

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-799

SUMMARY REVIEW

Division Director Review

APPLICANT: Mutual Pharmaceutical Company

DRUG: Quinine Sulfate (no trade name proposed)

NDA/Indication: NDA 21-799 / Treatment of uncomplicated *Plasmodium falciparum* malaria

DATE OF SUBMISSION: October 13, 2004

PDUFA GOAL DATE: August 14, 2005

FORMULATION: Capsules, 324 mg (269 mg quinine free base)

RECOMMENDATIONS:

Approval:

This 505(b)(2) application for quinine sulfate for the indication, "treatment of uncomplicated *Plasmodium falciparum* malaria," should be approved. The dosing regimen is 648 mg (two 324 mg capsules) given q8h for 7 days.

In addition, a regimen consisting of includes quinine sulfate for 7 days and concurrent tetracycline 250 mg q6h also for 7 days was effective and this information is reflected in the labeling.

Post Marketing Commitments:

1. Risk Management Plan that includes the following elements (submitted by Mutual August 11, 2005):
 - 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.
Implementation date: August 11, 2006
2. Post-marketing Surveillance for Adverse Events:
 - Provide twice-yearly analyses for 3 years post-approval 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 will be provided in conjunction with the quarterly updates of post-marketing adverse events associated with oral quinine sulfate required under 21 CFR 314.80(c)(2) and in addition to the 15-day reporting for all serious adverse events required under 21 CFR 314.80(c)(1).
Initial study report submission date: February 2006
Final report submission date: February 2009

BACKGROUND:

Both malaria and quinine have a long history. Quinine, in contrast to more recently discovered antimicrobials we have reviewed, has a lengthy and interesting history, dating back to 1638.

- Legend has it that the name *cinchona* came from the countess of Chinchon, the wife of a Peruvian viceroy, who was cured of a malarial type of fever by using the bark of the cinchona tree in 1638¹. It was supposedly introduced to European medicine in 1640 by the countess of Chinchon, even before botanists had identified and named the species of tree. Quinine bark was first advertised for sale in England in 1658, and was made official in the British Pharmacopoeia in 1677.
- Throughout the mid-1600s to mid-1800s quinine bark was the primary treatment for malaria and it evidenced remarkable results. It was also used for fever, indigestion, mouth and throat diseases, and cancer.
- In 1820 two scientists, Pelletier and Caventou, isolated an alkaloid chemical in the bark which provided the highest antimalarial effect and named it *quinine*. Once discovered, methods were developed to extract only the quinine alkaloid from the natural bark to sell as an antimalarial drug.
- Quinine sulfate was widely used, as shown in this excerpt from the *American Journal of Pharmacy*, 1887, vol 59. on a presentation made by John Flack on Pharmacy in India, November 27, 1886. “Many American preparations are used and the United States Pharmacopoeia is to be found in every drug store. American patent medicines have a very large sale, and among the non-secret preparations Parke, Davis & Co.'s Fluid Extracts and McKesson & Robbins' Capsuled Pills have become best known. The quantity of McKesson & Robbins' Quinine Capsules that are sold is marvelous. Of course this is a country of fevers and malaria, and the perfection which these capsules have reached have impressed themselves on the medical men, and the natives are among the most frequent buyers. To sell them in bottles of one hundred is of very frequent occurrence.”²
- The upheavals of the Second World War led to changes in the market which still remain in effect today. When Java was occupied by the Japanese in 1942, the Allies' supply of quinine was cut off. South American sources of cinchona trees and quinine bark were once again in demand, but new plantations were planted by the Allies in Africa as well. This dire shortage of quinine fueled research for developing and producing a synthetic version of the quinine alkaloid rather than relying on the natural bark. In 1944 scientists were able to synthesize the quinine alkaloid in the laboratory.

During World War II, drug supply was curtailed and investigation of other antimalarial products started, the US Army was instrumental in the development of some of these.

- Drugs like mepacrine and chloroquine were developed to counter quinine shortages.³ When the Japanese invaded Java in 1941, quinine supplies to most of the world stopped, so these alternatives were welcome.

Marketing of Quinine Sulfate in the United States

As shown in the excerpt cited above from the *American Journal of Pharmacy*, quinine was available/marketed in the US since before 1906 when the FD&C Act was enacted. Four NDAs were found in the FDA records, none of the NDAs was for the treatment of malaria. One possible explanation for the absence of an NDA for malaria is that quinine was already available OTC for the treatment of malaria, and no one submitted a new drug application for this use.

- NDA 206 – quinine sulfate in Modern Cold Tablets for relief of minor aches and pains
- NDA 227 – quinine sulfate, no further data available
- NDA 805 – quinine bisulphate in vaginal jelly, Feminine Hygienic Preparation
- NDA 4425 – quinine bisulfate in “private formula”, use not specified

¹ <http://www.rain-tree.com/quinine.htm>, August, 2005

² <http://www.ibiblio.org/herbmed/eclectic/journals/ajp1887/02-india-plants.html>, August, 2005

³ <http://www.chm.bris.ac.uk/motm/quinine/quininev.htm>, August, 2005

The above NDA's were submitted following the 1938 amendments because "new drugs" could not be introduced into interstate commerce unless an application was filed that included a report the new drug was safe for use. The 1962 Drug Amendments required that products be effective, and in 1968 FDA established the Drug Efficacy Study Implementation (DESI) Review with National Academy of Sciences/National Research Council on all marketed drugs.⁴

Quinine Sulfate and Nocturnal Leg Cramps

Presumably as part of the DESI process, a 1977 OTC Advisory Panel concluded that quinine sulfate should not be available OTC for leg cramps until a study showing the drug to be effective is determined, and the Agency published this in FR on November 8, 1985, p 46592.

Subsequently, a Citizen's Petition was sent in by Sydney Wolf and Private Citizen seeking that use of quinine in leg cramps be banned due to reports of death in some patients.

FDA published 59 FR 43252 on Aug. 22, 1994, creating 21 CFR 310.546 and concluding that quinine sulfate was not generally recognized as safe and effective for use in treatment and/or prevention of nocturnal leg cramps.⁵

Sec. 310.546 Drug products containing active ingredients offered over-the-counter (OTC) for the treatment and/or prevention of nocturnal leg muscle cramps.

(a) Quinine sulfate alone or in combination with vitamin E has been present in over-the-counter (OTC) drug products for the treatment and/or prevention of nocturnal leg muscle cramps, i.e., a condition of localized pain in the lower extremities usually occurring in middle life and beyond with no regular pattern concerning time or severity. There is a lack of adequate data to establish general recognition of the safety and effectiveness of quinine sulfate, vitamin E, or any other ingredients for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps. In the doses used to treat or prevent this condition, quinine sulfate has caused adverse events such as transient visual and auditory disturbances, dizziness, fever, nausea, vomiting, and diarrhea. Quinine sulfate may cause unpredictable serious and life-threatening hypersensitivity reactions requiring medical intervention and hospitalization; fatalities have been reported. The risk associated with use of quinine sulfate, in the absence of evidence of its effectiveness, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition. Based upon the adverse benefit-to-risk ratio, any drug product containing quinine or quinine sulfate cannot be considered generally recognized as safe for the treatment and/or prevention of nocturnal leg muscle cramps.

(b) Any OTC drug product that is labeled, represented, or promoted for the treatment and/or prevention of nocturnal leg muscle cramps is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter 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 act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use for the treatment and/or prevention of nocturnal leg muscle cramps is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of

⁴ A Practical Guide to Food and Drug Law and Regulations, KR Pina and WL Pines, second edition © 2002 FDLI, www.fdl.org

⁵ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>

investigational new drugs set forth in part 312 of this chapter.

(d) After February 22, 1995, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Subsequent to this Federal Register and CFR publication, FDA ordered companies to stop marketing of quinine sulfate for use in leg cramps, as summarized in the following document.

FDA Orders Stop to Marketing Of Quinine for Night Leg Cramps⁶

Less than a year after ordering a halt to the marketing of over-the-counter (OTC) quinine sulfate for night leg cramps based on its serious risks, FDA ordered a stop to the marketing of prescription quinine for this use because even under a doctor's care, its risks outweigh any possible benefits.

In January, FDA sent warning letters to 44 companies stating that it is unlawful to market their quinine sulfate products for night leg cramp relief because FDA has not approved the drug for this use. By the end of March, all major manufacturers and distributors had stopped labeling their products for this use, including Marion Merrell Dow, the manufacturer of the original and best-known quinine drug, Quinamm.

From 1969 through June 1992, FDA received 157 reports of health problems related to quinine use, including 23 that resulted in death. Nonserious problems included temporary sight and hearing disturbances, dizziness, fever, nausea, vomiting, and diarrhea. Serious problems included thrombocytopenia, a destruction of blood platelets that can lead to massive bleeding and sometimes death.

After weighing the benefits and risks of OTC quinine sulfate for night leg cramps, FDA concluded that quinine is not safe and effective for this use because:

- * No studies demonstrate that quinine is effective against night leg cramps.
- * Night leg cramps are not a threat to life or health.
- * Health risks outweigh any small potential benefits.

Based on this finding, the agency published a rule in the Aug. 22, 1994, Federal Register prohibiting OTC marketing of the drug for leg cramps.

Comment:

The reason for including this background information on quinine sulfate and leg cramps is because despite the fact that the FR notice was published in 1994 and warning letters were sent out, there continues to be extensive off label prescription of quinine for leg cramp and related conditions, as reported by ODS during their query of the IMS system. As noted earlier approximately — scripts for quinine sulfate were written within the last year.⁷ Meanwhile, there were 1278 reported cases of malaria in the US in 2003, according to CDC. [MMWR: June 3, 2005 / 54 (SS02); 25-39.] As a result, with the approval of the quinine NDA, the Division has negotiated with Mutual to include the following elements as part of the Risk Management Program.

Package insert

- *updated adverse event information*
- *statement in INDICATIONS AND USAGE that efficacy of quinine in leg cramps has not been established*
- *information in WARNINGS regarding leg cramps and adverse events*

⁶ http://www.fda.gov/fdac/departs/695_updates.html

⁷ ODS consult from Michael Evans

Patient Package insert

- *Synopsis of indications and adverse events in consumer language*

Dear Dr. letter

- *Mutual to include information on approved indication, adverse events*

Educational Program

- *Mutual to design program to educate / remind health care professionals on indications and adverse events*

However, although the FDA has a responsibility to promote and protect the public health, the practice of medicine and use of an approved drug is not within the FDA's jurisdiction; rather it is up to states and medical licensing boards to regulate the practice of medicine⁸ outside FDA-approved labeling. And while a physician may decide how to prescribe quinine sulfate, the FDA has made its position clear with the publication of the 1994 FR notice and language in 21 CFR 310.546.

Quinine Sulfate and Malaria

In 1998, another FR notice [63 FR 13528, Mar. 20, 1998] dealing with quinine sulfate was published creating section 21 CFR 310.547 regarding OTC product containing quinine for the treatment of malaria and concluded that the products cannot be safely used without the supervision of a doctor. Furthermore, quinine sulfate for use in malaria was considered a new drug and needed to go through the NDA process for approval. Mutual's submission of an NDA for their quinine sulfate is consistent with this regulation.

Sec. 310.547 Drug products containing quinine offered over-the-counter (OTC) for the treatment and/or prevention of malaria.

(a) Quinine and quinine salts have been used OTC for the treatment and/or prevention of malaria, a serious and potentially life-threatening disease. Quinine is no longer the drug of choice for the treatment and/or prevention of most types of malaria. In addition, there are serious and complicating aspects of the disease itself and some potentially serious and life-threatening risks associated with the use of quinine at doses employed for the treatment of malaria. There is a lack of adequate data to establish general recognition of the safety of quinine drug products for OTC use in the treatment and/or prevention of malaria. Therefore, quinine or quinine salts cannot be safely and effectively used for the treatment and/or prevention of malaria except under the care and supervision of a doctor.

(b) Any OTC drug product containing quinine or quinine salts 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 under section 505 of the act and part 314 of this chapter 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 act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use for the treatment and/or prevention of malaria is safe and effective for the purpose

⁸ A Practical Guide to Food and Drug Law and Regulations, KR Pina and WL Pines, second edition © 2002 FDLI, www.fdpi.org Chapter 3, page 53.

intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After April 20, 1998, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

[63 FR 13528, Mar. 20, 1998]

Comment: The wording of this FR notice/ CFR section states that quinine cannot be safely and effectively used for the treatment and/or prevention of malaria except under the care and supervision of a doctor, thus implying (as was concluded also in this review), that quinine can be used safely and effectively for the treatment of uncomplicated malaria as a prescription medication.

Availability of Quinine Sulfate:

Currently, there are a number of companies, including Mutual, that supply quinine sulfate in the United States,⁹ as shown in the table below. None of these have an approved NDA.

#	NDC Number	Product Information	Manufacturer/Distributor
1	00172-4171	Quinine Capsules (200 mg) 	Ivax Pharmaceuticals Inc
2	00172-4172	Quinine Capsules (325 mg) 	Ivax Pharmaceuticals Inc
3	00223-1561	Quinine Capsules (325 mg)	Consolidated Midland Corp
4	00591-0716	Quinine Capsules (325 mg) 	Watson Pharmaceuticals Inc
5	00603-5622	Quinine Capsules (325 mg) 	Qualitest Pharmaceuticals Inc
6	00677-1647	Quinine Capsules (324 mg) 	Mutual/United Research Laboratories
7	53489-0221	Quinine Capsules (324 mg) 	Mutual Pharmaceutical Co Inc
8	54807-0621	Quinine Capsules (5 gr)	Rid Inc
9	54868-2858	Quinine Capsules (325 mg)	Physicians Total Care Inc
10	64125-0120	Quinine Capsules (325 mg)	Excellium Pharmaceutical Inc
11	62584-0740	Quinine Sulfate Tablets (260 mg)	American Health Packaging
12	00172-3001	Quinine Tablets (260 mg) 	Ivax Pharmaceuticals Inc
13	00182-1213	Quinine Tablets (260 mg)	Goldline Laboratories Inc/IVAX Pharmaceuticals

⁹ <http://cpip.gsm.com>

14	00182-8615	Quinine Tablets (260 mg)	Goldline Laboratories Inc/IVAX Pharmaceuticals
15	00591-0715	Quinine Tablets (260 mg) 	Watson Pharmaceuticals Inc
16	00603-5618	Quinine Tablets (260 mg) 	Qualitest Pharmaceuticals Inc
17	00677-1892	Quinine Tablets (260 mg)	Mutual/United Research Laboratories
18	00904-0564	Quinine Tablets (260 mg)	Major Pharmaceuticals Inc
19	53489-0462	Quinine Tablets (260 mg)	Mutual Pharmaceutical Co Inc
20	54868-3652	Quinine Tablets (260 mg)	Physicians Total Care Inc
21	55289-0243	Quinine Tablets (260 mg)	PD-RX Pharmaceuticals Inc
22	64125-0121	Quinine Tablets (260 mg)	Excellium Pharmaceutical Inc
23	00904-5648	Quinine Capsules (325 mg) (no longer marketed in the US)	Major Pharmaceuticals Inc
24	52544-0716	Quinine Capsules (325 mg) (no longer marketed in the US) 	Watson Pharmaceuticals Inc
25	00603-5621	Quinine Sulfate (325 mg) (no longer marketed in the US)	Qualitest Pharmaceuticals Inc
26	00904-0604	Quinine Sulfate (260 mg) (no longer marketed in the US)	Major Pharmaceuticals Inc
27	52544-0715	Quinine Tablets (260 mg) (no longer marketed in the US) 	Watson Pharmaceuticals Inc

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Malaria

Malaria is a protozoal disease, transmitted by the *Anopheles* mosquito, caused by *Plasmodium falciparum*. It is a very old disease and prehistoric man is thought to have suffered from malaria. Malaria probably originated in Africa and accompanied human migration to the Mediterranean shores, India and South East Asia. In the past it used to be common in the marshy areas around Rome and the name is derived from the Italian, (mal-aria) or "bad air"; it was also known as Roman fever.

- Hippocrates was the first to describe the manifestations of the disease, and relate them to the time of year and to where the patients lived - before this, the supernatural was blamed.¹⁰
- Charles Louis Alphonse Laveran, a French army surgeon stationed in Constantine, Algeria, was the first to notice parasites in the blood of a patient suffering from malaria. This occurred on the 6th of November 1880. For his discovery, Laveran was awarded the Nobel Prize in 1907.¹¹
- While it was recognised that the *Anopheles* mosquito played a key role in the transmission of the disease it was not until 1948 that all the stages in its life cycle were identified.¹²

¹⁰ <http://www-micro.msb.le.ac.uk/224/Bradley/History.html>, August 8, 2005

¹¹ <http://www.cdc.gov/malaria/history/#quinine>, August 11, 2005

- Malaria had been eradicated in the US due to the CDC's efforts starting at its inception on July 1, 1946. The Communicable Disease Center, as CDC was first known, coordinated the National Malaria Eradication Program, a cooperative undertaking by state and local health agencies of 13 Southeastern states. By the end of 1949, over 4,650,000 housespray applications had been made. In 1947, 15,000 malaria cases were reported. By 1950, only 2,000 cases were reported. By 1951, malaria was considered eradicated from the United States.¹³
- The World Health Organization estimates that each year 300-500 million cases of malaria occur and more than 1 million people die of malaria. About 1,300 cases of malaria are diagnosed in the United States each year. The vast majority of cases in the United States are in travelers and immigrants returning from malaria-risk areas, many from sub-Saharan Africa and the Indian subcontinent.¹⁴
- CDC received reports of 1,278 cases of malaria with an onset of symptoms in 2003, including seven fatal cases, among persons in the United States or one of its territories. This number represents a decrease of 4.4% from the 1,337 cases reported for 2002. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 53.3%, 22.9%, 3.6%, and 2.6% of cases, respectively.¹⁵

Malaria is a life-threatening disease. Although the precise risk of mortality to an individual is unknown, the assumption is that a non-immune traveler to an endemic area would, if infected, develop clinical infection and, if untreated, probably succumb to infection. Various groups have looked at the epidemiology of malaria to understand transmission and disease. For example, Quakyi et al looked at malaria prevalence in Cameroon. In 1994, 43% of the 377 people examined were slide-positive for malaria parasites and in 1995, 40% of the population (80 of 200) tested were slide-positive for malaria. The highest parasite rate was in children in the 0–0.5-year age group (78%). Parasite prevalence ranged from 58% to 67% in children 0.6–10 years old, and then decreased to 34% in children 11–15 years old. The lowest rate (30%) was found in adults 16–65 years old.¹⁶ In a different study, Gisela et al studied seasonal patterns of mortality in Burkina Faso, West Africa, and noted crude mortality rates were 14.5/1000 (95% CI 14.1–15.0) for the overall population, 51.3/1000 (95% CI 47.5–55.4) for infants, and 29.9/1000 (95% CI 28.2–31) for children aged 1–4 years. The under five mortality rate is 34.9/1000 (95% CI 33.3–36.5). High infant and childhood mortality rates were associated with the time around the end of the rainy season; malaria was shown to be the greatest contributor to childhood morbidity and mortality in... Burkina Faso.¹⁷ Such studies are consistent with the recognized morbidity and mortality due to malaria, particularly in children less than 5 years of age. The authors also stated that the recently observed increase in childhood mortality could be caused by the increasing resistance against the malaria firstline drug chloroquine in the area.

Although the rate, risk of infection and mortality may decline with age in endemic countries due to development of partial immunity, patients continue to die of this infection. Most travelers, on the other hand, do not have partial immunity and therefore unequivocally need treatment. Uncomplicated malaria must be treated to prevent patient from developing severe malaria. Risk of mortality with severe malaria is considered high. Quinine acts against the erythrocyte schizont form of the *Plasmodium falciparum* parasite, and has no effect on the gametocyte or the

¹² <http://www.rph.wa.gov.au/labs/haem/malaria/history.html>, August 8, 2005

¹³ <http://www.cdc.gov/malaria/history/#quinine>

¹⁴ <http://www.cdc.gov/ncidod/dpd/parasites/malaria/default.htm>, August 8, 2005

¹⁵ <http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5402a2.htm>, August 11, 2005

¹⁶ Quakyi IA, Leke RGF, Befidi-Mengue R et al, The epidemiology of *Plasmodium falciparum* malaria in two Cameroonian villages: Simbok And Etoa, *Am. J. Trop. Med. Hyg.*, 63(5, 6), 2000, pp. 222–230.

¹⁷ Gisela KW, Hammer GP, Muller O, Kouyate B, Becher H. Season of death and birth predict patterns of mortality in Burkina Faso, *International Journal of Epidemiology*, August 2, 2005 (electronic printing)

sporozoite and pre-erythrocytic (liver) forms. Although quinine has been used for prophylaxis historically, the toxicity and spectrum of activity do not make it an ideal agent for prophylaxis.

The CDC recommendations regarding malaria¹⁸

P. falciparum or Species Not Identified

For *P. falciparum* infections acquired in areas without chloroquine-resistant strains, which include Central America west of the Panama Canal, Haiti, the Dominican Republic, and most of the Middle East, patients should be treated with oral chloroquine. A chloroquine dose of 600 mg base (= 1,000 mg salt) should be given initially, followed by 300 mg base (= 500 mg salt) at 6, 24, and 48 hours after the initial dose for a total chloroquine dose of 1,500 mg base (=2,500 mg salt). For *P. falciparum* infections acquired in areas with chloroquine-resistant strains, three treatment options are available. The first two treatment options are quinine sulfate plus doxycycline, tetracycline, or clindamycin; or atovaquone-proguanil (Malarone). Both of these options are very efficacious. For the quinine sulfate combination options, quinine sulfate plus either doxycycline or tetracycline is generally preferred to quinine sulfate plus clindamycin because there are more data on the efficacy of quinine plus doxycycline or tetracycline. Quinine treatment should continue for 7 days for infections acquired in Southeast Asia and for 3 days for infections acquired in Africa or South America. The third option, mefloquine, is associated with a higher rate of severe neuropsychiatric reactions when used at treatment doses. We recommend this third option only when the quinine sulfate combination or atovaquone-proguanil options cannot be used.

WHO recommendations for Malaria :^{19, 20}

In Nov 13-17, 2000, WHO held meeting and discussed treatment regimens for malaria, published as WHO/CDS/RBM/2001.33. In this document, quinine alone was considered as second line antimalarial therapy in various African countries and as second line therapy (in combination with tetracycline) in several South American countries. First line use was not recommended, as summarized in the excerpt below.

Quinine

Decreasing sensitivity to quinine has been detected in areas of South-East Asia where it has been extensively used as the first-line treatment for malaria and in some parts of South America. Patient adherence to a 7-day regimen as a single drug or in combination with other drugs such as tetracyclines is low, leading to incomplete treatment and parasite recrudescences. This may have led to the selection of resistant parasites. There is some cross-resistance between quinine and mefloquine, suggesting that the wide use of quinine in Thailand might have influenced the development of resistance to mefloquine in that country (31). Strains of *P. falciparum* from Africa are generally highly sensitive to quinine.

The following text is taken from the WHO document "Antimalarial Drug Combination Therapy, Report of WHO Technical Consultation, April 4-5, 2001 (Roll Back Malaria, WHO/CDS/RBM/2001.35)²¹

¹⁸ <http://www.cdc.gov/ncidod/dpd/parasites/malaria/default.htm>, August 8, 2005

¹⁹ http://www.who.int/malaria/docs/who_recommended.htm

²⁰ http://www.who.int/malaria/docs/who_appt_position_references.htm

²¹ <http://rbm.who.int/wmr2005/html/a6.htm>

In areas with decreasing susceptibility of *P. falciparum* to quinine where a seven-day course of quinine is not fully curative, the addition of the relatively slow-acting drug tetracycline ensures a high cure rate (48). Co-administration of quinine plus tetracycline has been employed in the treatment of uncomplicated *falciparum* malaria since the late 1970s.

Doxycycline, derived from oxytetracycline, has an identical spectrum of activity as tetracycline and is currently also being used in combination with quinine. Doxycycline is more completely absorbed, more lipid-soluble and more stable, and less likely to transform to a toxic product. It also has a longer plasma half-life than tetracycline. Since the costs of tetracycline and doxycycline are equivalent, the once daily regimen of doxycycline offers considerable operational advantages over tetracycline, which must be administered four times daily.

The practical constraints with the combined treatment of quinine and tetracyclines relate mainly to patient adherence and safety. Patient adherence is strongly influenced by adverse reactions to quinine and the cumbersome nature of the drug regimen that requires eight-hourly doses of quinine for three to seven days, and six-hourly doses of tetracycline for seven days (in total 37 to 49 drug doses). The regimen can be considerably simplified by the once daily use of doxycycline instead of tetracycline. Tetracycline and doxycycline are contra-indicated in pregnant women, breastfeeding women and children less than eight years of age.

As a result of the above, it is difficult to recommend quinine plus tetracyclines as a first-line treatment for uncomplicated malaria. However, quinine plus doxycycline (preferably) could be considered as an option for treating patients who have failed to respond to first-line and/or second-line treatment and are still able to take oral medication.

Since 2001, the WHO has recommended that ACTs (artemisinin-containing therapy) be adopted as first-line treatment for malaria. As of June 2005²², 51 countries, 34 of them in Africa, have followed WHO's recommendations. The resulting surge in demand - from 2 million treatment courses in 2003 to 30 million courses in 2004 and a projected 70 million treatment courses for 2005 - led to a shortfall of artemisinin and ACTs, which WHO announced in November 2004. WHO convened a meeting in Tanzania to develop strategies to avert a future shortage. There are however, no currently approved artemisinin-class drug products in the US.

International Perspective

As part of the review, product labeling from various foreign countries was reviewed. In some countries, quinine sulfate is approved for the treatment of malaria; in other countries the indication of nocturnal leg cramps is also included, demonstrating that there continues to be a difference in views about quinine's efficacy. One such product is Lennon, marketed in South Africa²³, and includes the following information:

PHARMACOLOGICAL ACTION:

Quinine is a highly active blood schizonticide and suppresses the asexual cycle of development of malaria parasites in the erythrocytes. It is effective both as a suppressive drug and in the overt clinical attack of malaria.

²² <http://www.who.int/mediacentre/news/releases/2005/pr24/en/index.html>

²³ <http://home.intekom.com/pharm/lennon/quinine.html>, August 8, 2005

In addition quinine exerts relaxant effects on skeletal muscle. It increases the tension responses to a single maximal stimulus delivered to the muscle directly or through the nerve but it increases the refractory period of muscle so that the response to tetanic stimulation is reduced. Recumbency leg muscle cramps and myotonia congenita are thus effectively relieved by treatment with quinine.

INDICATIONS:

Quinine sulphate tablets are indicated mainly in the resistant strains of plasmodium falciparum malaria. It is also indicated as a muscle relaxant in myotonia congenita and myotonic contraction as well as nocturnal muscle cramps. A secondary indication is its use in the diagnostic test for myasthenia gravis.

Current armamentarium of FDA approved products for the treatment of malaria

A number of products are currently approved for the treatment of malaria. While each has been demonstrated to be effective, increasing resistance to chloroquine and sulfadoxine-pyrimethamine, makes availability of other antimalarials important. In addition, the adverse event profile means that some patients are not able to tolerate one or more of these drugs, and alternative drugs need to be available.

- chloroquine (Aralen®) – resistance
- sulfadoxine-pyrimethamine (Fansidar®) – resistance
- mefloquine (Lariam®) – neuropsychiatric adverse events
- atovaquone-proguanil, (Malarone®)
- primaquine ® - relapsing malaria
- quinacrine (Atabrine®)
- quinidine sulfate - IV only for life threatening malaria
- halofantrine (Halfan) - FDA-approved, but not marketed in the US - cardiotoxicity

MUTUAL'S QUININE SULFATE APPLICATION

Mutual Pharmaceuticals approached the Agency about obtaining approval for quinine sulfate 324 mg capsules and Pre-NDA meetings were held June 15, 2003 and May 24, 2004 during which the CMC, preclinical and clinical information needed to support a 505(b)(2) application was discussed and agreed to.

Mutual Pharma has manufactured the capsules for 15 years and manufacturing was acceptable, complied with FDA and ICH standards. Quinine is a alkaloid isolated from the cinchona bark

Mutual was granted orphan drug designation for “treatment of malaria” for quinine sulfate on June 3, 2004.

The company submitted their NDA on October 13, 2004, and included information from the published literature, and clinical pharmacology studies that compared the Mutual capsules to the marketed Thai GPO (Government Pharmaceuticals Organization) 300 mg quinine base formulation. The latter was chosen because it was used and studied in several of the publications on quinine clinical studies.

The applicant requested Priority review for NDA 21-799, but did not meet the criteria outlined in the Manual of Policies and Procedures (MaPP) 6020.3 on Priority Review Policy²⁴ and was given a Standard review.

P -- Priority review

The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.

S -- Standard review

All non-priority applications will be considered standard applications.

Data were reviewed to support the following wording in the INDICATIONS AND USAGE section:

Treatment of Malaria: Quinine sulfate is indicated only for treatment of uncomplicated *Plasmodium 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.

Furthermore, the Division determined that the following information should also be included in this section to assure safe use of the product, and in recognition of the Citizen's Petition and FR notice regarding use in nocturnal leg cramps.

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.

Material Reviewed:

The applicant had done an extensive search of the literature from 1974 through 2004 and identified over 1000 publications dealing with quinine and malaria. Of these, the applicant and FDA reviewers determined that 21 comparative studies of oral quinine sulfate would be reviewed in depth and 14 comparative studies of IV quinine would be examined for supportive data. The publications were reviewed with attention to blinding, randomization and follow up. The studies ranged in quality from poor to good. Overall, approximately 2,495 patients were enrolled in these trials and 1,456 were randomized to an oral quinine regimen.

Use of Published Data to support a New Drug Application:

²⁴ <http://www.fda.gov/cder/mapp.htm>

The Guidance for Industry document, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, describes desirable characteristics of published studies which increase the probability that they can be relied on to support approval of a new product.²⁵

- a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
- b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
- c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
- d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).
- e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

Although the quality of the studies varied, for the most part, the studies were consistent in that they met the characteristics described in the 5 points above. However, in addition to the comparative, randomized studies that provided quantitative information on efficacy, there is extensive literature and experience that substantiates the efficacy and safety of quinine for the treatment of malaria, including published textbooks. Interestingly, it was observed that the search of the literature did not disclose significant comparative studies in the early 1900's; a possible explanation was that quinine was the only available effective therapy, and its activity was not in question. Instead, as other antimalarial products became available, comparative studies were undertaken to characterize safe, effective and practical regimens for the treatment of malaria.

Efficacy: *See Reviews by Drs. Mary Singer /Eileen Navarro*

In general, the studies reported clinical and parasitological outcomes at 28 days. Many studies reported also on the time to fever resolution (FCT) and time to parasite clearance (PCT).

General Discussion of Endpoints²⁶

A number of outcome measures have been proposed by the World Health Organization (WHO) to assess efficacy of antimalarial regimens (<http://www.paho.org/english/ad/dpc/cd/mal-who-manual-pfalciparum.htm>) (WHO, 2003). These endpoints are described below:

Early Treatment Failure:

- Development of danger signs or severe malaria on days 1, 2, or 3, in the presence of parasitemia
- Parasitemia on day 2 higher than day 0 count regardless of axillary temperature
- Parasitemia on day 3 with axillary temperature $\geq 37.5^{\circ}\text{C}$
- Parasitemia on day 3 $\geq 25\%$ of count on day 0

Late Treatment Failure:

- **Late Clinical Failure:**

²⁵ www.fda.gov/cder/guidance

²⁶ Medical Officer Review by Dr Mary Singer

- Development of danger signs or severe malaria after day 3 in the presence of parasitemia, without previously meeting criteria for Early Treatment Failure
- Development of parasitemia and axillary temperature $\geq 37.5^{\circ}\text{C}$ on any day from day 4 to 14 (day 4-28 for areas of intense transmission) without previously meeting criteria for Early Treatment Failure
- **Late Parasitological Failure:**
 - Presence of parasitemia on day 14 (day 7-28 in areas of intense transmission) and axillary temperature $< 37.5^{\circ}\text{C}$ with previously meeting any of the criteria for Early Treatment Failure or Late Clinical Failure

Adequate Clinical and Parasitological Response:

- Absence of parasitemia on day 14 (day 28 for areas of intense transmission) regardless of axillary temperature, without previously meeting any of the criteria for Early or Late Treatment Failure

Most of the randomized, controlled studies did not describe a primary endpoint, but evaluated cure at 28 days. The WHO definitions for parasitological response and level of resistance used in this review were as follows (WHO 2000):

- **S:** (sensitive) = initial clearance of parasitemia, without recrudescence during follow-up period (*modified for this review to clearance of parasitemia by day 7, and no recrudescence within 28 days. This is referred to as "cure" or "28-day cure", the primary endpoint for this review.*)
- **RI:** (resistant) = initial clearance of parasitemia, but recrudescence by day 8 or more (*modified for this review to clearance of parasite within 7 days but recrudescence by day 28*)
- **RII:** (resistant) = initial clearance or reduction of parasitemia to $< 25\%$ initial value, and recrudescence on day 7 (*modified for this review to marked reduction of parasitemia but no clearance by day 7*)
- **RIII:** (resistant) = no initial reduction of parasitemia, or increase in parasitemia (*modified for this review to no marked reduction in parasitemia within 48 hours*)

Exposure-Response Relationships: *See Reviews by Drs. Gerlie Gieser/Mary Singer*

As summarized by Dr Singer,

As reviewed by White²⁷ (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. 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.

²⁷ White NJ. Assessment of the Pharmacodynamic Properties of Antimalarial Drugs in Vivo. Minireview. Antimicrob Agents Chemother July 1997. 41(7):1413-1422.

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.

Information on quinine dosing regimens and duration was evaluated by Earle et al²⁸ and showed that elimination of parasitemia with quinine was more efficient with a longer (6-8 day) regimen than a shorter regimen (4 days). Furthermore, they were able to show that while one strain of *Plasmodium* (McClendon) responded to quinine therapy when mean quinine plasma concentrations exceeded approximately 6 mg/L, another strain (Costa) failed to respond consistently at the same exposure. Thus the Costa strain was more resistant to quinine therapy than the McClendon strain.

Studies supporting the proposed dosage regimen: See Reviews by Drs. Mary Singer/LaRee Tracy, including Table 1 (below)

- In vitro and in vivo animal data
- Clinical pharmacology findings including exposure/response data
- Findings of low efficacy with 1.5 day or 3 day quinine monotherapy regimen (Metzger, Kresman)
- Finding of improved efficacy when 3 day quinine is combined with other drug (Duarte, Rahman, Salcedo, Metzger,
- Finding of good efficacy with 7 day quinine regimen (Pukrittayakam, Rahman, Bich, DeVries, Ache)
- Finding of good efficacy when 7 day quinine regimen was combined with another drug (Pukrittayakam, Fungladda, DeAlencar, Bunnag, Vanijanonta, Looareesuwan, Karbwant)

As noted by Dr Tracy,

Studies evaluating a quinine 10 mg/kg tid x 7 day monotherapy regimen showed cure rates were 82-86% (61-70%) in the evaluable (ITT) populations and one additional study of 48 patients from Brazil had a cure rate of 100% in both populations. In studies evaluating quinine 10 mg/kg tid in combination with tetracycline for 7 days the cure rates were 94-100% (68-95%) in the evaluable (ITT) populations (one study not reporting ITT rates). Cure, defined as parasite clearance by day 7 without recrudescence at day 28, varied due to drug resistance patterns across malaria endemic study regions. Lost to follow-up led to the observed lower cure rates in the ITT population.

From a regulatory perspective, a number of findings as summarized above supported the efficacy of the product, and overall, the totality of the evidence supports the approval of quinine sulfate in the 505(b)(2) application.

INFORMATION TO INCLUDE IN LABELING: CLINICAL STUDIES section

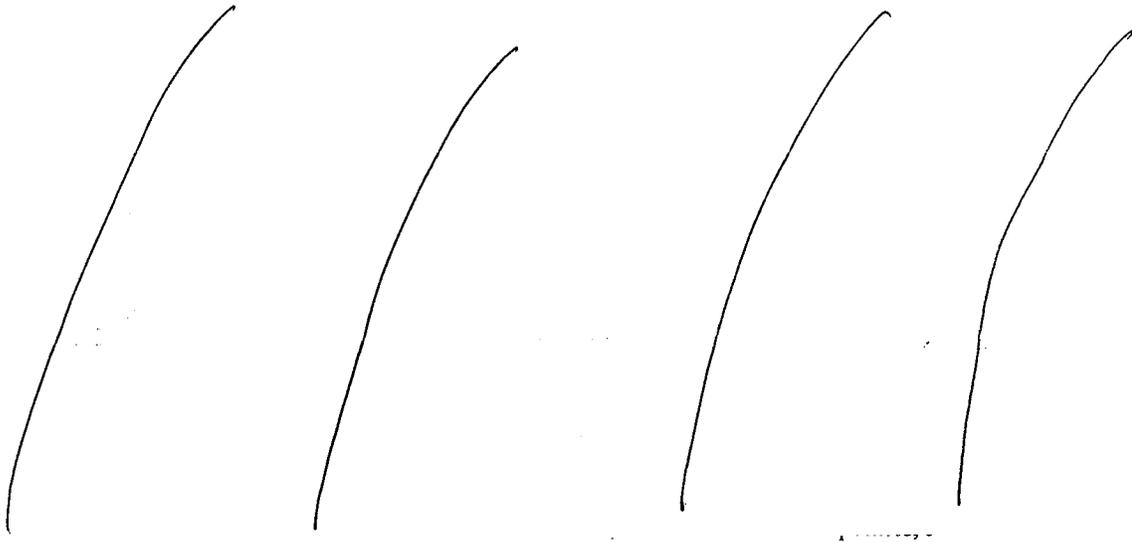
²⁸ Earle DP, RW Berliner et al. Studies on the Chemotherapy of the human malarías. II Method fo the quantitative assay of suppressive antimalarial action in falciparum malaria. J clin Invest 1948:27(3);75-79.

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 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process



SUMMARY:

Quinine is the oldest known treatment for *Plasmodium falciparum* malaria, a life threatening infection that infects potentially 500 million persons worldwide and is responsible for approximately 1 million deaths annually. Once considered first line therapy for malaria, quinine resistance has been seen in some parts of the world, and led to the use of quinine in combination with tetracycline, clindamycin or doxycycline. Clinical studies conducted in the last decades show that the product is still effective, with rates of 80-100% reported in comparative studies (in contrast to chloroquine rates of 30% reported from studies). When quinine is used in combination with tetracycline, the rates appear somewhat higher, usually 90-100%, but no studies were large enough, or the difference dramatic enough, to reach statistical significance. Therefore, the labeling will reflect both regimens. In these studies of uncomplicated malaria, failure is characterized by RI resistance with recrudescence by 28 days after treatment, however, in these studies patients from malaria endemic areas did not progress to develop severe malaria. On the other hand, Taylor and Strickland³³ state that any *P. falciparum* infection in a nonimmune individual should be considered a potential medical emergency. The patient should be hospitalized and observed carefully for any complications. Serial blood films should be done every q6-8 hours and a patient switched to alternative therapy if parasitemia is not reduced in 48 hours. The toxicity and q8h dosing regimen of quinine must also be considered when selecting an antimalarial agent. Thus, the selection of a specific antimalarial product(s) for a specific patients will be guided by various factors including the resistance patterns of malaria in the region where malaria was acquired, the known adverse event profile, the severity of disease.

The approval of this application constitutes the first FDA approval of a New Drug Application for quinine sulfate for the treatment of uncomplicated *Plasmodium falciparum* malaria.

End of Document

³³ Taylor TE and GT Strickland. Chapter 92. Malaria in Hunter's Tropical Medicine and Emerging Infectious Diseases, Eighth Edition ©2000 W.B. Saunders Company.

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