears to be approximately 10-fold less potent than quinidine in this respect. Quinine, like quinidine, blocks outward potassium (K) and calcium (Ca) channels, inhibits K- and Ca-induced muscle contraction, and blocks HERG channels. Quinine and quinidine both prolong conduction time, but only quinidine prolongs refractoriness. Quinine causes hypotension, and increases heart rate and myocardial contractility in dogs and other animals. The vasodilatory effect of quinine may be due an α -blocking effect, or to a direct action on smooth muscle.

Quinine Effects on Skeletal Muscle

Quinine increases the refractory period of skeletal muscle, diminishing the response to tetanic stimulation. Quinine also decreased the excitability of the motor end-plate, reducing the response to repetitive nerve stimulation and to acetylcholine. Additionally, quinine antagonizes the action of physostigmine on skeletal muscle to the same degree as curare.

Ototoxicity of Quinine

Repeat-dose toxicity studies in rats revealed no signs of ototoxicity; however, dose-related ototoxicity has been observed in several animal species, including guinea pigs, and chinchillas. The mechanisms of ototoxicity may include vasoconstriction and decreased cochlear blood flow, and reversible alterations of outer hair cells in the cochlea.

Effect of Quinine on Vision

In two 13-week, repeat-dose toxicity studies in rats, ophthalmological examination showed no adverse effects.

Hypoglycemia

Quinine has been associated with hypoglycemia and hyperinsulinemia in malaria infected patients treated with quinine, as discussed further in the IRS (section 7). There are reports of quinine potentiation of glucose-induced insulin release by isolated rat pancreatic islet cells (Okitolonda, et al., 1986).

In another study, however, hypoglycemia was not observed after single-dose or chronic administration of quinine in a rat model. Increased insulin, however, was noted in those animals (Okitolonda, et al., 1986).

Genotoxicity/Mutagenicity

Genotoxicity studies of quinine were positive in the Ames bacterial mutation assay with metabolic activation and in the sister chromatid exchange assay in mice. However, genotoxicity findings were not positive in the sex-linked recessive lethal test performed in *Drosophila*, in the *in vivo* mouse micronucleus assay, or in the chromosomal aberration assay in mice and Chinese hamsters.

Carcinogenicity

No formal carcinogenicity studies have been performed with quinine. These studies are not required at this time, because quinine sulfate will not be indicated for chronic use in humans with this NDA approval.

Reproductive Toxicology

Teratogenic effects have been observed in rabbits, guinea pigs, chinchillas, and dogs, but not in mice and monkeys. Teratogenic effects in rabbits included death *in utero*, degenerated auditory nerve and spiral ganglion, anencephaly, and microcephaly. In chinchillas, death and growth suppression *in utero* were observed; while in guinea pigs, hemorrhage and mitochondrial changes in the cochlea were reported. The lowest observed adverse effect levels (LOAELs) for teratogenicity were 200 mg/kg/day (1600 mg/m²/day) for the guinea pig, 130 mg/kg/day or 1560 mg/m²/day in the rabbit, and 150 mg/kg/day for the chinchilla. In a 60 kg person, the proposed dose of quinine sulfate for the treatment of *P. falciparum* malaria is 32.4 mg/kg/day or 1199 mg/m²/day, (only slightly lower than the LOAEL for guinea pigs and rabbits).

The No Observed Effect Levels (NOAELs) for reproductive toxicity were 500 mg/kg/day or 1500 mg/m²/day in the mouse, 300 mg/kg/day or 1800 mg/m²/day in the rat, 50 mg/kg/day or 1000 mg/m²/day in the dog, and 200 mg/kg/day or 2400 mg/m²/day in the monkey. Except for the dog, the NOAELs were all 1 to 2 X the human equivalent dose on a mg/m²/day basis. The NOAEL for the dog was 17% lower than the estimated human dose of 1199 mg/m²/day.

Table 4: NOAELs for Reproductive Toxicity of Quinine in comparison to Proposed Human Dose (summarized from section 5.5 Nonclinical Pharmacology and Toxicology)

Animal	NOAEL (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	NOAEL (mg/m ² /day)	Estimated X Proposed Human Dose (1199 mg/m ² /day)
Mouse	500	42	1500	1.3 X
Rat	300	50	1800	1.5 X
Dog	50	28	1000	0.8 X
Monkey	200	65	2400	2.0 X

Medical Officer Comments: Quinine has been associated with teratogenic effects in some animal species as shown above. Case reports have described congenital abnormalities, including deafness and optic nerve hypoplasia in infants born to pregnant mothers who took quinine doses several times higher than the dose recommended for treatment of malaria. However, epidemiological studies in women exposed to quinine during pregnancy have not shown an increased risk of congenital abnormalities.

Quinine sulfate may have deleterious effects on prenatal and postnatal development in rats. In a study in which female rats received quinine sulfate in drinking water before, during pregnancy and in the postnatal period, pups had lower body weights at birth and during lactation, as well as

delayed eruption of teeth and eye opening during during lactation. The estimated dose received (by the mother) was 20 mg/kg/day or 120 mg/m²/day, a dose approximately 10% of the proposed human dose equivalent to 32.4 mg/kg/day or 1199 mg/m²/day for a 60 kg patient.

Studies to evaluate the effect of quinine upon fertility in animals or in man have not been conducted.

Pharmacology/Toxicology Conclusions

The preclinical studies show that the main target organs for quinine toxicity are the heart, the inner ear, and skeletal muscle. As reviewed in the IRS (section 7) the major target organs for quinine toxicity in humans are the heart, blood vessels, the inner ear, the eye, skeletal muscle, and the gastrointestinal tract. The histopathological changes in the liver of rats exposed chronically to quinine, also suggest a potential for hepatotoxicity. Except for granulomatous hepatitis, which is thought to be secondary to a hypersensitivity reaction in humans, there are few reports of human hepatotoxicity, including liver function test abnormalities with quinine, described in the literature.

Quinine was teratogenic in several animal species. Similarly, with high doses, usually in the setting of quinine overdose or attempted self-abortion, case reports of congenital abnormalities, including deafness and optic nerve hypoplasia, have been described in human infants exposed to quinine *in utero*. No fertility or carcinogenicity studies have been conducted in animals.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This is a 505(b) 2 application, and except for 2 bioequivalence studies sponsored by the applicant, all the data for review of efficacy and safety were obtained from published literature. The applicant performed a literature search from 1951 to 2004 to locate randomized, controlled clinical trials which evaluated oral quinine for treatment of uncomplicated *P. falciparum* malaria. Databases searched included MEDLINE (1966 to 2004), EMBASE (1974 to 2004), JICST-E-plus (1985-2004), Biosis Previews (1969-2004), and OLDMEDLINE (1951 to 1974). The following table summarizes the results of the applicant's electronic literature search. Approximately 1300 unique citations were identified and reviewed by the applicant for inclusion in this NDA submission, as part of the body of evidence supporting the use of quinine for treatment of *P. falciparum* malaria.

Table 5: Results of Applicants Electronic Search of Worldwide Literature for References to Studies on Quinine Sulfate and Malaria (Applicant's Table 1, Integrated Summary of Efficacy, ISE)

Date of Search	Strategy	No. of Unique Citations
5 December 2002	Quinine sulfate reviews	59
10 January 2003	Quinine sulfate and malaria (no reviews)	135
16 July 2003	Quinine and malaria (no reviews), randomized, placebo, controlled, efficacy, or trial	1226
1 July 2004	Quinine and malaria (no reviews), randomized, placebo, controlled, efficacy, or trial in 2003 and 2004 (update of 16 July 03 search)	110

The applicant also performed a manual literature search from older editions of standard medical textbooks, and by searching the table of contents of the Journal of Clinical Investigation in the 1940's and 1950's, on microfilm at the National Library of Medicine, Washington, D.C. Only one publication of interested was identified in the latter search.

From the literature search described above, the applicant located 21 randomized, controlled studies of oral quinine monotherapy or combination therapy for treatment of uncomplicated *P. falciparum* malaria, which were submitted for review of efficacy and safety with this NDA. These studies were the major source of efficacy evaluation for this review. Additional review of the literature by the medical officer and statistical reviewer identified one recent randomized, controlled pediatric study comparing quinine combination therapy to another antimalarial agent (Ramharter, et al., 2005), and 2 additional randomized, controlled studies in pregnant women (McGready, et al., 2001; Buonysong, 2001), which were reviewed to evaluate efficacy of quinine sulfate in pregnant women with malaria. No additional randomized, controlled trials of oral quinine for treatment of uncomplicated *P. falciparum* malaria in adults were found in our searches.

Medical Officer Comments: The applicant's search strategy was validated by the Statistical Reviewer, Ms. LaRee Tracy, who ran an independent literature search using the same strategy, and found no additional publications that fulfilled the search criteria. We concluded that there did not appear to be any bias in study selection by the applicant.

The applicant also provided 12 nonrandomized studies which evaluated quinine monotherapy or combination therapy as secondary or supportive data. These studies were reviewed for quinine safety rather than efficacy for this review. Additionally, 14 randomized, controlled studies on use of parenteral quinine for treatment of severe malaria were submitted in support of the application. These studies were reviewed briefly for efficacy, and in more depth for quinine safety for this review. At the request of the Division, the applicant submitted some additional

information regarding quinine efficacy on 17 June, 2005, and one of the studies cited (Kremsner, et al., 1994) was included for efficacy and safety evaluation.

For the review of safety, the applicant summarized safety data from the randomized and non-randomized studies noted above, in addition to safety data from the two bioequivalence studies submitted by the applicant, postmarketing data from the FDA AERS database from 1969 to 30 June, 2003, and from the WHO database from 1968 to March 2004. A literature review was performed by the applicant for human safety information regarding quinine sulfate. Databases searched were MEDLINE (1966 to 2004), EMBASE (1974 to 2004), JCIST-Eplus (1985-2004), and Biosis Previews (1969 to 2004). This search resulted in 21,606 citations linked to quinine alone. Subsequent searches were restricted to side effects, adverse events, and drug reactions reported with quinine in humans, and resulted in 2601 citations. The search was then narrowed to non-review articles and to publications from 1993 to 2004. After review of titles and abstracts, a total of 192 published references were used to provide safety information for this NDA. In addition, a recent review on antimalarial drug safety was included (Taylor and White, 2004). The applicant also submitted product labeling for oral quinine from 4 foreign countries with the original application.

The 120-safety update was provided by the applicant on 28 March, 2005. This document included additional labels for 17 quinine products from 7 foreign countries. Additionally, the safety update included additional references from the literature regarding safety of quinine, electrocardiographic data from the bioequivalence study RO4-0376, and updates information from the FDA AERS database through December 2003, as well as updated postmarketing data from the WHO database through November, 2004.

4.2 Tables of Clinical Studies

The bioequivalence studies sponsored by the applicant are shown in the following table. These studies provided pharmacokinetic data, as well as safety data, including electrocardiographic data.

Table 6: Bioequivalence Studies sponsored by Mutual Pharma (Applicant's Table 3.21, NDA 21-799 Summary)

Population	N [M/F]	Mean Age (Years) [Range]	Ethnicity	Design	Doses
Healthy, non-smoking adults (RA3-085)	27 [12/15]	24.2 [18 - 47]	Caucasian 26 Hispanic 1	Randomized, open-label, single-dose, three-way crossover study to compare the rate and extent of absorption under fasted conditions of Treatment A and B and to determine the effect of food (Treatment B)	Test—Treatment A (fasted) and Treatment C (fed): Mutual Pharma's quinine sulfate 1 × 324 mg capsule Lot No. BB 102 0105 Reference—Treatment B (fasted): GPO's quinine sulfate 1 × 300 mg capsule Lot No. F.450661
Healthy, non-smoking adults (R04-0376)	24 [13/11]	33.0 [19 - 61]	Caucasian 23 Native American 1	Randomized, open-label, single-dose, two-way crossover study to compare the dose proportionality of Treatment A and B under fasted conditions	Treatment A— Mutual Pharma's quinine sulfate 1 × 324 mg capsule Lot No. BB 102 0105 Treatment B— Mutual Pharma's quinine sulfate 2 × 324 mg capsule Lot No. BB 102 0105

The published, randomized, controlled clinical studies submitted for evaluation of efficacy and safety for oral quinine monotherapy therapy are shown in the following table.

Table 7: Randomized, controlled Clinical Trials of Oral Quinine Monotherapy for Treatment of Uncomplicated Malaria (Applicant's Table 3.65, NDA 21-799 Summary)

Author, year [Country]	No. Patients Enrolled / Completed	Demographics			Design
		Sex M:F	Mean or Median Age [range] (years)	Malaria Endemic Area	
RANDOMIZED, DOUBLE-BLIND STUDIES (N=1)					
Watt <i>et al.</i> , 1988 (Philippines)	20/20	20:0	28 [16 - 49]	Philippines	Randomized, double-blind comparison of quinine monotherapy and chloroquine
RANDOMIZED, OPEN-LABEL STUDIES (N=10)					
Pukrittayakamee <i>et al.</i> , 2004 (Thailand)	176/142	176:0	25 [14 - 62]	Thailand	Randomized, open-label study of quinine-containing combination treatment that includes a quinine monotherapy arm
Mueller <i>et al.</i> , 2004 (Congo)	132/98	N/A	N/A	S. Kivu Province of Congo	Randomized, open-label study of Artemisia tea vs. quinine
Ache <i>et al.</i> , 2002 (Venezuela)	165/165	121/44	38.5 [N/A]	Venezuela	Randomized, open-label study of anti-malarial drug monotherapy that includes quinine monotherapy
Rahman <i>et al.</i> , 2001 (Bangladesh)	425 / 413	380/33	26 [15 - 60]	Bangladesh	Randomized, open-label study of quinine-containing combination treatment that includes a quinine monotherapy arm
Pukrittayakamee <i>et al.</i> , 2000 (Thailand)	204 / 161	204:0	26 [15 - 64]	Thailand	Randomized, open-label study of quinine-containing combination treatment that includes a quinine monotherapy arm
McGrandy <i>et al.</i> , 2000 (Thailand)	115 / 108	0/115	24.5 [15 - 37]	Thailand	Randomized, open-label study of quinine monotherapy vs. mefloquine + artesunate in pregnant women
de Vries <i>et al.</i> , 2000 (Vietnam)	268 / 221 ¹	216/52	26 [7 - 64]	Vietnam	Randomized, open-label study of quinine-containing combination treatment that includes a quinine monotherapy arm
Bich <i>et al.</i> , 1998 (Vietnam)	157 ² / 118 ³	128/29 ⁴	26 [9 - 66] ⁴	Southern Vietnam	Randomized, open-label study of quinine-containing combination treatment that includes a quinine monotherapy arm
Metzger <i>et al.</i> , 1995 (Gabon)	120/108	57/51 ⁴	33 [15 - 70]	Western Africa	Randomized, open-label study of quinine-containing combination treatment that includes a quinine monotherapy arm
Seegal <i>et al.</i> , 1974 (Thailand)	51/47	51:0	23 [15 - 53]	Thailand	Randomized, open-label comparison of quinine and WR 33063
TOTALS	1833 / 1601	1562/324 (10 studies)	24.5 [7 - 70]		

*Entry criteria (actual values not provided)

¹Of the 268 patients enrolled, 5 were not evaluable (early dropouts), 5 were lost before Day 7 after initial recovery and parasitic clearance, and 37 were lost between Day 7 and 28

²Data analysis comprised 157 cases (161 patients enrolled; however, four cases were *P. vivax* infection)

³Of the 157 patients enrolled, 6 were not evaluable (early dropouts), 6 were lost before Day 7 after initial recovery and parasitic clearance, and 27 were lost between Day 7 and 28

⁴Demographic data provided only for patients completing follow-up

Medical Officer Comments: Only one of these studies had blinded treatment arms (Watt, *et al.*, 1988), and this was a small study which did not have a 28-day endpoint for evaluation of efficacy. Note also that pediatric patients are included in many of these studies; however, efficacy and safety data were not provided separately for adults and children in any of the publications.

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The published, randomized, controlled studies submitted for evaluation of quinine combination therapy are shown in the following table. Six of these studies are also listed in the table above because a quinine monotherapy comparator was used.

Table 8: Randomized, controlled Clinical Trials of Oral Quinine Combination Therapy for Treatment of Uncomplicated Malaria (Applicant's Table 3.73, NDA 21-799 Summary)

Author, year [Country]	No. Patients Enrolled / Completed	Sex M/F	Mean or Median Age [range] (years)	Malaria Endemic Area	Design
RANDOMIZED, BLINDED STUDY (N=1)					
<u>Duarte et al., 1996</u> (Brazil)	176 / 167	145 / 31	31 [14 - 70]	Brazilian Amazon	Randomized, triple-blind ¹ comparison of Q + TCN and ART + TCN
RANDOMIZED, OPEN-LABEL STUDIES (N=15)					
<u>Pukrittayakamee et al., 2004</u> (Thailand)*	176 / 142	176 / 0	25 [14 - 62**]	Thailand	Randomized, open-label comparison of Q + TCN or PQ vs. PQ + ART and Q monotherapy
<u>Rahman et al., 2001</u> (Bangladesh)*	425 / 413	380 / 33	26 [15 - 60]	Bangladesh	Randomized, open-label comparison of Q + S/P vs. CQ + M or Q monotherapy
<u>Pukrittayakamee et al., 2000</u> (Thailand)*	204 / 161	204 / 0	26 [15 - 64**]	Thailand	Randomized, open-label comparison of Q + TCN or CL or Q monotherapy
<u>de Vries et al., 2000</u> (Vietnam)*	268 / 221	216 / 52	26 [7 - 64]	Vietnam	Randomized, open-label study of Q + ART vs. quinine monotherapy
<u>Fumaladda et al., 1998</u> (Thailand)	137 / 114	120 / 17	31 [15 - 60**]	Thailand	Randomized, open-label study of Q + TCN
<u>Salcedo et al., 1997</u> (Brazil)	42 / 26	35 / 7	31.7 [8 - 64]	Eastern Amazon Region	Randomized, open-label comparison of Q + T vs. A + T, vs. M ⁶
<u>de Alencar et al., 1997</u> (Brazil)	175 / 154	154 / 0	29 [18 - 65**]	Brazilian Amazon region	Randomized, open-label comparison of Q + TCN vs. AT/P
<u>Bunnaz et al., 1996</u> (Thailand)	90 / 86	90 / 0	24 [16 - 54]	Thailand	Randomized, open-label study of Q + TCN
<u>Vannanonta et al., 1996</u> (Thailand)	50 / 36	50 / 0	25 [14 - 51]	Thailand	Randomized, open-label comparison of Q + T vs. Q + CQ
<u>Bich et al., 1996</u> (Vietnam)*	161 / 157	128 / 29 ¹	26 [9 - 66]	Southern Vietnam	Randomized, open-label comparison of Q + ART, DOX + ART, and Q monotherapy
<u>Metzger et al., 1995</u> (Gabon)*	120 / 108	57 / 51 ³	32 [15 - 71]	Western Africa	Randomized, open-label comparison of Q + CL, Q + DOX, and Q monotherapy
<u>Loareesuwan et al., 1994</u> (Thailand)	102 / 93	75 / 27	29 [16 - 67]	Thailand	Randomized, open-label comparison of Q + TCN vs. M + TCN
<u>Karbwane et al., 1994</u> (Thailand)	64 / 60	64 / 0	24 [15 - 35]	Thailand	Randomized, open-label comparison of Q + T vs. A
<u>Kremsner et al., 1988</u> (Brazil)	115 / 95	74 / 20 ⁵	15 [14 - >40]	Amazon region	Randomized, open-label comparison of AM vs. Q + SP vs. Q + C

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Table 7 (continued): Randomized, controlled Clinical Trials of Oral Quinine Combination Therapy for Treatment of Uncomplicated Malaria (Applicant's Table 3.73, NDA 21-799 Summary)

Author, year [Country]	No. Patients Enrolled / Completed	Sex M/F	Mean or Median Age [range] (years)	Malaria Endemic Area	Design
da Souza <i>et al.</i> , 1995 (Brazil)	100 / 99	100 / 0	NP [18 - 55**]	Paragominas area of Brazil	Randomized, open-label comparison of Q + S/P vs. M
TOTALS	Enrolled: 2405 Completed: 2132	2068 / 267 (Enrolled, 13 Studies; Completed 3 Studies)	26.7 [9 - 71]		

NP=not provided; Q=quinine; TCN=tetracycline; ART= artemisinin; PQ=primaquine; CL=clindamycin; S/P= sulfadoxine/pyrimethamine; M=mefloquine; AT/P=atovaquone/primaquine; DOX=doxycycline; CQ=chloroquine; AM=amodiaquine

*Previously discussed in Section 3.9.2.1.1, Quinine Monotherapy

**Entry criteria

¹Breakdown provided only for population completing follow-up

²Western Africa

³Patients, observers (physicians and laboratory technicians), and data analysts were blinded

⁴Translated into English from original publication

⁵Breakdown provided only for population completing follow-up; additionally the publication table of demographics is missing one patient's gender

⁶This study included both intravenous and oral artesunate and quinine dosing regimens using the same dose/duration. Efficacy parameters were grouped by medication, regardless of the route of administration.

Medical Officer Comments: Note that only one of these studies was blinded to treatment medication (Duarte, *et al.*, 1996). Note also that pediatric patients are included in many of these studies; however, efficacy and safety data were not provided separately for adults and children in any of the publications.

Reviews of the published literature by the Medical Officer and Statistical Reviewer located additional randomized controlled studies which were reviewed for this NDA. One of these was a pediatric study, and although a pediatric indication for quinine sulfate was not requested with this NDA, this was a randomized, controlled study which evaluated quinine in combination with antimicrobial drugs, and was useful in comparing the efficacy of quinine monotherapy with combination therapy. An additional study was provided by the applicant 17 June, 2005, in response to the Division's request for further information regarding the efficacy of quinine combination therapy. These pediatric studies are listed in the following table.

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Table 9: Additional Randomized, Controlled Studies reviewed for Evaluation of Oral Quinine Efficacy in Treatment of uncomplicated *P. Falciparum* Malaria (Pediatric Studies)

Author, year (Country)	No. Patients Enrolled/Completed	Gender M/F	Age [range] (years)	Malaria Endemic Area	Design
Kremsner, et al., 1994 (Gabon)	144/130	79/51*	[4-15]	Gabon	Randomized, open-label, active-controlled Q vs. QC vs. CQ vs CQC
Ramharter, et al., 2005 (Gabon)	100/94	53/47	[3-12]	Gabon	Randomized, open-label, active-controlled QC vs. AC

*data provided only on patients who completed study

Q= quinine; QC= quinine + clindamycin; CQ= chloroquinine; CQC= chloroquinine + clindamycin; AC= artesunate +clindamycin

Additionally, two other randomized, controlled trials were identified from a literature search. These were studies which evaluated efficacy of quinine monotherapy or combination therapy for treatment of *P. falciparum* malaria in pregnant women. These studies were also reviewed for this application because the applicant only submitted one study in pregnant women. Aside from efficacy data, these studies also provided additional safety data on the use of quinine in pregnancy.

Table 10: Additional Randomized, Controlled Studies used for Evaluation of Oral Quinine safety and efficacy in Treatment of uncomplicated *P. Falciparum* Malaria (Studies in Pregnant Women)

Author, year (Country)	No. Patients Enrolled/Completed	Gender M/F	Age (years)	Malaria Endemic Area	Design
Bounyasong, (2001)	60/57	0/60	Mean 26.5	Thailand	Randomized, open-label, active-controlled Q vs. A-M
McGready, et al., 2001	131/129	0/131	Range 15-41	Thailand	Randomized, open-label, active-controlled Q7C7 vs A7

A-M= artesunate + mefloquine; Q= quinine; Q7C7= 7 days quinine + 7 days clindamycin; A7= 7 days artesunate

The applicant also provided 14 randomized studies for evaluation of efficacy and safety of parenteral quinine for treatment of severe malaria. These were considered supportive data, and were reviewed briefly for efficacy, and in more detail for quinine safety for this review. The following table lists the studies of parenteral quinine use for treatment of severe malaria.

Table 11: Published Randomized, Controlled Clinical Trials of Quinine Parenteral Therapy for Treatment of Severe *P. falciparum* Malaria (Applicant's Table 3.69 NDA 21-799 Summary)

Author, year (Country)	No. Patients Enrolled	Demographics			Design
		Sex M/F	Mean or Median Age [range] (years)	Malaria Endemic Area	
RANDOMIZED, DOUBLE-BLIND STUDIES					
INTRAVENOUS QUININE (N=1)					
<u>Singh et al., 2000</u> (India)	52	33/19	NR [15 - >60]	India	Randomized, double-blind comparison of IM A and IV Q
INTRAMUSCULAR QUININE (N=1)					
<u>Tran et al., 1996</u> (Vietnam)	561	425/135	30 [15 - 79]	Vietnam	Randomized, double-blind comparison of IM A and IM Q; Q followed by a single dose of SP
RANDOMIZED, OPEN-LABEL STUDIES					
INTRAVENOUS QUININE (N=11)					
<u>Newton et al., 2003</u> (Thailand)	113	79/34	25 ± NR [15 - 66]	Western Thailand	Randomized, open-label comparison of IV A and IV Q with the addition of M, T, or D
<u>Satti et al., 2002</u> (Sudan)	77	NR	NR [NR] ²	Sudan	Randomized, open-label comparison of IV A and IV Q
<u>Adam et al., 2002</u> (Sudan)	41	20/21	3.8 ± NR [NR]	Eastern Sudan	Randomized, open-label comparison of IM A and IV Q
<u>Faiz et al., 2001</u> (Bangladesh)	105	78/27	29 ± NR [14 - 50]	Bangladesh	Randomized, open-label comparison of IM A and IV Q
<u>Thuma et al., 2000</u> (Zambia)	92	47/45	3.6 ± NR [NR]	Zambia	Randomized, open-label comparison of IM A and IV Q
<u>Moyou-Somo et al., 2001</u> (Cameroon)	106	49/43 ³	3.3 ± NR [NR]	Cameroon	Randomized, open-label comparison of IM A and IV Q
<u>Taylor et al., 1998</u> (Malawi)	183	39/42	3.1 ± NR [NR]	Blantyre, Malawi	Randomized, open-label comparison of IM A and IV Q followed by a single dose of SP
<u>Olumese et al., 1999</u> (Nigeria)	103	NR	3.1 ± 1.7 [0.9 - 5]	Ibadan, Nigeria	Randomized, open-label comparison of IM A and IV Q
<u>Murphy et al., 1996</u> (Kenya)	160	80/80	2.3 ± NR [0.4 - 12]	Kenya	Randomized, open-label comparison of IM A and IV Q followed by a single dose of SP
<u>Karbwang et al., 1995</u> (Thailand)	102	92/10	26.5 ± NR [15 - 55]	Thailand	Randomized, open-label comparison of IM A and IV Q
<u>Karbwang et al., 1992</u> (Thailand)	26	25/1	31 ± NR [NR] ³	Thailand	Randomized, open-label clinical trial of IM A and IV Q
INTRAMUSCULAR QUININE (N=1)					
<u>Van Hensbroek et al., 1996</u> (Gambia)	288	143/145	3.8 ± 1.8 [NR]	Gambia, West Africa	Randomized, open-label clinical trial of IM artesether and IM quinine

Q=quinine; A=sulfamethoxazole or artesether; SP=sulfadoxine/pyrimethamine; M=mefloquine; T=tetracycline;

D=doxycycline

¹Demographics provided for only those 102 patients included in the efficacy analysis

²Children < 10 years

³Adults and children older than 15 years

Medical Officer Comments: A number of these studies enrolled only pediatric patients (Satti, et al., 2002; Adam, et al., 2002; Thuma, et al., 2000; Moyou-Somo, et al., 2001;

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Olumese et al., 1999; Murphy, et al., 1996; and van Hensbroek, et al., 1996), and most included 14 and 15 year-old patients in addition to adults.

4.3 Review Strategy

The 21 randomized, controlled studies submitted by the applicant which evaluated oral quinine mono- and combination therapy for treatment of uncomplicated *P. falciparum* malaria were considered the primary studies for determination of efficacy. Individual study reviews are included in Appendix, section 10.1; and conclusions from the studies regarding quinine efficacy are summarized in the Integrated Review of Efficacy (IRE) in this review. Among these studies, several were not included when determining overall ranges of quinine efficacy because of problems with studies such as randomization methods, combining treatment groups for analysis, and other mainly statistical issues. These are issues are discussed in the IRE of this review, and by Ms. LaRee Tracy, the Statistical Reviewer, in the Statistical review.

For the safety evaluation, safety data taken from the individual studies was summarized for each study (see Appendix, section 10. 1), and where feasible, adverse event data was pooled from similar studies to estimate the incidence of adverse events in the Integrated Review of Safety (IRS) of this review. Safety data from the randomized studies of oral quinine monotherapy and combination therapy, from the non-randomized studies of oral quinine monotherapy and combination therapy were used for the safety evaluation in addition to the randomized studies of parenteral quinine for severe malaria. Case reports provided by the applicant with the original NDA submission and with the 120-day safety update, as well as from literature searches were included in this safety review by organ system. Quinine product labels from 11 foreign countries provided by the applicant were also reviewed for additional safety information, which is included in this review.

Additionally, the postmarketing data from the FDA and WHO databases submitted by the applicant was reviewed for quinine safety. The Office of Drug Safety (ODS) was consulted to review the postmarketing safety data for quinine, particularly with respect serious adverse events to cardiac (particularly with events of hypotension, QT prolongation, torsades de pointes, or other cardiac arrhythmias) hematological events, hypersensitivity and skin reactions, renal failure, vision disorders (particularly blindness, optic nerve damage), hearing loss or deafness, and teratogenicity.

The Pregnancy and Lactation team was also consulted regarding the appropriate pregnancy labeling for quinine sulfate, because the older literature, mainly on quinine overdose toxicity reported congenital abnormalities in infants born to mothers who had ingested quinine. Recommendations from this team were incorporated into the final labeling proposal.

DDMACand DMETS were also consulted regarding the final product labeling for quinine sulfate. Recommendations from these consultants and recommendation were considered in the final labeling proposal.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted for audit of the study site for the bioequivalence study RA3-590, conducted at _____

_____. Following inspection, the DSI recommended that the data from this study could be considered for Agency review. No additional inspections were performed.

Because this was a 505 (b) 2 application, and the data for safety and efficacy review were all derived from the published literature, there were no case report forms of patient data to review, with the exception of electrocardiographic data and adverse event information obtained from case report forms from the applicant's bioequivalence study. Clinical Studies were reviewed by the medical officer individually for data quality (see individual study reports in Appendix, section 10.1, and a summary of study quality in the IRE, section 6 of this review).

4.5 Compliance with Good Clinical Practices

Most of the studies reviewed noted that informed consent was obtained and that studies were conducted in accordance with good ethical standards. However, because this review was based on the published literature, only minimal information could be obtained regarding good clinical practices. The applicant stated that the bioequivalence studies sponsored by Mutual Pharmaceutical Company, Inc. were conducted in full compliance with applicable local, state, and federal laws and regulations and in accordance with good clinical practice.

4.6 Financial Disclosures

The applicant disclosed the financial arrangements with the clinical investigators for the bioequivalence studies, RA3-085 and RO4-00376, and these do not raise any concerns about the integrity of data from these studies. Because the clinical studies were all based on published studies in the literature, financial disclosures are not applicable.

5 CLINICAL PHARMACOLOGY

For full details regarding the clinical pharmacology of quinine sulfate, see Clinical Pharmacology review by Dr. Gerlie Gieser. A brief summary of the clinical pharmacology of quinine sulfate as it relates to the clinical review is provided in this section.

5.1 Pharmacokinetics

Bioequivalence of the applicant's product, quinine sulfate oral 324 mg capsules to the Government Pharmaceutical Organization, Bangkok Metropolis, Thailand's formulation of quinine sulfate, 300 mg tablets was demonstrated in study RA3-085. In the dose proportionality study, R04-0376, no significant difference was noted in dose-normalized AUC between a 324 mg and a 648 mg single oral dose of Mutual Pharmaceutical's quinine sulfate capsules, although there was a less than proportional increase in peak quinine concentration at the higher dose.

Pharmacokinetic data on quinine sulfate was obtained from the literature by the applicant for this NDA. Quinine is about 75-80% absorbed following oral administration, reaching peak plasma concentrations in approximately 2 to 4 hours. In the dose-proportionality study sponsored by Mutual Pharmaceutical Company, when (2) 324 mg capsules of quinine sulfate were administered, the mean peak quinine level was 3.2 µg/mL, achieved approximately 2.8 hours post-dose. Administration with a high fat meal did not result in a significant change in oral availability of quinine from a single oral 324 mg dose of the applicant's capsule.

Quinine is distributed widely, with reported volume of distribution of 1.4 to 3.8 L/kg in healthy adults, with decreased values for this parameter in patients with severe malaria. Quinine does not concentrate in erythrocytes, and does not freely cross the blood-brain barrier. The mean cerebrospinal fluid to plasma ratio reported for quinine is 0.7. Quinine crosses the placenta, with mean cord plasma to maternal plasma concentration ratio of 0.32. The drug is also found in breast milk, with the mean milk-plasma concentration ratio of 0.31.

Quinine is eliminated almost exclusively by hepatic metabolism via the cytochrome P450 system, mainly by the isozyme, CYP 3A4, but also by CYP 2C19, to a lesser extent. The major metabolite, 3-hydroxyquinine, also has some antiparasitic activity. The elimination half life of quinine is 10-11 hours, with a range of 7 to 13 hours. Quinine exhibits linear dose-related pharmacokinetics in the range of 250 to 1000 mg. Only about 20% of quinine is excreted unchanged in urine.

The pharmacokinetic properties of quinine differ considerably in patients with malaria in comparison to healthy subjects. The systemic clearance and volume of distribution are reduced in proportion to disease severity. However, protein binding of quinine is increased in patients with malaria, due to increased levels of α -1-glycoprotein, resulting in lower unbound quinine fractions. Thus, although patients with acute malaria may have higher total levels of plasma quinine than healthy subjects, plasma concentrations usually decrease in the recovery phase of the infection. Quinine clearance is also reduced in elderly patients, and in those with hepatic or renal impairment. No alteration in dosing is required for elderly patients, or patients with mild to moderate renal or hepatic dysfunction; however dose adjustment is necessary in patients with severe chronic renal failure. The pharmacokinetics of quinine has not been studied in patients with severe hepatic dysfunction.

A number of drug interactions have been reported with quinine. These are discussed in detail in Dr. Gieser's review. In brief, quinine is metabolized mainly by CYP3A4. Drugs that affect the activity of this cytochrome P450 enzyme may alter plasma quinine concentrations. Drugs that inhibit CYP3A4, such as ketoconazole, troleandomycin, erythromycin, and others, increase quinine exposure; while drugs that induce CYP3A4, such as rifampin, decrease quinine exposure. Furthermore, *in vitro* and *in vivo* evidence collectively suggest that quinine has the potential to influence the metabolism of other drugs that are substrates of CYP3A4 and CYP2D6. For example, quinine was shown to inhibit the metabolism of the CYP3A4 substrates, carbamazepine and Phenobarbital. Increased levels of astemizole, a CYP3A4 substrate were reported in a patient on chronic astemizole therapy, who experienced torsades de pointes after receiving oral quinine for treatment of nocturnal leg cramps.

Quinine inhibits the isozyme, CYP2D6, which is involved in the metabolism of a number of drugs. One study showed decreased metabolism of desipramine in patients pre-treated with quinine, especially in rapid metabolizers. Formal drug interaction studies have not been performed with most of the other drugs metabolized by the CYP2D6 pathway, but result in increased levels of quinine or the other drug are possible.

Other important drug interactions with quinine include decreased quinine absorption with antacids, and increased quinine exposure with cimetidine. Plasma quinine levels are increased approximately 2-fold when used concomitantly with tetracycline for the treatment of malaria, although the mechanism of this interaction is not clear. In one study performed in patients with acute malaria 8 patients were treated with quinine alone and 8 were treated with quinine plus tetracycline (Karbwang, et al., 1991). Trough plasma quinine concentrations were above the MIC (10 micrograms/mL) throughout the 7 day treatment period in the group which received combination therapy, but not in the quinine monotherapy group. Recrudescence rates were higher in the monotherapy group than in those who received combination therapy (2/8, 25% vs. 0%, respectively). Adverse events were not reported in this study.

Medical Officer Comments: The drug interaction between quinine and tetracycline resulting in increased quinine plasma concentrations could explain higher cure rates with the combination of quinine plus tetracycline in comparison to quinine alone, as reported in a number of clinical studies (Pukrittayakamee, et al., 2000) and Pukrittayakamee, et al, 2004). However, whether this combination results in increased quinine toxicity has not been systematically evaluated.

Digoxin levels may be increased with concomitant administration of quinine. In a study of 4 healthy subjects who received both digoxin and quinine, the mean steady state AUC of digoxin was increased by 33%, and steady state biliary clearance of digoxin was increased by 35%.

Medical Officer Comments: We have proposed a statement in the label recommending the monitoring of digoxin levels if quinine and digoxin are used concomitantly.

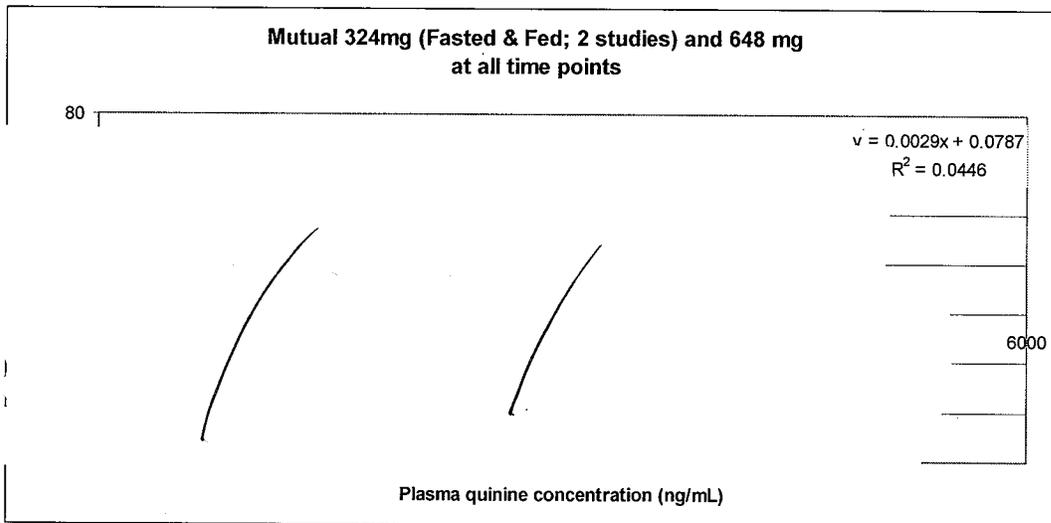
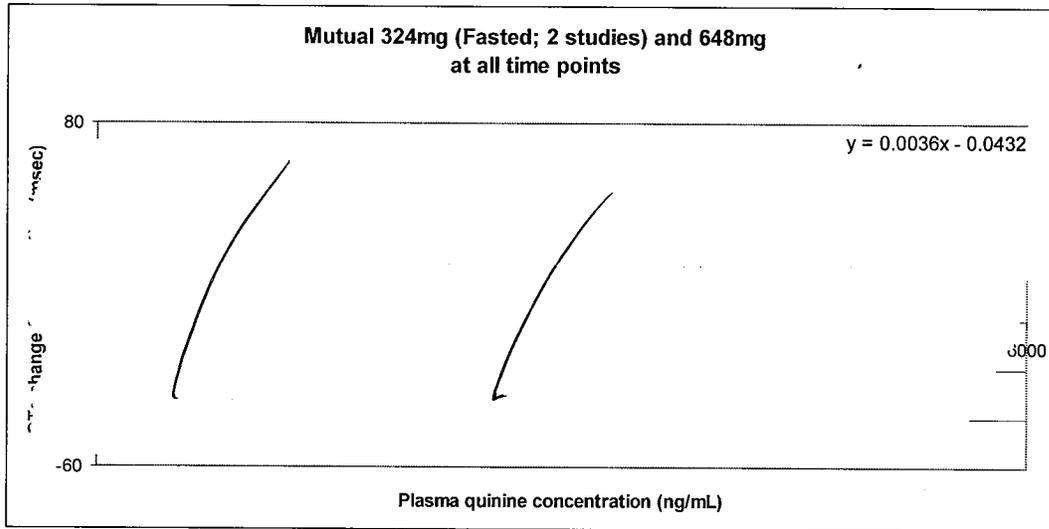
5.2 Pharmacodynamics

QT prolongation in Mutual Pharmaceutical Company's Bioequivalence Studies

Quinine, like its diastereomer, quinidine has antiarrhythmic activity, and similarly prolongs conduction time and increases the QTc interval, albeit to a lesser extent than quinidine. The electrocardiographic data from the two pharmacokinetic studies provided by the applicant, have been reviewed in detailed by Dr. Gerlie Gieser, and are further discussed in the IRS, section 7 of this review. In brief, there was mild QTc prolongation in healthy subjects after single-dose oral 324 mg and 648 mg quinine sulfate administration. A temporal relationship was observed between mean plasma quinine concentrations and mean QTc change from baseline. Maximum QTc change occurred at around the Tmax of plasma quinine (2-4 hours post-dose). When linear regression analysis was used to determine if there was a relationship between QTc change from baseline and plasma quinine concentration, a weak positive correlation was found in females > males. These linear regression analyses, performed by the the Clinical Pharmacology Reviewer,

Dr. Gieser, are shown in Figures 3 and 4 below. QT prolongation with quinine has also been documented in the literature, as discussed in the IRS, section 7.

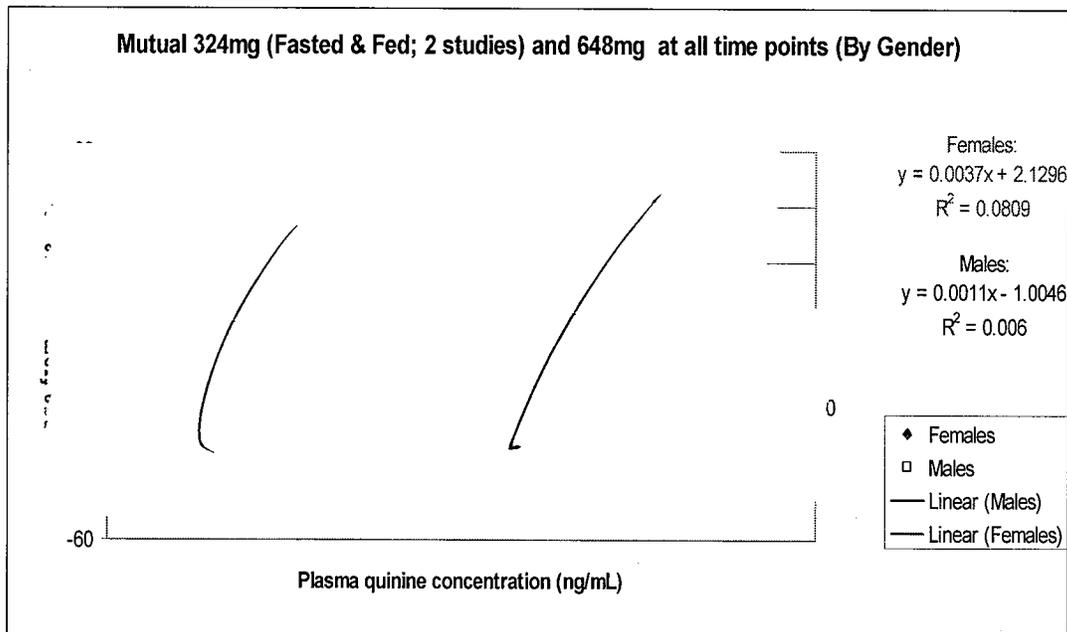
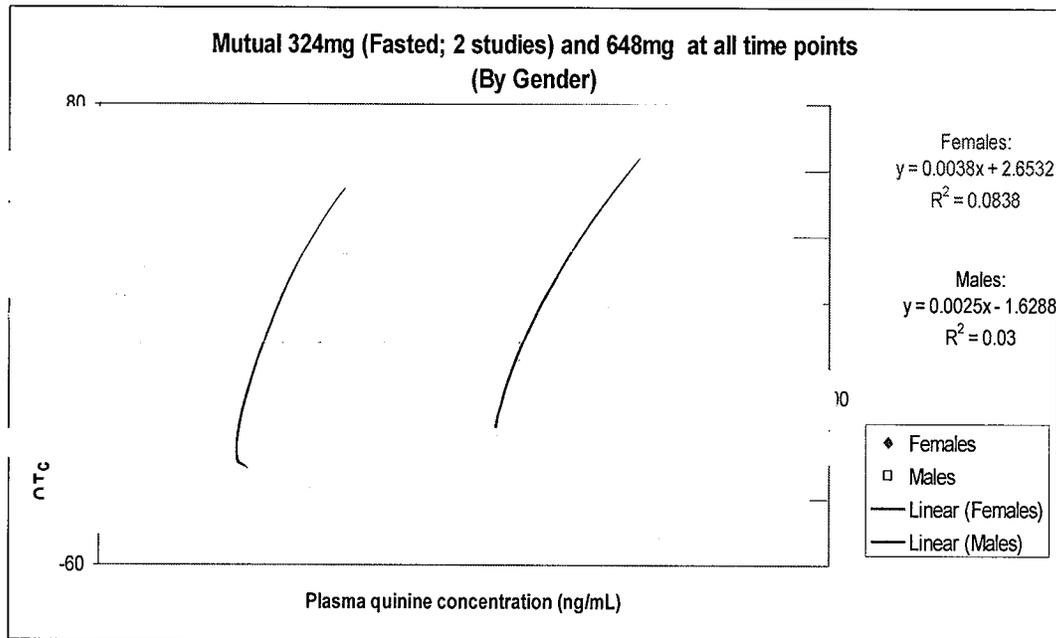
Figure 3. Linear Regression Analysis of QTc Change from Baseline as a function of Plasma Quinine Concentration (from Dr. Gerlie Gieser's Clinical Pharmacology Review)



Medical Officer Comments: The correlation coefficients R^2 between plasma quinine and QTc change from baseline were not high, due to intersubject variability in QTc values. However, for these studies there was a slight positive relationship between plasma quinine concentration and QTc change from baseline, regardless of whether subject was fasted or fed. These studies were performed in healthy subjects who received a single

dose of quinine and may not reflect the extent of QT prolongation in patients with malaria treated with quinine at clinically relevant doses.

Figure 4. Linear Regression Analysis of QTc Change from Baseline as a function of Plasma Quinine Concentration Stratified by Gender (from Dr. Gerlie Gieser's Clinical Pharmacology Review)



***Medical Officer Comments:** This analysis showed that the R^2 (correlation coefficient) was higher when the data were stratified by gender, and was higher for females than males. It should be noted that the mean age of female subjects in the two studies was somewhat higher in females than males and the mean body weight and body surface areas were slightly higher in female than male subjects. However, female gender has been associated with an increased risk of prolonged QT interval.*

Potential Interaction of Quinine with Mefloquine, Halofantrine, and other drugs known to prolong QTc Intervals

In vitro studies with human liver microsomes showed that quinine has the potential to inhibit the metabolism of mefloquine, and clinical studies have demonstrated increased QTc intervals in patients who received concomitant quinine and mefloquine (Na-Bangchang, et al., 1999). Prolonged QTc intervals may increase the risk of torsades de pointes or other ventricular arrhythmias such as ventricular tachycardia and fibrillation. An *in vitro* study with human liver microsomes demonstrated that quinine and quinidine inhibited metabolism of halofantrine via cytochrome P450 3A4 (Baune, et al 1999). Thus quinine could potentiate the cardiotoxicity of the antimalarial drug, halofantrine. No studies were found which described potential pharmacodynamic or pharmacokinetic interactions of quinine with other antimalarial drugs.

Case reports in the literature and in the postmarketing database have documented torsades de pointe with quinine used concomitantly with astemizole an antihistamine known to prolong the QT interval, and no longer marketed in the U.S. Fatal torsades de pointes was described in an elderly female who received erythromycin in addition to quinine for nocturnal leg cramps, in an AERS postmarketing adverse event report. This case however, was confounded by other concomitant medications, specifically, dopamine, which may be arrhythmogenic. Additionally, there has been at least one postmarketing adverse event report of ventricular tachycardia in a patient who received cisapride (currently available in the U.S. only under limited circumstances). Although data is limited, the concomitant use of quinine with other drugs known to cause QTc prolongation could result in significant QTc prolongation and potentially fatal cardiac dysrhythmias.

***Medical Officer Comments:** For the final product labeling we have proposed a Warning regarding use of mefloquine or halofantrine with quinine and regarding use of other drugs known to cause QT prolongation, including Class I and III antiarrhythmic agents, as well as with astemizole, terfenadine, cisapride, and other drugs associated with QT prolongation. The proposed Warning also cautions against quinine sulfate use in patients with hypokalemia _____, and other cardiac conditions which may increase the risk of torsades de pointes. We have also proposed a Contraindication regarding the use of quinine in patients with known QT prolongation.*

Potential Interaction with Neuromuscular blocking agents

Because quinine has effects on skeletal muscle, i.e. neuromuscular blocking activity, it could potentially aggravate muscle weakness in patients with myasthenia gravis or similar conditions, and it could potentiate the activity of neuromuscular blocking agents such as pancuronium, succinylcholine, and tubocurarine.

Medical Officer Comments: In the final product labeling, we have proposed that quinine use is contraindicated in patients with myasthenia gravis. Additionally, the potential pharmacodynamic interaction of quinine with neuromuscular blocking agents will be discussed under Drug Interactions.

Potential Interaction with Warfarin

Quinine may inhibit hepatic enzymes in the vitamin K dependent coagulation pathway, and could potentially enhance activity of warfarin or similar anticoagulants. However, there is little supportive data in the literature regarding this potential interaction.

5.3 Exposure-Response Relationships

As reviewed by White (1996), the therapeutic concentration range of quinine in patients with malaria is probably 8 to 20 mg/L for total plasma quinine, or 0.8 to 2 mg/L for free or unbound quinine. The duration of quinine plasma concentrations above a certain level may also be important for clearance of parasitemia and cure. One study in Thailand (Pukritayakamee, et al., 2003) showed that *P. falciparum* recrudescence rates were significantly higher in patients who received a 7-day course of quinine plus rifampin than in those who received a 7-day course of quinine alone. Rifampin is known to increase quinine metabolism, and decrease plasma quinine levels. Based on the data provided in this study, The Clinical Pharmacology Reviewer, Dr. Gerlie Gieser determined that patients who maintained total quinine concentrations > 7.5 mg/L for 7 days did not experience recrudescence.

As discussed in more detail by Dr. Geiser, Clinical Pharmacology Reviewer, pharmacokinetic modeling demonstrated that the target total plasma concentration of quinine, approximately 8 mg/L could be reached in healthy subjects within 3 days of treatment with 648 mg quinine sulfate every 8 hours. Higher steady state plasma concentrations may be achieved in patients with malaria, depending on disease severity, because of reduced plasma quinine clearance in patients with malaria, particularly during the acute phase. The estimated steady state plasma quinine concentration during the acute phase in this model was 9 to 16 mg/L; while total plasma quinine concentrations decline during recovery, due to increased clearance. With concomitant administration of tetracycline, systemic quinine levels could be increased to levels ranging from 18 to 32 mg/L in plasma.

Medical Officer Comments: Quinine toxicity has been reported at plasma levels ≥ 10 mg/L (blindness) and > 16 mg/L (cardiotoxicity), as further reviewed in the ISS. Therefore, the therapeutic index of quinine is quite narrow, and may be exceeded in some patients who received the proposed dose of 648 mg 3 times daily, depending on disease severity. Patients receiving oral quinine sulfate for uncomplicated malaria should be monitored routinely for signs of quinine toxicity.

In an early clinical study in which acute *P. falciparum* malaria was induced in human subjects (Earle, et al., 1948), the importance of plasma quinine concentration and duration of therapy was demonstrated. In 15 subjects treated for 4 days with a quinine dose which resulted in mean

plasma concentrations ranging from 2.1 to 10.4 mg/L, only 1 patient was cured at 21 days, 13 patients had recrudescence within that time frame, and 1 patient did not improve with treatment. When the duration of therapy was extended to 6 days in 13 patients, those with plasma quinine concentrations of 5.6 mg/L or higher (7/7), were cured, while 5/6 of those with plasma quinine concentrations between 2.4 and 5.4 mg/L had recrudescence within 21 days. Further investigation demonstrated that 5/6 patients treated for 8 days who had plasma quinine concentrations between 3.2 and 7.2 mg/L were considered cured. The authors also noted that one patient in the study died of cerebral malaria despite treatment, although the quinine dose and duration of therapy that patient received was not specified.

Medical Officer Comments: This study would not be considered ethical by today's standards, but does contribute significantly to our understanding of the exposure-response relationship of quinine for treatment of malaria. Clearly, both effective plasma concentration and duration of quinine therapy are important for cure of P. falciparum.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for quinine sulfate is treatment of uncomplicated *P. falciparum* malaria.

Medical Officer Comment: We have proposed the following statement for the INDICATIONS and USAGE section of the final product labeling: "Quinine sulfate is indicated for only for treatment of uncomplicated P. falciparum malaria. Quinine sulfate has been shown to be effective in geographical regions where resistance to chloroquine has been documented (See Clinical Studies). Quinine sulfate oral capsules are not approved for patients with severe or complicated P. falciparum malaria."

Additionally, because of the extensive off-label use of quinine in this country for treatment or prevention of nocturnal leg cramps, the following statements were proposed for this section:

"Quinine sulfate oral capsules are not approved for prevention of malaria.

Quinine sulfate oral capsules are not approved for the treatment or prevention of nocturnal leg cramps."

Medical Officer Comments: The Agency's 1994 final rule, described in 59 FR 432, prohibited marketing of quinine for treatment or prevention of leg cramps, because efficacy and safety of quinine for this indication has not been shown.

6.1.1 Methods

The randomized, controlled studies of oral quinine monotherapy and combination therapy submitted by the applicant in support of this NDA were reviewed for efficacy. Among those studies, those considered primary (pivotal) studies for this review were identified by the Medical

Officer and Statistical Reviewer. Additional randomized, controlled studies obtained by a literature search performed by the FDA reviewers after the original NDA was submitted, were also included in the review of efficacy. All randomized controlled studies were reviewed individually (see Appendix, section 10.1). The clinical studies reviewed for efficacy are tabulated section 4.2 above. The following tables show those studies identified as primary (pivotal) for this review, as well as those studies not included in overall determination of efficacy because of problems with the study such as method of randomization, or use of a different endpoint.

Table 12: Randomized Controlled Trials of Quinine Monotherapy

Studies Submitted by Applicant:	Study Included in Comparison of Efficacy across Studies	Reasons for not including study in Comparison of Efficacy across Studies
Watt, et al., 1988	No	Different timing of endpoint
Pukrittayakamee, et al., 2004	Yes	NA
Mueller, et al., 2004	Yes	NA
Ache, et al, 2002	Yes- primary study	NA
Rahman, et al., 2001	No	Changed treatment arm in middle of study
Pukrittayakamee, et al., 2000	Yes-primary study	NA
McGready, et al., 2000	No	Different timing of endpoint
De Vries, et al., 2000	No	Continuation of previous study (Bich, et al., 1996); and change of treatment arm
Bich, et al., 1996	Yes	NA
Metzger, et al., 1995	No	Significant difference in dosing and duration of quinine therapy
Segal, et al., 1974	No	Early study in Thailand, prior to significant quinine resistance