

Lupus Anticoagulants

Lupus anticoagulants, which are a type of antiphospholipid antibody, have been associated with clinical events such as thrombosis (arterial or venous), and thrombocytopenia. Lupus anticoagulants are found in some individuals with a connective tissue disorders such as systemic lupus erythematosus, malignancy, liver disease, or in pregnancy. A number of drugs, including chlorpromazine, procainamide, hydralazine, phenytoin, and quinidine, have been associated with the presence of lupus anticoagulants. Bird, et al., (1995) performed a retrospective case-control study of 31 patients over 60 years old who were identified as having lupus anticoagulants in serum (identified by hematological testing). Some of these individual also have clinical features of antiphospholipid syndrome. Among these 31 patients, 10/31 (23%) were taking quinine for leg cramps, 11/31 (35%) were taking quinidine for cardiac arrhythmias, and 2 (6%) were taking both medications. Among age- and gender-matched controls, 3/31 (10%) were taking quinine and none were taking quinidine. The difference in exposure to chinchona alkaloids (quinine or quinidine) between cases and controls 23/31 (73%) vs. 3/31 (10%) was statistically significant ($p = < 0.001$ by Fisher's exact test). In 3/5 (60%) patients who discontinued use of quinine or quinidine, lupus anticoagulants were still detectable 9-20 months later.

Hypoprothrombinemia

Quinine reportedly decreases hepatic synthesis of vitamin K dependent clotting factors and hypoprothrombinemia with quinine use has been described. No literature was provided by the applicant in support of this claim.

Medical Officer Comments: The concomitant use of coumadin or other oral anticoagulants with quinine may increase the hypoprothrombinemic effect of these drugs, and ————— monitoring of prothrombin time may be necessary. This potential effect of quinine is described in the PRECAUTIONS/Drug Interactions section of the proposed label.

Postmarketing Hematological Adverse Events

In the applicant's analysis, thrombocytopenia was the most common of the postmarketing adverse events reported to the AERS and WHO databases. A total of 173 unique cases of thrombocytopenia were reviewed by ODS. Most cases were in females (112/171, 65.5%), and leg cramps was the most common indication (123/139, 88.5%), Thrombocytopenia resulted in hospitalization in 129 cases and death in 15; and approximately one-third of cases required an intervention such as platelet transfusion or plasma exchange. Thrombocytopenia was listed as the cause of death in 3/81 (3.7%) of all deaths reported to the AERS database, as reviewed by ODS.

As reviewed by ODS, there were 25 unique cases of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS). Most of these cases were in females (20/25, 80%), and most cases were in patients receiving quinine for leg cramps (24/25, 96%). The average patient age was 55, ranging from 21 to 75 years. A total of 23 of 24 cases (96%) reviewed were determined to have a positive association with quinine use, and 12/25 (48%) patients reported previous quinine use.

Leukopenia was reported in 15 unique cases reviewed by ODS. Most 9/15 (60%) were females. Leukopenia resulted in hospitalization in 9 cases, and death in 2 cases. Agranulocytosis was reported in 5 unique cases, 4 of which resulted in hospitalization and 1 in death. The patient that died was an 85 year-old male receiving quinine for leg cramps. The death however, was attributed to ceftriaxone, which the patient was receiving for septic arthritis.

Additional postmarketing hematological events reported to AERS, included epistaxis, purpura, hemolytic uremic syndrome, aplastic anemia, gingival bleeding, ecchymosis, coagulopathy, leukocytosis, gastric hemorrhage, coombs positive hemolytic anemia, bone marrow depression, petechiae, pharyngeal hemorrhage, mouth hemorrhage, gastrointestinal hemorrhage, hemoptysis, idiopathic thrombocytopenic purpura, subcutaneous hemorrhage, hematemeses, hemorrhage, increased eosinophil count, eosinophilia, mucosal hemorrhage, vaginal hemorrhage, iron deficiency anemia, eye hemorrhage, febrile neutropenia, Felty's syndrome, decreased hematocrit, decreased hemoglobin, decreased platelets, pancytopenia, rectal hemorrhage, hemolytic anemia, hemolysis, hemorrhage, hemorrhagic stroke, intraventricular hemorrhage, serum sickness, pulmonary hemorrhage, retroperitoneal hemorrhage, decreased prothrombin level, antiphospholipid antibodies, and thrombosis. These events were not reviewed individually to assess a causal relationship to quinine.

Medical Officer Comment: The actual incidence of quinine-associated thrombocytopenia is unknown due to the nature of the voluntary postmarketing adverse event reporting system. In the pharmacokinetic studies sponsored by the applicant, after a single 324 mg or 648 mg dose of quinine sulfate, no thrombocytopenia was reported in 50 subjects.

6. Metabolic Adverse Events with Quinine

Hypoglycemia

Information regarding quinine-associated hypoglycemia was obtained mainly from clinical studies of patients who received intravenous quinine for severe malaria. Hypoglycemia was reported as an adverse event in none of the 50 healthy subjects who received single-dose quinine sulfate in the applicant's bioequivalence studies. In the randomized, clinical trials of oral quinine sulfate for treatment of uncomplicated *P. falciparum* malaria, hypoglycemia was reported in not reported in any patients. However, these data are limited, given apparent ascertainment and/or reporting bias in many of these studies. In the randomized, controlled studies of parenteral quinine for treatment of severe *P. falciparum* malaria, hypoglycemia was reported as an adverse event in approximately 16% patients.

Medical Officer Comments: Hypoglycemia is a frequent complication of severe P. falciparum malaria and attribution of hypoglycemia to quinine would be difficult in this setting.

As reviewed by Taylor and White (2004), the use of intravenous quinine in severe malaria has been associated with hypoglycemia in up to 10 % patients, due to increased pancreatic secretion of insulin. Hypoglycemia and hyperinsulinemia have also been reported in healthy volunteers

who received intravenous quinine (White, et al., 1983). Additionally, the incidence of profound hypoglycemia in pregnant women treated with quinine for severe malaria may approach 50% (Taylor, et al., 2004). In a study of 12 pregnant women in the third trimester of pregnancy, who were treated with intravenous followed by oral quinine (20 mg/kg loading dose, followed by 10mg/kg every 8 hours for 7 days), 7/12 (58%) of patients became hypoglycemic, 2 prior to quinine treatment and 5 within 3 to 6 hours after quinine infusion (Looareesuwan, et al., 1985).

Hypoglycemia, associated with hyperinsulinemia also occurs as a complication of severe *P. falciparum* malaria (White, 1983; Davis, et al., 2002). Hypoglycemia has also been reported in a pregnant woman with severe malaria taking oral quinine (Kochar, et al., 1995); and in a patient taking oral quinine for leg cramps (Limberg, et al., 1993).

The incidence of hypoglycemia in a randomized, open-label study of rectal artemisinin and intravenous quinine (followed by oral quinine) in patients with severe malaria in Ethiopia was 63.3% (19/33) in patients who received quinine, and 10% (3/32) patients treated with rectal artemisinin (Birku, et al., 1999). In a randomized, open-label trial of quinine (intravenous followed by oral), vs. artesunate in 113 adults with severe falciparum malaria in Thailand, 28% (15/54) of patients who received quinine, and 10% (6/59) of those treated with artesunate developed hypoglycemia (Newton, et al., 2003).

Kawo, et al.(1991) reported no hypoglycemia in 97 children (0-7 years old) in Dar es Salaam with severe malaria who received intravenous (10 mg/kg in 5% glucose every 8 hours) followed by oral quinine for a total of 10 days, although hypoglycemia may have been averted in this study because quinine was infused in a dextrose solution. In a prospective, uncontrolled study of quinine (intravenous followed by oral) for treatment of severe falciparum malaria in Malawian children (ages 7 months to 8 years), hypoglycemia was found in 19 children pre-treatment (7 of these patients had recurrent hypoglycemia after treatment with quinine), but in none of 76 patients who were normoglycemic pre-treatment (Taylor, 1988). Notably, intravenous quinine was infused slowly (over 2-3 hours) in a 5% dextrose solution in this study. In this study, mortality was higher in children who had pre-treatment hypoglycemia (7/19, 37%) than in those who were normoglycemic (3/76, 4%). Additionally, 5/12 (42%) survivors with baseline hypoglycemia had significant neurologic sequelae at the time of hospital discharge, in comparison to 5/73 (7%) survivors among those who were normoglycemic.

Postmarketing Adverse Events

Postmarketing adverse events identified in the AERS database included hypoglycemia, diabetes mellitus, increased thyroid stimulating hormone, and anorexia. Electrolyte abnormalities reported as serious adverse events included hypokalemia, hyperkalemia, decreased calcium, hyperglycemia, hypomagnesemia, lactic acidosis, increased INR, increased prothrombin time, decreased prothrombin time, vitamin C and zinc deficiencies. These events, however, were not assessed individually for a possible relationship to quinine.

ODS reviewed 7 adverse event reports of hypoglycemia (3 reports) or diabetes mellitus (4 reports) with serious outcomes in the AERS database. Of the 3 cases of hypoglycemia, all 3 patients had end-stage renal disease. Two cases resulted in death. Glucose levels were reported

as < 50 mg/dL, < 1 mmol/L and “1”. Hypoglycemic coma was reported in one case, and seizures and hypoglycemia in the other, although specific causes of death were not reported. Hypoglycemia was attributed to quinine by the “reporter” in all 3 cases. Diabetes was not attributed to quinine in any of the 4 cases, and in 2 cases, diabetes was pre-existing.

Medical Officer Comments: Although usually associated with intravenous quinine administration, oral quinine exposure has also been associated with hypoglycemia, as reviewed above. We have proposed a PRECAUTION regarding hypoglycemia in the final product labeling.

“Hypoglycemia:

Quinine stimulates release of insulin from the pancreas, and patients, especially pregnant women, may experience clinically significant hypoglycemia.”

7. Musculoskeletal System Adverse Events with Quinine

Quinine can cause muscle weakness by inhibiting acetylcholinesterase release by interfering with calcium influx at the nerve terminal, and has been used to diagnose myasthenia gravis (Brumback, 1981). However, because quinine can provoke myasthenic crisis, this practice has been largely discontinued. Both quinine and quinidine (and chloroquine) have been shown to increase the refractory period of muscle, diminishing the response to tetanic stimulation, and decrease the excitability of motor end-plate regions, reducing response to acetylcholine and repetitive nerve stimulation (Sieb, et al., 1996). Because of its effects on skeletal muscle, quinine has been used for treatment of myotonia congenital and nocturnal leg cramps. Quinine may also potentiate the effects of neuromuscular blocking agents. One case has been described of a patient who developed apnea and respiratory depression after receiving quinine several hours after pancuronium during an operative procedure (reported in DrugDex Online).

Postmarketing adverse events reported to the AERS database included arthralgia, myalgia, myopathy, musculoskeletal stiffness, joint stiffness, muscle spasms, rhabdomyolysis, gangrene, and neck pain. These events, however, were not reviewed individually to determine a potential relationship to quinine.

Medical Officer Comments: Because of the effects of quinine on skeletal muscle, we have proposed listing myasthenia gravis as a CONTRAINDICATION to oral quinine use for uncomplicated falciparum malaria. We also propose to list treatment and/or prevention of nocturnal leg cramps with quinine sulfate as a WARNING given the absence of proven effectiveness and multiple safety issues with quinine. Additionally, we have proposed a WARNING regarding the concomitant use of neuromuscular blocking agents, such as pancuronium, succinylcholine and tubocurarine with quinine sulfate.

8. Nervous System and Psychiatric Adverse Events with Quinine

Some central nervous system (CNS) adverse events are part of the spectrum of symptoms referred to as cinchonism, which occur commonly with quinine, including headache, hearing impairment, tinnitus, nausea and visual disturbance. However, the risk of more serious adverse events may increase with increasing quinine dosage (Phillips-Howard and Kuile, 1995). In

quinine overdosage, ataxia, seizures, and coma have been described, as reviewed by Bateman and Dyson (1986). Seizures were also reported in a patient who received concomitant mefloquine and quinine for malaria (Miyashita, et al., 1994). The applicant also noted a case report of acute dystonic reaction in a patient who received quinine for presumed malaria (Fernandez-Moreno, et al., 2003). There was one case report of suicide (Adam, and Elbashir, 2004) which may be the same as that reported to the AERS postmarketing database, and described previously. In this case, a 27 year-old male from Eastern Sudan with malaria was started on 600 mg quinine in 5% dextrose, intravenously 3 times daily. He had received a full-course of chloroquine 7 days prior to hospitalization. Five hours later, he was found dead after hanging himself. The patient had no history of mental illness.

Postmarketing neuropsychiatric adverse events reported to the AERS database, identified by ODS as occurring in patients with a serious outcome included headache, grand mal convulsion, cerebellar syndrome, dizziness, confusional state, coma, depressed level of consciousness, status epilepticus, stroke, cerebrovascular accident, cerebral infarction, intracranial hemorrhage, paraplegia, paralysis, facial palsy, Guillain-Barre syndrome, muscle twitching, muscle spasms, tremor, hallucination, depersonalization, paranoia, psychotic disorder, major depression and completed suicide. Other events in this category included aphasia, delirium, paresthesia, neuropathy, polyneuropathy, hypertonia, difficulty walking, encephalitis, sleep disorder, and insomnia. These events, however were not further evaluated to determine a potential relationship to quinine.

One death in the AERS postmarketing database was reported in a patient who received intravenous quinine (600 mg, unknown duration) for malaria. This patient committed suicide by hanging approximately 5 hours after quinine dosing. This patient had no history of mental illness, and had received chloroquine a few days previously.

Medical Officer Comments: Except for headache, a symptom of cinchonism, most of these events appear to be uncommon; however, the actual incidence is unknown. We have proposed listing neuropsychiatric adverse events in the ADVERSE EVENTS section of the final product label. Additionally, we have proposed a WARNING regarding concomitant use of mefloquine and quinine sulfate with regard to the potential for both QT prolongation and increased risk of seizures.

9. Special Senses

Ototoxicity

Symptoms of ototoxicity with quinine have been described for many years, and range from mild, transient hearing impairment, tinnitus, to vertigo, and sensorineural hearing loss. In a study by Tange, et al. (1997), and Claessen, et al. (1998) audiometric changes following quinine administration in 9 of 12 healthy subjects who receive a single 300 mg intravenous dose of quinine were described. Hearing loss, measured audiometrically in these subjects occurred 2 to 4 hours after the quinine infusion, at a mean quinine maximal plasma concentration of 2 mg/L. Most hearing loss was in the high frequency range. However, no subjective hearing loss was noted, and the audiometric changes were reversible in all but 1 subject. In the same study, all 9

patients with *P. falciparum* malaria experience ototoxicity (hearing loss, tinnitus, or dizziness) during treatment with quinine 600 mg administered intravenously every 8 hours for 3 days. Hearing loss was maximal on the third day of quinine infusion, and occurred in the standard and high frequency ranges, but was fully reversible in all patients. In a double-blind, four-way crossover study which enrolled 32 healthy volunteers, daily consumption of up to 160 mg/day quinine for 21 days did not significantly alter audiometric responses (Drewitt, et al., 1993). In 10 adult patients with acute falciparum malaria, who received quinine orally or intravenously, or in combination with tetracycline, all experience hearing loss in the high frequency range after the first dose of quinine. Tinnitus also occurred in 7/10 (70%) patients. Hearing loss improved as plasma concentration declined, and resolved after the drug was stopped (Roche, et al., 1990).

In a small randomized, controlled study in Kenya, the incidence of hearing loss was higher in patients (≥ 14 year old) who received a loading dose of intravenous quinine (20 mg/kg) (10/17, 60%) than in the control group who did not receive a loading dose prior to treatment with 10 mg/kg quinine every 8 hours for a minimum of 24 hours before switching to oral quinine (3/16, 19%) (Tombe, et al., 1992).

Hearing impairment with quinine administration was independent of the route of administration, but was fully reversible in 6 healthy volunteers (Paintaud, et al., 1994). Subjective hearing impairment and tinnitus occurred most frequently when plasma quinine concentration was > 15 $\mu\text{moles/L}$, and no symptoms were reported when concentrations were below 5 $\mu\text{moles/L}$ in 6 healthy volunteers (Alvan, et al., 1991). The mechanism of hearing impairment may be related to function of the outer hair cells of the cochlea (Karlsson, et al., 1995).

Postmarketing Adverse Events

ODS reviewed 28 unique cases with serious outcomes classified by System Organ Class as Ear and Labyrinth Disorders. These adverse events included deafness with tinnitus (11 reports), deafness without tinnitus (9 reports), and tinnitus (8 reports). Outcomes include death (2), hospitalization (10), disability (2), required intervention (1) and other (5). The deaths were due to an apparent overdose in one patient, and to an underlying disease in the other. Permanent effects were reported in 2 patients with tinnitus and in 9 patients with hearing loss. A positive association between the hearing disorder and quinine use was determined in most 23/28 (82%) reports

Medical Officer Comments: Hearing impairment, tinnitus, and vertigo are all considered symptoms of cinchonism, and appear to be relatively common in patients who receive quinine. Hearing impairment associated with quinine appears to be reversible upon quinine discontinuation in most cases, although irreversible deafness has been described, mainly in the setting of quinine overdose, but there were also reports of permanent hearing loss in the postmarketing database. These adverse events are described in the ADVERSE EVENTS section of the proposed label.

Ocular Toxicity

Mild visual disturbances, including blurred vision and changes in color perception with quinine have been described as part of the symptom complex of cinchonism (Bateman and Dyson, 1986). Other visual signs or symptoms described with quinine use are photophobia, diplopia, night blindness, constricted visual fields, scotomata, mydriasis, and blindness (Tracey and Webster, 2001). Ocular toxicity and blindness have been most commonly associated with quinine overdose, but there are several reports of transient blindness or visual impairments with quinine exposure under other circumstances, including treatment of acute malaria with intravenous quinine (De Perri, et al., 2002; Naraqui, et al., 1992), or with chronic tonic water ingestion (Horgan, et al., 1995). In children with cerebral malaria receiving intravenous quinine, photoreceptor function was transiently depressed (Lochead, et al., 2003). The exact mechanism of ocular toxicity and visual loss is unknown.

In the setting of quinine overdose, ocular toxicity, particularly blindness, may be delayed (6-15 hours after overdose) and dependent upon plasma quinine concentration. In one study, plasma quinine concentrations above 10 mg/L were associated with an increased risk of permanent visual impairment (Bateman, et al., 1985). Ophthalmologic changes described after quinine ingestion and onset of blindness include progressive constriction of the retinal arterioles, macular cherry red spot, macular edema, and optic atrophy. Some degree of visual recovery generally occurs, and although permanent visual impairment may be severe, some patients recover completely. The mechanism of quinine-induced blindness is not clear, but may be due to the toxic effect of quinine on the retina (Bateman and Dyson, 1986).

Postmarketing adverse events reported to AERS and identified by ODS as occurring in patients with serious outcomes included optic neuritis, papilloedema, retinal hemorrhage, blurred vision, decreased visual acuity, retinal disorder, and visual disturbance. These events however were not further evaluated for potential relationship to quinine.

Postmarketing Adverse Events

ODS reviewed 28 unique adverse events with serious outcomes classified under Vision Disorders. These events included blindness (7), visual disturbance (6), double vision/blurred vision (4), worsening vision, abnormal vision, visual field defect, and miosis (1 each), as well as droopy eye, eye trouble, eyelid ptosis, swollen tear duct, and retinal hemorrhage (1 each). Among the 7 cases of blindness, 6 were associated with overdose, and 3 had permanent damage. Outcomes included death (4), hospitalization (14), disability (2), and other (5). None of the deaths were directly related to the visual problem. Four patients experienced permanent or ongoing events, including permanent loss of vision (1), permanent changes to retinal and optic nerves (1), abnormal vision with papilloedema and retinal hemorrhage (1), pale and ischemic retina (1).

Medical Officer Comments: Visual symptoms such as blurred vision and changes in color perception are part of the cinchonism symptom complex, and as such, may be relatively frequent adverse events associated with quinine use. Irreversible blindness,

however, appears to be rare, except in cases of quinine overdose. Visual adverse events are listed in the ADVERSE EVENTS section of the proposed label.

10. Respiratory System Adverse Events with Quinine

Quinine has not generally been associated with pulmonary toxicity. The applicant found a single case report of transient pulmonary infiltrates, associated temporally with exposure to a single 325 mg dose of quinine sulfate for nocturnal leg cramps in a 45 year-old woman with no history of pulmonary disease. Hypoxia and pulmonary infiltrates resolved within 24 hours, and no other cause for the episode was identified (Krantz, et al., 2002).

A literature search by the medical officer identified a case report of transient acute pulmonary edema and hypotension which occurred 30 to 40 minutes after taking a single 300 mg tablet of quinine sulfate for leg cramps on 2 separate occasions (Everts, et al., 2004). Additionally, adult respiratory distress syndrome (ARDS) has been described after quinine overdose (Wenstone, et al., 1989).

Postmarketing respiratory adverse events reported to AERS included apnea, asthma, dyspnea, wheezing, stridor, hyperventilation, decreased oxygen saturation, respiratory distress, pulmonary edema, lung disorder, pulmonary embolism, cough, bronchitis, lower respiratory tract infection, emphysema, pleural effusion, and pneumonia. These events were not evaluated further to determine possible relationship to quinine sulfate.

Medical Officer Comments: Asthma was listed in the applicant's proposed label as an adverse event associated with quinine use, and is reported as a postmarketing adverse event. However, literature describing quinine-associated asthma was not provided for this NDA, nor was any references found in a literature search by the medical officer. Nevertheless, because of the postmarketing report of asthma associated with quinine use, it will be included in the listing of ADVERSE EVENTS in the final product labeling. Severe malaria can be associated with pulmonary edema or ARDS, so attributing such adverse events to quinine in patients treated for severe malaria would be difficult. However, the single case reported by Everts, et al. (2004), indicates that pulmonary edema can occur in patients without malaria receiving single dose of oral quinine.

11. Skin Reactions Associated with Quinine

Purpura

Purpura associated with quinine-induced thrombocytopenia or thrombotic thrombocytopenic purpura (TTP) was described in the section on hematological adverse events above. TTP associated with ingestion of tonic water has been referred to as "cocktail pupura" (Belkin, 1967).

Urticaria

Urticaria, pruritus, and skin flushing are the most common manifestations of quinine hypersensitivity (Taylor and White, 2004).

Allergic Contact Dermatitis

Contact dermatitis related to exposure to quinine in a topical balm was reported in a 15-month old child (Dias, et al., 1994), and in a 31-year old man who used a quinine-containing hair lotion (Tapadinhar, et al., 1994). Additionally, there are reports of quinine-induced contact dermatitis which occurred during occupational exposure (Wahlberg and Boman, 1981).

Photosensitivity

A number of case reports have documented the occurrence of photosensitivity reactions associated with quinine. The first report by Ljunggran et al., (1986) described an eczematous dermatitis in a distribution consistent with light exposure in a 72 year-old woman who had been taking quinine hydrochloride once or twice a week over a 4 year period for leg cramps. Histopathology and phototesting after re-exposure to quinine confirmed the diagnosis. Other types of photosensitivity-type skin reactions reported include lichenoid photosensitivity (Thomas, et al., 1986; Dawson, et al., 1995), skin reactions mimicking mycosis fungoides (Okun, et al., 1994), and a persistent photosensitivity reaction characterized by diffuse erythema, scaling, and a Koebner reaction in a 41 year-old female who was taking quinine for nocturnal leg cramps, after phototherapy for psoriasis (Guzzo, and Kaidbey, 1990).

Cutaneous Vasculitis

Several case reports describe cutaneous vasculitic rashes temporally associated with use of quinine for nocturnal leg cramps (Price, et al., 1992; Mathur, et al., 1990).

Acral necrosis

Abreu-Gerke, et al., 2000 reported a case of an 87 year old woman who developed red skin lesions on the fingers of both hands and several toes, 1 month after starting quinine sulfate 200 mg/day for nocturnal leg cramps. Several of these lesions progressed to acral necrosis. The authors attributed the acral cyanosis to quinine-induced vascular spasm. Acral necrosis was also described in a case report of a 65 year-old male after taking one 300 mg dose of quinine sulfate for nocturnal leg cramps. This patient was also diagnosed with quinine-induced hemolytic uremic syndrome (Agarwal, et al., 2002).

Fixed Drug Eruption

Ingestion of tonic water containing quinine was associated temporally and by re-challenge with a fixed drug eruption as described in one case report (Asero, 2003).

Toxic epidermal necrolysis

One case report of toxic epidermal necrolysis caused by "gin and tonic" is described in the literature (Callaway and Tate, 1974).

Stevens-Johnson syndrome

There are two case reports of Stevens-Johnson syndrome found in the literature, one was in a patient with acute renal failure and G6PD deficiency (Kothari, et al., 1977); while the other was in a patient treated with quinine plus pyrimethamine-sulfadoxine (Gaston Brustenga, et al., 1986).

Postmarketing Adverse Events

ODS reviewed 101 unique adverse event reports with serious outcomes which described hypersensitivity or skin reactions. These events included rash (60), erythema multiiforme (4), blisters (4), Stevens-Johnson syndrome (2), erythema and pemphigoid, 1 each. There were 28 non-skin hypersensitivity events, including dyspnea/bronchospasm (10), angioedema (6), hypotension/syncope (5), anaphylaxis (4), adult respiratory distress syndrome (4), and acute pulmonary edema (4). Outcomes included death (6), hospitalization (49), life-threatening (1), disability (2), required intervention (3), and other (14). The most common indication was leg cramps, listed in 68/79 (86%) of those events which reported indication.

Other postmarketing adverse events reported to AERS included the skin rashes, dermatitis, and other skin reactions listed under hypersensitivity reactions, in addition to skin necrosis, skin discoloration, cellulitis, petechiae, purpura, leukocytoclastic vasculitis, subcutaneous hemorrhage, and others. These events were not further reviewed to determine causality.

Medical Officer Comments: Serious skin rashes associated with quinine use appear to occur infrequently. However, as rashes generally represent a hypersensitivity reaction, we have proposed a CONTRAINDICATION regarding quinine use in patients with known hypersensitivity to quinine, and a PRECAUTION which describes some serious hypersensitivity reactions as follows:

“Hypersensitivity:

Serious hypersensitivity reactions reported with quinine sulfate include anaphylactic shock, anaphylactoid reactions, urticaria, serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, facial edema, bronchospasm, and pruritus. (See CONTRAINDICATIONS) “

12. Renal Adverse Events

Acute renal failure is a clinical manifestation of severe malaria, and also occurs in the setting of blackwater fever with acute intravascular hemolysis and hemoglobinuria. As reviewed by Pawar, et al. (1994), who summarized 11 cases of quinine-associated acute renal failure from the literature, most cases have been associated with hemolytic uremic syndrome or disseminated intravascular coagulation. Acute interstitial nephritis, generally considered to be a drug-induced hypersensitivity reaction has also been reported in a case report of biopsy-proven acute interstitial nephritis associated with use of quinine for nocturnal leg cramps (Pawar, et al., 1994).

Postmarketing Adverse Events

ODS reviewed 49 unique reports of renal failure, and 2 reports of nephritis, all with serious outcomes. Renal failure was reported in more females (30) than males (19), with an average age of 56 years (range 18-84 years). Outcomes included death (9), hospitalization (36), disability (2), and other (1). Nephritis was reported in a 65 year-old male with a hypersensitivity reaction, exfoliative dermatitis, and leukocytosis. The patient was receiving a number of concomitant medications, including carbamazepime, but the reactions were temporally related to quinine initiation and resolved when quinine was discontinued. The second case of nephritis was a case a

biopsy-proven interstitial nephritis and hemolytic anemia, previously reported in the literature. These events occurred in a 73 year-old female who used quinine intermittently for leg cramps.

Additional postmarketing adverse events reported to AERS and identified by ODS as occurring in patients with serious outcomes included anuria, increased BUN and creatinine, renal failure, acute renal failure, hemodialysis, proteinuria, nocturia, and renal atrophy. These events were not reviewed further to assess potential causal relationship with quinine.

Medical Officer Comments: Renal failure may occur in the setting of severe P. falciparum malaria, and in that setting it may be difficult to distinguish an adverse event related to quinine and a complication of the disease process. Renal adverse events, including renal failure, and others, are listed in the ADVERSE EVENTS section of the proposed label.

7.1.4 Other Search Strategies

Oral quinine labeling from other countries was provided by the Applicant, and reviewed to compare the adverse event profile reported for the indication of malaria and for other indications (nocturnal leg cramps, and myotonia), as shown in the following tables.

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Table 44: Indications and Recommended Dose of Oral Quinine in Foreign Labels*

Country of Origin for Oral Quinine Label	Date of last labeling	Pharmaceutical Sponsor	Indication (s)	Recommended Dosage regimen (adults)	Recommended Duration
U.S. (proposed label- this NDA)	2005	Mutual Pharmaceutical	Uncomplicated malaria	648 mg tid	7 days
Australia	1997	Aventis Pharmaceuticals	Leg cramps	300-600 mg qHS	
			Congenital myotonia	NS	
			Diagnosis of myasthenia gravis	NS	
			Suppression of malaria	600 mg q 8h	7 days
Denmark	2001	The Danish Medicines Agency	Nightly leg cramps	100-200 mg qHS	10 days
France	2001	SN Laboratories LAFRAN	Uncomplicated malaria	8 mg/kg q 8h	5-7 days
Germany	NS	Merck dura	Malaria	1-1.25 g quinine HCl daily	7 days
			Nocturnal calf cramps	0.25 g after evening meal and 0.25 g HS	NS
The Netherlands	1999	Dagra Pharma	Non-serious chloroquine-resistant tropical malaria	600 mg q8h	7 days after fever resolution
New Zealand	1999	Pacific Pharmaceuticals	Treatment of chloroquine-resistant malaria as combination therapy	600-650 mg q8h	Minimum of 3 days (7 days in Southeast Asia)
			Nocturnal recumbency leg muscle cramps	200-300 mg HS with additional dose following	NS

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				PM meal, if needed	
South Africa	1974	Lennon	Nocturnal leg cramps	300-600 mg "at night"	NS
			Myotonia congenita	NS	NS
			falciparum malaria	600 mg every 8 hours	7 days
			Diagnosis of myasthenia gravis	NS	NS
Sweden	NS	NM Pharma	Alternative treatment in severe acute malaria	10 mg/kg tid	7 days
			Myotonia congenita and myotonia atrophica	300-600 mg bid-tid	NS
Taiwan	NS	Shinlon Pharmaceutical Company	Treatment of malaria caused by chloroquine-resistant P. falciparum	500 mg qid	3-7 days
			Maintenance treatment of malaria	260 mg bid	6 weeks

* Most recent available label information is presented (labels provided by Applicant)

Clinical Review
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 {Insert Application and Submission Number}
 {Insert Product Trade and Generic Name}

Table 45: Adverse Events Listed in Foreign Labels for oral Quinine

AE	U.S. (proposed)	Australia	Denmark	France	Germany	Netherlands	New Zealand	South Africa	Sweden	Taiwan
Body as a Whole:										
Cinchonism*	x	x	x	x	x	x	x	x	x	x
Hypersensitivity reactions**	x				x			x	x	x
Fever							x	x	x	x
Cardiovascular System:					x					
QTc interval prolongation	x		x	x						
Arrhythmia	x									
Ventricular fibrillation	x									
Ventricular tachycardia		x								
Anginal symptoms	x	x				x				x
tachycardia	x									
Irregular rhythm	x									
Premature ventricular contractions	x									
QRS widening		x								
Disturbance of cardiac rhythm or conduction		x	x							
Hypotension		x								
Cardiac arrest						x				
Hematological:										
Agranulocytosis	x	x				x	x	x	x	x

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Quinine Sulfate Capsules USP, 324 mg

*Cinchonism is a symptom complex which may include one or more of the following: tinnitus, blurred vision, vasodilatation, sweating, headache, nausea, disturbance in color vision, and dysphoria. More severe cinchonism may include vomiting, diarrhea, abdominal pain, vertigo, deafness, blindness, and disturbances of cardiac rhythm or conduction.

**Hypersensitivity reactions with quinine include cutaneous flushing, pruritus, skin rashes, fever, gastric distress, tinnitus, visual impairment

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Medical Officer Comments: The most common adverse events reported in foreign labels for oral quinine were cinchonism, tinnitus, cutaneous rashes, pruritus, nausea, vomiting headache, _____ and thrombocytopenia, and visual disturbances. Most of the adverse events noted in these labels were also described in the literature, or in the AERS database for postmarketing adverse events. We have proposed including these adverse events in the ADVERSE EVENTS section of the final product labeling for quinine sulfate.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse event data was summarized by the applicant from the studies submitted for efficacy analysis. Some of these studies did not report adverse events, and there was no comprehensive description of all adverse events in any of the studies. Thus, the actual incidence of adverse events in these studies is unknown, and can only be estimated from the data provided. Additional information from the literature and from the postmarketing data has provided some insight into the relative incidence of adverse events associated with quinine.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Not applicable

7.1.5.3 Incidence of common adverse events

The actual incidence of specific adverse events can only be estimated from the published studies of quinine for treatment of uncomplicated *P. falciparum* malaria because of possible ascertainment, reporting, and publication bias, as discussed previously. An attempt was made in this section to estimate the incidence of specific adverse events from the randomized, controlled studies submitted for evaluation of efficacy and safety, the applicant's bioequivalence studies, from published case reports, case series and reviews, and from the AERS postmarketing data for quinine sulfate.

7.1.5.4 Common adverse event tables

The most common adverse events reported in the two pharmacokinetic studies and the randomized, controlled studies with oral and parenteral quinine submitted for this NDA are shown in the table below. These data represent an estimate of adverse event incidence for the randomized controlled trials. Only studies in which adverse events were enumerated by treatment group were included in this analysis. Additionally, adverse events may not have been elicited the same way in all of the studies, so these data only reflect a rough estimate of adverse events overall.

Table 46: Summary of Estimated Incidence of Common Adverse Events Reported in Subjects or Patients who received Quinine in Studies Submitted with NDA

Common Adverse Events	Mutual pharmacokinetic studies (healthy subjects)	RCT with oral quinine (patients with uncomplicated malaria)	RCT with parenteral quinine (patients with severe malaria)
	n/N (%)	n/N (%)	n/N (%)
Headache	9/50 (18.0)	NR	NR
Sore throat	5/50 (10.0)	NR	NR
Nausea	5/50 (10.0)	NR	NR
Dizziness	3/50 (6.0)	48/222 (21.6)	4/822 (0.5)
Tinnitus	NR	53/222 (23.8)	NR
Impaired hearing	NR	6/222 (2.7)	2/822 (0.2)
Hypoglycemia	NR	NR	132/822 (16.1)
QTc prolongation > 500 msec	0	NR	60/822 (7.3)
Vomiting	1/50 (2.0)	1/222 (0.5)	21/822 (2.6)

N= number of patients/subjects who received quinine

n= number of patients/subjects who experienced adverse event

NR = not reported

Medical Officer Comments: The pattern of common adverse events differed significantly in healthy subjects, in patients with uncomplicated malaria who received oral quinine, and in patients with severe malaria who received parenteral quinine. This may be due, in part, to underlying disease, or lack thereof, multiple vs. single dose regimens (patients vs. subjects), and route of quinine administration. This is particularly obvious with the parenteral quinine studies, in which hypoglycemia and significant QTc prolongation were common adverse events; but were not reported in studies with oral quinine or in the pharmacokinetics studies. It would also appear that tinnitus, dizziness, and hearing loss associated with multiple oral doses of quinine rather than single oral doses, or with parenteral quinine. Patients receiving parenteral quinine generally have severe malaria and may not be able to report these subjective symptoms.

Adverse Events Reported in Pharmacokinetic Studies of Oral Quinine

Adverse events reported in the two pharmacokinetic studies performed for this NDA are shown in the following tables. In study RA3-085, a randomized, open-label, single-dose, three-way crossover study comparing bioequivalence of quinine sulfate 324 mg (Mutual Pharmaceutical) with 300 mg quinine sulfate (GPO, Bangkok, Thailand), 27 subjects (12 men and 15 women) were enrolled, and 25 completed the study. Adverse events were reported in 11 of 27 (41%) subjects. A total of 32 adverse events were reported; and none of the events was considered serious. The adverse events which occurred in this study are shown in the table below. The most common adverse events reported were headache, sore throat, and nausea. In their summary the applicant reported twenty two of 32 (68.8%) adverse events were considered at least possibly

drug-related. However, in review of the adverse event dataset, there were 17 adverse events considered possibly or probably related in 8 subjects. Drug-related adverse events included headache (9 events), nausea (3 events), vomiting (2), and heartburn (1), stiff neck (1), and viral syndrome (1).

Table 47: Adverse Events in Bioequivalence Study RA3-085 (Applicant's Table 5, ISS)

No. of Subjects Reporting Adverse Events at Least Once in Mutual Pharma's Single-dose Quinine Sulfate Bioequivalence Study RA3-085

Adverse Event	n (%)		
	Mutual Pharma's 324 mg Capsule N=27	GPC's 300 mg Tablet N=25 ¹	Total N=27
Headache	5 (18.5%)	3 (11.5%)	6 (22.2%)
Sore Throat	4 (14.8%)	0 (0%)	4 (14.8%)
Nausea	2 (7.4%)	2 (7.7%)	3 (11.1%)
Sinus Pressure	1 (3.7%)	0 (0%)	1 (3.7%)
Syncope	0 (0%)	1 (3.8%)	1 (3.7%)
Nasal Congestion	1 (3.7%)	0 (0%)	1 (3.7%)
Upper Respiratory Infection	1 (3.7%)	0 (0%)	1 (3.7%)
Vomiting	1 (3.7%)	1 (3.8%)	1 (3.7%)
Dyspepsia	1 (3.7%)	0 (0%)	1 (3.7%)
Viral Syndrome	1 (3.7%)	0 (0%)	1 (3.7%)
Stiff Neck	1 (3.7%)	0 (0%)	1 (3.7%)

¹ Does not include Subject No. 25, who elected to withdraw for personal reasons prior to receiving this treatment, and Subject No. 11, who only received Mutual's formulation (fed).

Medical Officer Comments: Information regarding the subject who had syncope was obtained from the datasets (adverse events, vital signs and ECG). This subject was a 20 year-old Caucasian female who had a syncopal episode lasting 2 minutes which occurred 24 hour after the quinine dose. An ECG recorded at the same time revealed a heart rate of 82 bpm, a PR interval of 140 msec, a QRS interval of 84 msec, a QT interval of 355 msec, and a QTc interval of 394 msec. None of these parameters differed from the subject's pre-dose baseline; and at no time post-baseline was the QTc interval longer than the baseline measurement. Vital signs were not recorded at the time of syncope. The investigator considered the adverse event mild, and the relationship to study drug was considered remote. The investigator's assessment appears reasonable given the ECG data for this subject.

In the dose-proportionality study, R04-0376, subjects received a single oral doses of one 324 mg quinine, and two 324 mg quinine in a randomized, two-way, crossover study under fasting conditions. Twenty four subjects were enrolled, 13 men, and 11 women. Thirteen subjects had a total of 30 adverse events, as shown in the table below. The most common adverse events were headache, dizziness, and nausea. A total of 11/30 (36.7%) adverse events were considered at least possibly drug-related. These 11 drug-related adverse events, which occurred in 7 subjects, included headache (2 events), nausea (2), and nightsweats, light-headedness, myalgia, diarrhea, dizziness, tinnitus, and upset stomach, each reported once. Adverse events in this study are shown in the following table.

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Table 48: Adverse Events in Bioequivalence Study R04-0376 (Applicant's Table 6 ISS)

No. of Subjects Reporting Adverse Events at Least Once in Mutual Pharma's Single-dose Quinine Sulfate Dose Proportionality Study R04-0376

Adverse Event	n (%)		
	Mutual Pharma 1 × 324 mg Capsule N=23	Mutual Pharma 2 × 324 mg Capsule N=23	Total N=23
Headache	2 (8.7%)	2 (8.7%)	4 (17.4%)
Dizziness	0 (0%)	3 (13.0%)	3 (13.0%)
Nausea	0 (0%)	3 (13.0%)	3 (13.0%)
Joint injury (swollen knee)	1 (4.3%)	0 (0%)	1 (4.3%)
Myalgia (leg muscles)	1 (4.3%)	0 (0%)	1 (4.3%)
Night sweats	1 (4.3%)	0 (0%)	1 (4.3%)
Pallor	1 (4.3%)	1 (4.3%)	1 (4.3%)
Syncope	1 (4.3%)	0 (0%)	1 (4.3%)
Upper respiratory tract infection	1 (4.3%)	0 (0%)	1 (4.3%)
Loss of appetite	0 (0%)	1 (4.3%)	1 (4.3%)
Diarrhea	0 (0%)	1 (4.3%)	1 (4.3%)
Menstrual cramps	0 (0%)	1 (4.3%)	1 (4.3%)
Body aches	0 (0%)	1 (4.3%)	1 (4.3%)
Leg pain	0 (0%)	1 (4.3%)	1 (4.3%)
Sore throat	0 (0%)	1 (4.3%)	1 (4.3%)
Chills	0 (0%)	1 (4.3%)	1 (4.3%)
Skin laceration	0 (0%)	1 (4.3%)	1 (4.3%)
Upset stomach	0 (0%)	1 (4.3%)	1 (4.3%)
Sweating increased	0 (0%)	1 (4.3%)	1 (4.3%)
Tinnitus	0 (0%)	1 (4.3%)	1 (4.3%)
Tonsillitis	0 (0%)	1 (4.3%)	1 (4.3%)

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Medical Officer Comments: Although more adverse events occurred in subjects who received the 648 mg dose of quinine, a dose-relationship for these adverse events cannot be determined with the limited number of patients who received quinine in this study.

Additional information regarding the subject who had syncope was obtained directly from the datasets (adverse events, vital signs, and ECG datasets). This was a 19 year-old Caucasian male who had 2 episodes of syncope which occurred approximately 3 and 4 hours after his first dose of quinine. The first episode was accompanied by pallor and lasted 1 minute; while the second event lasted 4 minutes. Vital signs measured at 1, 2, and 4 hours post-dose revealed a slight drop in BP from 122/69 mm to 109/61 mm, 106/74 mm, and 110/62 mm, respectively; while heart rate also dropped from 92 bpm at baseline to 74 bpm, 85 bpm, and 69 bpm, at 1-, 2-, and 4- hours post dose, respectively. ECG data revealed no significant change in PR, QRS, QT or QTc intervals from baseline at 2- or 4- hours post dose; and the maximum QTc recorded for this patient was 400 msec (+27 msec from baseline of 385 msec) at 4 hours post-dose. However, the patient's screening QTc was 414 msec, so the QTc changes seen post-dose are most likely due to normal variation. The investigator considered the syncopal episodes mild, and unrelated to study drug, which upon review of these data, appears reasonable.

The following table shows the adverse events characterized by quinine dose in the two pharmacokinetic studies combined. Dizziness occurred in 3 subjects who received a 648 mg quinine dose and in none of those who received 324 mg quinine.

Table 49: Overall incidence of Adverse Events in Combined Studies RA3-085 and R04-076 with Oral Quinine (Applicant's Table 4, ISS)

Summary of Adverse Events with Mutual Pharma's Quinine Sulfate Capsules in Single-Dose Pharmacokinetic Studies

Adverse Event	n (%)		
	Mutual Pharma 1 × 324 mg capsule N = 50	Mutual Pharma 2 × 324 mg capsule N = 23	Total N = 50
Headache	7 (14.0%)	2 (8.7%)	9 (18.0%)
Sore throat	4 (8.0%)	1 (4.3%)	5 (10.0%)
Nausea	2 (4.0%)	3 (13.0%)	5 (10.0%)
Upper respiratory tract infection	2 (4.0%)	0 (0%)	2 (4.0%)
Joint injury (swollen knee)	1 (2.0%)	0 (0%)	1 (2.0%)
Myalgia (leg muscles)	1 (2.0%)	0 (0%)	1 (2.0%)
Night sweats	1 (2.0%)	0 (0%)	1 (2.0%)
Pallor	1 (2.0%)	1 (4.3%)	2 (4.0%)
Syncope	1 (2.0%)	0 (0%)	1 (2.0%)
Upset stomach	1 (2.0%)	1 (4.3%)	2 (4.0%)
Sinus Pressure	1 (2.0%)	0 (0%)	1 (2.0%)
Nasal congestion	1 (2.0%)	0 (0%)	1 (2.0%)
Vomiting	1 (2.0%)	0 (0%)	1 (2.0%)
Viral syndrome	1 (2.0%)	0 (0%)	1 (2.0%)
Stiff neck	1 (2.0%)	0 (0%)	1 (2.0%)
Dizziness	0 (0%)	3 (13.0%)	3 (6.0%)
Loss of appetite	0 (0%)	1 (4.3%)	1 (2.0%)
Diarrhea	0 (0%)	1 (4.3%)	1 (2.0%)
Menstrual cramps	0 (0%)	1 (4.3%)	1 (2.0%)
Body aches	0 (0%)	1 (4.3%)	1 (2.0%)
Leg pain	0 (0%)	1 (4.3%)	1 (2.0%)
Chills	0 (0%)	1 (4.3%)	1 (2.0%)
Skin laceration	0 (0%)	1 (4.3%)	1 (2.0%)
Sweating increased	0 (0%)	1 (4.3%)	1 (2.0%)
Tinnitus	0 (0%)	1 (4.3%)	1 (2.0%)
Tonsillitis	0 (0%)	1 (4.3%)	1 (2.0%)

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Medical Officer Comments: The number of subjects in these studies was too small to determine any dose-relationship for adverse events, and most adverse events were reported only once. However, headache and dizziness were the most common adverse events overall. Note that adverse events (including the case of syncope) associated with the Thailand-GPO formulation of quinine sulfate were not included in this table.

Adverse Events reported in Published Randomized, Controlled Trials of Oral Quinine for Uncomplicated Malaria

Adverse events reported in the randomized, controlled trials are listed in the table below for quinine and the comparator. Adverse events were not reported in all of these studies, so the overall incidence of adverse events cannot be determined accurately. The table below shows adverse events reported in the individual studies submitted as pivotal for this NDA.

Table 50: Adverse Events Reported in the Randomized, Controlled Trials of Oral Quinine Monotherapy for treatment of Uncomplicated Malaria (adapted from Applicant's Table 7, ISS, and from individual study reports)

Study	Adverse Event	Quinine n/N (%)	Comparator(s)	Comparator n/N (%)
Watt, et al, 1988	Vomiting	1/10 (10%)	C	1/10 (10%)
	Dizziness	2/10 (20%)		0/10 (0)
	Tinnitus	2/10 (20%)		0/10 (0)
	Diarrhea	2/10 (20%)		2/10 (20%)
	Pruritis	0		1/10 (10%)
Pukrittayakamee, S., et al., 2004	NR	NR*	A; Q+T; Q+P, A+P	NR*
Mueller, et al, 2004**	Tinnitus	11/43 (27%)	Artemesia preparations	0/72 (0)
Ache, et al., 2002	NR	NR	C; SP	NR
Rahman, et al., 2001	NR	NR	C; Q+SP	NR
Pukrittayakamee, S., et al., 2000	Gastro-intestinal symptoms †	3/68 (4.4%)	Q+T:	2/68 (2.9%)
			Q+C	1/68 (1.5%)
	Tinnitus	NR separately for quinine alone 193/204 (93.7% all patients)	Q+T; Q+C	NR separately for quinine combination 193/204 (93.7% all patients)
	Cinchonism	Similar in all groups; incidence NR	Q+T; Q+C	Similar in all groups; incidence NR
McGready, et al., 2000	Headache	NR separately for quinine alone. No difference between treatment groups 81/108 (75%) overall	Mefloquine+artesunate	NR separately for comparator. No difference between groups 81/108 (75%) overall
	Muscle and joint pain	NR separately for quinine alone No difference between treatment groups 73/108 (68%) overall		NR separately for comparator. No difference between treatment groups 73/108 (68%) overall
	Dizziness	37/42 (87%)		30/66 (45%)
	Tinnitus	66%		17%
	Anorexia	No difference		No difference

		between treatment groups 62% (67/108) overall		between treatment groups 62% (67/108) overall
De Vries, et al., 2000	Hemo-globinuria	NR for quinine alone. 2/268 (0.7%) overall	Q+Artemisinin	NR for comparator alone. 2/268 (0.7%) overall
	Cinchonism	Incidence NR		Incidence NR
Bich, et al., 1996	Dizziness	9/59 (15.3%)	Artemisinin + quinine	4/45 (8.9%)
			Artemisinin + doxycycline	4/53 (7.5%)
	Tinnitus	13/59 (22.0%)	Artemisinin + quinine	5/45 (11.1)
			Artemisinin + doxycycline	1/53 (1.9)
	Impaired hearing	6/59 (10.2%)	Artemisinin + quinine	5/45 (11.1)
			Artemisinin + doxycycline	0/53
	Excess salivation	2/59 (3.4%)	Artemisinin + quinine	0/45
			Artemisinin + doxycycline	0/53
	Dry mouth	4/59 (6.8)	Artemisinin + quinine	1/45 (2.2)
			Artemisinin + doxycycline	1/53 (1.9)
Metzger, et al., 1995	Dizziness	NR for quinine alone. 27/108 (25%) all treatment groups#	Quinine + clindamycin Quinine + doxycycline	NR for quinine combination. 27/108 (25%) all treatment groups#
	Abdominal pain	NR for quinine alone. 22/108 (20%) all treatment groups#		NR for quinine combination. 22/108 (20%) all treatment groups#
	Nausea	NR for quinine alone. 19/108 (18%) all treatment groups#		NR for quinine combination. 19/108 (18%) all treatment groups#
	Diarrhea	NR for quinine alone. 13/108		NR for quinine combination. 13

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		(12%) all treatment groups#		/108 (12%) all treatment groups#
	Vomiting	NR for quinine alone.12/108 (11%) all treatment groups#		NR for quinine combination.12/108 (11%) all treatment groups
Segal, et al., 1974	NR††	NR††	NR††	NR††

NR= not reported

*authors mention that no allergic rashes were reported in any of studied patients

C= chloroquine; A= artesunate; Q+T= quinine + tetracycline; Q+P= quinine + primaquine;

A+P= artesunate + primaquine; SP= sulfadoxine-pyramethamine; Q + SP = quinine

+sulfadoxine-pyrimethamine

**authors state that other adverse events were similar between treatment groups, but did not specify events or incidence of events

† Nausea, vomiting, abdominal pain or diarrhea

Authors reported no significant difference between treatment groups

NR†† Adverse event data not reported as incidence, but as patient-days. See individual study report in Appendix, section 10.1.

Medical Officer Comments: Adverse event data were not elicited systematically in most of these studies, so the incidence of adverse events reported for each treatment group can only be estimated. Quinine combination therapy was a frequent comparator in these studies, which diminishes the utility of comparative data. Additionally, in most cases, no attempt was made to identify drug-related adverse events as opposed to those which could be attributed to malaria. In some cases, adverse events were not reported separately for treatment groups so comparisons between treatments cannot be made. However, some patterns emerged from these data, notably, tinnitus and dizziness were reported more frequently in patients who received quinine than the comparator(s).

In an attempt to estimate the overall incidence of adverse events reported in these studies, adverse events were combined across studies in those which reported adverse events separately for each treatment group, with the exception of the study by Segal, et al, (1974) because number patient-days rather than numbers of patients who experienced the events was reported in the latter. These data are presented in the table below.

Table 51: Estimated Incidence of Adverse Events in Randomized, Controlled Trials of Quinine Monotherapy in patients with uncomplicated malaria (calculated from previous Table)

Adverse Event	Patients who received oral quinine in RCT* N= 222	Patients who received comparator in RCT* N= 269
	n (%)	
Tinnitus	53 (23.8)	17 (4.5)
Dizziness	48 (21.6)	38 (9.9)
Impaired hearing	6 (2.7)	0
Dry mouth	4 (1.8)	2 (0.5)
Gastrointestinal symptoms	3 (1.3)	3 (0.8)
Diarrhea	2 (0.1)	2 (0.5)
Excess salivation	2 (0.1)	0
Vomiting	1 (0.5)	1 (0.3)
Pruritus	0	1 (0.3)

*RCT= randomized, controlled trials. Studies included in this analysis were Watts, et al., 1988 (chloroquine comparator); Mueller, et al., 2004 (artemisinin tea comparator); Pukrittayakamee, et al., 2000 (quinine + tetracycline and quinine + clindamycin comparators); McGready, et al., 2000 (mefloquine-artesunate comparator); Bich, et al., 1996 (artesunate+quinine and artesunate+doxycycline comparators)

Medical Officer Comments: Although these data are only a rough estimate of incidence, tinnitus, dizziness and impaired hearing were the most common adverse events in patients treated with quinine in the combined studies. Because of the differences in study design, and adverse event ascertainment and reporting, combining data from these studies may not be valid. Additionally, because quinine combination therapy was used as a comparator in some of these studies, the relatively high incidence of tinnitus and dizziness in the combined comparator groups is not unexpected.

Adverse Events Reported in Published Non-Randomized Studies of Oral Quinine Treatment for Uncomplicated Malaria

Adverse events were not elicited systematically or were not reported in most of these studies. The table below shows the adverse events reported with quinine in these studies.

Table 52: Adverse Events in Patients treated with oral Quinine in nonrandomized Studies (adapted from Applicant's Table 8, ISS)

Study	Quinine N	Quinine dose	Comparator	Duration of treatment (days)	Adverse Events Reported (n)
Mohapatra, et al., 2003	19	10 mg/kg tid	None	5-7	Tinnitus (2, 10.5%); tinnitus, dizziness and gastritis (7, 36.8%), nausea and vomiting (3, 15.8%)
Pineli, et al., 1999	454	10 mg/kg tid	None	7	NR
Babalola, et al., 1998	6	10 mg/kg q12 hours on first day, then tid	None	7	Reportedly no adverse events
Sowunmi, 1996	11	10 mg/kg q 12 h on first day, then tid	None	7	NR
Ringwald, et al., 1995	22	500 mg tid	None	3	Tinnitus (19, 86.4%); hypoacusis (13, 59.1%); vertigo (11, 50%); stomach pain (5, 22.7%); vomiting (5, 22.7%)
Bhalli and Samiullah, 2001	59	10 mg/kg tid	None	7	NR
Giboda and Denis, 1988	43	1.5 g (base) qd	Quinine plus tetracycline	10	NR

N= number of patients treated with quinine

n=number of patients with adverse event

NR= not reported

Medical Officer Comments: Because adverse events were not collected systematically in most of these studies, an overall incidence cannot be determined. A relatively high incidence of tinnitus, dizziness and gastritis (36.8%) was noted in the study reported by Mohapatra, et al., 2003. In this study, only 19 patients were treated with quinine, after failing both chloroquine and sulfadoxine-pyrimethamine. The authors noted that 11

patients discontinued treatment due to adverse events (7 with tinnitus, dizziness and gastritis, and 3 with nausea and vomiting. An additional patient refused quinine after 5 days of treatment. Quinine is considered a gastric irritant, and we have proposed wording in the DOSAGE and ADMINISTRATION section of the final product label, recommending that quinine sulfate should be taken with food.

In the study by Ringwald, et al. (1995), the incidence of adverse events was also relatively high, but most of these events are symptoms of cinchonism, and are not unexpected. None of patients in this study however, discontinued quinine due to adverse events.

Adverse Events in Studies of Oral Quinine in Combination with other Antimalarial Drugs for Treatment of Uncomplicated Malaria

The applicant also summarized the adverse events reported in randomized studies using quinine in combination with another antimalarial agent, as shown in the table below.

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Table 53: Summary of Adverse Events Reported in Published Studies of Quinine in combination with other antimalarial drugs for Treatment of Uncomplicated *P. falciparum* malaria (Applicant's Table 10, ISS)

Adverse Events¹ in Published Randomized Studies of Oral Quinine in Combination with Other Antimalarials for Treatment of Uncomplicated *P. falciparum* Malaria

Study	N (Treatment/ Duration Code ²)	Adverse Events		
		Resulting in DC (n)	Serious/ Deaths (n)	Other
Duarte <i>et al.</i> , 1996 (Brazil)	88 (Q3T7)	3 (severe vomiting)	0/0	Majority of patients had one or more AE, mainly dizziness (34%), tinnitus (24%), and abdominal pain (24%), and all were consistent with known profile.
Pakritavakamee <i>et al.</i> , 2004 (Thailand)*	30 (Q7T7)	0	0/0	No AEs were reported.
Rahman <i>et al.</i> , 2001 (Bangladesh)*	145 (Q3SP1)	0	0/0	No AEs were reported.
Pakritavakamee <i>et al.</i> , 2000 (Thailand)*	68 (Q7C7)	0	0/0	AEs were consistent with known profile. 2 Q7C7 and 1 Q7T7 patient(s) developed GI symptoms. The majority of patients developed tinnitus, and there were incidences of cinchonism.
	68 (Q7T7)	0	0/0	
de Vries <i>et al.</i> , 2000, (Vietnam)*	96 (A1Q3)	2 (hemoglobi- nuria)	0/0	Two patients had hemoglobinuria after 24 hours of treatment and were discontinued. AEs were "not considered to be a clinically significant problem". Cinchonism was reported in all patient groups.
	88 (A1Q5)		0/0	
Fungladda <i>et al.</i> , 1998, (Thailand)	60 (Q7T7)	0	0/0	80% of patients had AEs consistent with known profile: headache, vomiting, dizziness, diarrhea, drowsiness, tinnitus, and body ache. Noncompliance was due to: tinnitus (50%), vomiting (16.7%), severe diarrhea (17%), and "could not tolerate" (16.7%).
Salcado <i>et al.</i> , 1997 (Brazil)	14 (Q3T7)	0	0/0	AEs were mild and self-limited and were consistent with known profile. 38% reported abdominal pain and 13% diarrhea.
de Alencar <i>et al.</i> , 1997, (Brazil)	77 (Q7T7)	0	0/0	90% of patients had AEs that were consistent with known profile. Most common were tinnitus (55), dizziness (39), and nausea (23).
Bunnag <i>et al.</i> , 1996 (Thailand)	48 (Q5T7)	0	0/0	AEs were consistent with known profile and were similar in the two treatment groups. Common AEs were nausea, vomiting, dizziness, loss of appetite, and tinnitus.
	42 (Q7T7)	0	0/0	
Vanjanonta <i>et al.</i> , 1996, (Thailand)	25 (Q7T7)	0	0/0	AEs were consistent with known profile and were mild. Cinchonism was common in both groups.
	25 (Q7CQ3)	0	0/0	
Bich <i>et al.</i> , 1996, (Vietnam)*	45 (A1Q3)	0	0/0	9 patients reported mild AEs: dizziness (4), tinnitus (5), and impaired hearing (4).
Metzger <i>et al.</i> , 1995, (Gabon)*	40 (Q1.5C3)	0	0/0	All AEs were mild and self-limited, and were consistent with known profile: dizziness, mild GI symptoms, abdominal pain, nausea, diarrhea, and vomiting.
	40 (Q1.5D3)	0	0/0	
Looreesuwan <i>et al.</i> , 1994, (Thailand)	52 (Q7T7)	0	0/0	Reported AEs were consistent with known profile: headache (82%), dizziness (70%), cinchonism (94%), nausea (52%), vomiting (28%), and abdominal pain (12%).
Kachwang <i>et al.</i> , 1994 (Thailand)	33 (Q7T7)	0	0/0	AEs were mild and self-limiting and consistent with known profile: tinnitus (29), dizziness (16), vomiting (30), and nausea (20).

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Q=quinine; T=tetracycline; C=clindamycin; D=doxycycline; A=artemisinin or artesunate;
 SP=sulfadoxine/pyrimethamine; AM=amodiaquine; CQ=chloroquine; AE(s)=adverse event(s)
 *Also reviewed in Monotherapy

¹Does not include abnormal laboratory tests or vital sign or ECG parameters

²Treatment/Duration codes = drug abbreviation followed by duration of treatment in days. Combination therapy is represented as first drug abbreviation, duration, second drug abbreviation, duration

Medical Officer Comments: Because combination therapy with quinine is frequent in clinical practice, and is recommended in the CDC guidelines for treatment of uncomplicated malaria (CDC 2004 Guidelines for Treatment of Malaria in the U.S.), comparing the relative incidence of adverse events in combination regimens to those with quinine alone is important to determine if there is an increased incidence of adverse events in combination regimens containing quinine. This comparison may also be helpful in identifying any potential drug-drug interactions which resulted in adverse events. Additionally, the incidence of adverse events in the quinine-containing regimen in comparison to non-quinine containing regimens may be useful in determining quinine-related adverse event. Data on comparative incidence of adverse events in studies that reported adverse events is provided below.

Table 54: Incidence of Adverse Events in oral Quinine Combination Therapy and Non-Quinine Comparator ††

Study	Quinine Combination	N	Adverse Events Reported n (%)	n (%)	Comparator Treatment	N	n (%)
Duarte, et al., 1996	QT	88	Dizziness	28 (31.8)	AS-T	88	7 (8.0)
			Abdominal pain	20 (22.7)			14 (15.9)
			Nausea	15 (17.0)			7 (8.0)
			Weakness	14 (15.9)			7 (8.0)
			Tinnitus	20 (22.7)			0
			Anorexia	14 (15.9)			4 (4.5)
			Vomiting	10 (11.4)			6 (6.8)
			Myalgia	10 (11.4)			6 (6.8)
			Sweating	12 (13.6)			3 (3.5)
			Headache	9 (10.3)			4 (4.5)
			Bitter taste	8 (9.1)			5 (5.7)
			Diarrhea	7 (8.0)			2 (2.3)
			De Alencar, et al., 1997	QT			77*
Dizziness	39 (50.6)	10 (13.0)					
Abdominal pain	18 (23.4)	20 (26.0)					
Nausea	22	12					

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				(28.6)			(15.6)
			Weakness	15 (19.5)			9 (11.7)
			Headache	9 (11.7)			17 (22.1)
			Diarrhea	9 (11.7)			5 (6.5)
			Anorexia	13 (16.9)			5 (6.5)
			Pruritus	4 (5.2)			6 (7.9)
			Vomiting	5 (6.5)			4 (5.2)
Looareesuwan, et al., 1994	QT	50	Headache	41 (82)	MT	52	35 (67)
			Dizziness	35 (70)			37 (71)
			Cinchonism	47 (94)			6 (12)
			Nausea	26 (52)			25 (48)
			Vomiting	14 (28)			7 (13)
Karbwang, et al., 1994	QT	33	Nausea	20 (60)	AS	31	14 (45)
			Dizziness	16 (48)			16 (52)
			Vomiting	30 (91)			8 (26)
			Tinnitus	29 (88)			0
			Convulsions	0			1 (3)
			Bradycardia	NE			7 (23)

N= number of patients in ITT population (received study drug)

QT= quinine + tetracycline; AS-T= artesunate + tetracycline; A-P= atovaquone-proguanil; MT= mefloquine + tetracycline; AS= artesunate

* Evaluable patients (adverse event data not presented for ITT population)

†Not all studies with quinine combination therapy are included in this table, some studies did not report adverse events, other studies of oral quinine monotherapy which used a quinine combination as comparator were included in Table_ above..

NE= not evaluated

Adverse event data from the studies listed in the table above were combined to estimate the incidence of adverse reactions in patients who received drug combinations containing quinine or another (non-quinine) regimen, as shown in the table below.

Table 55: Summary of Adverse Events in Combination Quinine Studies (calculated from table above)†

Adverse Event	Quinine Combination N=248	Comparator* N=248
Dizziness	118 (47.5)	70 (28.2)
Tinnitus	104 (41.9)	3 (1.2)
Nausea	83 (33.5)	81 (32.6)
Headache	59 (23.7)	56 (22.6)
Vomiting	54 (21.8)	21 (8.5)
Cinchonism	47 (18.9)	6 (2.4)
Abdominal pain	38 (15.3)	34 (13.7)
Weakness	29 (11.7)	16 (6.5)
Anorexia	27 (10.9)	9 (3.6)
Diarrhea	17 (6.9)	10 (4.0)
Sweating	12 (4.8)	3 (1.2)
Myalgia	10 (4.0)	6 (2.4)
Bitter taste	8 (3.2)	5 (2.0)
Pruritus	4 (1.6)	6 (2.4)
Bradycardia	Not evaluated	7 (2.8)
Seizure	0	1 (0.4)

*Comparators included astesunate-tetracycline, atovaquone-proguanil, mefloquine-tetracycline, and artesunate

†Studies included Duarte, et al., 1996, De Alcencar, et al., 1997, Looareesuwan, et al., 1994, and Karbwang, et al., 1994

Medical Officer Comments: This analysis is limited by different study designs, as well as differences in adverse event ascertainment and reporting. Those events which were reported significantly (approximately 2-fold or higher) more frequently in patients who received quinine combination therapy than in those who received non-quinine-containing regimens were dizziness, tinnitus, vomiting, cinchonism, weakness, anorexia, and sweating, all reactions known to be associated with quinine use.

Adverse Events in Studies of Oral Quinine Monotherapy vs. Quinine Combination Therapy

To assess whether adverse events differed between treatment groups in studies which compared quinine monotherapy to quinine combination therapy, adverse events reported in studies which evaluated both are shown in the following table. Only one of these studies provided sufficient comparative information regarding adverse effects in patients who received 7-day regimens of quinine monotherapy vs. combination therapy. In Pukrittayakamee, et al. (2000), the incidence of gastrointestinal adverse events (nausea, vomiting, diarrhea, abdominal pain) was similar in patients who received quinine monotherapy or quinine plus tetracycline or quinine plus clindamycin. The incidence of cinchonism was reportedly similar in all 3 treatment groups, and

tinnitus occurred in almost all (93%) patients in the study. In the study by Metzger, et al. (1995), in which patients received only 1.5 days (3 doses) of quinine alone or in combination with clindamycin or doxycycline, the incidence of the adverse events reported was similar among the 3 treatment groups. In the pediatric study by Kresmner, et al. (1994), in which patients received short course (3 days) quinine monotherapy or quinine in combination with clindamycin for 3 days, dizziness was reported more frequently in patients who received quinine monotherapy (9/31, 29%) than in patients who received quinine plus clindamycin (1/34, 3%), otherwise the incidence of adverse events was fairly similar between treatment groups. There is no known pharmacokinetic interaction between quinine and clindamycin (e.g. increased quinine metabolism) that would explain why dizziness occurred more frequently in patients who received quinine monotherapy. Based on these limited data, there does not appear to be any significant difference in the incidence of adverse events in quinine combination regimens containing tetracycline, doxycycline, or clindamycin, in comparison to quinine alone.

Table 56: Incidence of Adverse Events in oral Quinine Combination Therapy and Quinine Monotherapy Comparator

Study	Adverse Event	Quinine Monotherapy (duration code)	Quinine Monotherapy n/N (%)	Quinine Combination Comparator (duration code)	Quinine Combination Comparator n/N (%)
Pukritayakamee, et al., 2004	NR	Q7	--	Q7T7	--
Pukrittayakamee, et al., 2000	Gastrointestinal symptoms**	Q7	3/68 (4.4)	Q7T7	2/68 (2.9)
				Q7C7	1/68 (1.5)
	Tinnitus	Q7	193/204 (93.7) for all treatment groups	Q7T7 and Q7C7	193/204 (93.7) for all treatment groups
	Cinchonism	Q7	Similar in all treatment groups, incidence NR	Q7T7 and Q7C7	Similar in all treatment groups, incidence NR
Metzger, et al., 1995	Dizziness	Q1.5	27/108 (25%) all treatment groups*	Q1.5C3	27/108 (25%) all treatment groups*
				Q1.5D3	27/108 (25%) all treatment groups
	Abdominal pain	Q1.5	22/108 (20%) all treatment groups*	Q1.5C3	22/108 (20%) all treatment groups*
				Q1.5D3	22/108 (20%) all treatment groups
	Nausea	Q1.5	19/108 (18%) all treatment groups*	Q1.5C3	19/108 (18%) all treatment groups*
				Q1.5D3	19/108 (18%) all treatment groups*
	Diarrhea	Q1.5	13/108 (12%) all	Q1.5C3	13/108 (12%) all

			treatment groups*		treatment groups*
				Q1.5D3	13/108 (12%) all treatment groups*
	Vomiting	Q1.5	12/108 (11%) all treatment groups*	Q1.5C3	12/108 (11%) all treatment groups*
				Q1.5D3	12/108 (11%) all treatment groups*
Kremsner, et al., 1994 (pediatric)	Dizziness	Q3	9/31 (29)	Q3C3	1/34 (3)
	Nausea	Q3	2/31 (6)	Q3C3	0
	Diarrhea	Q3	0	Q3C3	2/34 (6)
	Abdominal pain	Q3	4/31 (13)	Q3C3	5/31 (15)
	Itching	Q3	0	Q3C3	1/34 (3)

NR = not reported Q7= 7 days of quinine; Q7T7= 7 days of quinine plus tetracycline; Q7C7= 7 days of quinine plus clindamycin; Q3= 3 days quinine; Q3C3= 3 days of quinine plus clindamycin; Q1.5= 1.5 days (3 doses) quinine; Q1.5 C3= 1.5 days quinine plus 3 days clindamycin; Q1.5 D3= 1.5 days quinine plus 3 days doxycycline

*Authors noted no significant difference between treatment groups, but data was not provided.

** Gastrointestinal symptoms included nausea, vomiting, diarrhea, and abdominal pain.

Medical Officer Comments: In one pharmacokinetic study of patients with acute uncomplicated P. falciparum malaria, the combination of quinine plus tetracycline resulted in plasma quinine concentrations about 2-fold higher than observed in patients who received quinine monotherapy (Karbwang, et al., 1991). Quinine toxicity appears related to plasma quinine concentration. Thus, the study by Pukrittayakamee, et al. (2000) was reassuring in that no difference was observed in the adverse effect profile in patients who received quinine monotherapy or quinine plus tetracycline or clindamycin. However, definitive conclusions regarding the safety of quinine combined with an antimicrobial agent such as tetracycline, doxycycline and clindamycin cannot be drawn from these limited data.

Adverse Events Reported in Published Studies of Parenteral Quinine for Treatment of Severe P. falciparum Malaria

For comparative purposes, randomized studies of parenteral quinine were submitted in support of this application. Adverse events were not elicited or reported systematically in all of these studies, but those reported are shown in the table below.

Table 57: Adverse Events in Patients who received Parenteral Quinine or comparator in RCTs (adapted from Applicant's Table 9, ISS)

Study	Quinine N	Quinine dose and duration	Adverse Events Reported in Quinine group (n)	Comparator(s) N	Comparator(s) dose and duration	Adverse Events Reported in Comparator group (n)
Singh, et al., 2000	26	10 mg/kg/day IV for 7 days	Hypotension (3); cinchonism (2); GI intolerance (7); myocarditis (1); hypoglycemia (4)	Artemether 26	4 mg/kg IM on first day; then 2 mg/kg/day for 4 days	GI intolerance (2)
Newton, et al., 2003	54	20 mg/kg IV loading dose; then 10 mg/kg tid for 7 days*	Hypoglycemia (15); cinchonism (number not reported)	Artesunate 59	2.4 mg/kg x 1 dose; then 1.2 mg/kg x 1 in 12 hours; then 1.2 mg/kg/day for 7 days**	Urticarial rash (1)
Satti, et al., 2002	39	10 mg/kg IV every 8 hours for 7 days*	Hypoglycemia (1)	Artemether 38	1.6 mg/kg/q12 hours for one day; then 1.6 mg/kg/day for 4 days	None reported
Adam, et al., 2002	21	20 mg/kg IV loading dose; then 10 mg/kg/8 hours for 7 days*	Hypoglycemia (1)	Artemether 20	3.2 mg/kg x 1 dose; then 1.6 mg/kg/day for 4 days	None reported
Faiz, et al., 2001	54	20 mg/kg IV loading dose; then 10 mg/kg/8 hours for 7 days*	vomiting (21); diarrhea (7); convulsions (17); neuropsychiatric side effects (8)	Artemether 51	Weight > 45 kg: 160 mg IM x 1; then 80 mg/kg/day for 4 days; weight < 45 kg: 3/2 mg/kg IM x 1; then 1/6 mg/kg/day for 4 days	Vomiting (18); diarrhea (8); convulsions (21); neuropsychiatric side effects (14)
Thuma, et al., 2000	44 (pediatric)	20 mg/kg IV loading dose; then 10 mg/kg/8 hours for 7 days*	34/44 (77%) patients‡	Artemotil 48	3.2 mg/kg initial dose; then 1.6 mg/kg/day for 5 days	36/48 (75%) patients‡
Moyou-Somo, et al., 2001	51 (pediatric)	20 mg/kg IV loading dose; then 10 mg/kg/8 hours for 6 days*	Blackwater fever (and death) following quinine (1)	Arteether 51	3.2 mg/kg IM initial dose; then 1.6 mg/kg daily for 4 days	None reported

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Taylor, et al., 1998	81 (pediatric)	20 mg/kg IV loading dose; then 10 mg/kg/8 hours (for minimum of 3 doses); followed by single dose SP	More patients in the quinine group than comparator showed QTc prolongation after treatment, but difference not statistically significant (incidence not specified)	Arthemether 83	3.2 mg/kg loading dose, then 1.6 mg/kg/day for minimum of 3 doses; followed by single dose SP	NR
Olumeses, et al., 1999	49 (pediatric)	20 mg/kg IV loading dose; then 10 mg/kg/8 hours for 7 days*	NR	Artemether 54	3.2 mg/kg IM initial dose; then 1.6 mg/kg daily for 4 more days	NR
Murphy, et al., 1996	71 (pediatric)	20 mg/kg IV loading dose; then 10 mg/kg/8 hours (for minimum of 3 doses); followed by single dose SP	Significant QTc (increased >25% baseline) (5)	Artemether 89	3.2 mg/kg IM initial dose; then 1.6 mg/kg daily for 5 days total	Significant QTc (increased >25% baseline) (20)
Karbwang, et al., 1995	52	20 mg/kg IV loading dose; then 10 mg/kg/8 hours for 7 days*	Most surviving patients developed tinnitus; severe hearing impairment (2); QTc prolongation (common), but no significant dysrhythmia; neutropenia (8)	Artemether 50	160 mg IM loading dose, followed by 80 mg daily for 6 more doses	Mild, transient pain at injection site. No significant ECG changes noted; neutropenia (10)
Karbwang, et al., 1992	12	20 mg/kg IV loading dose; then 10 mg/kg/8 hours for 7 days*	Dizziness and vertigo (4)	Artemether 14	160 mg IM loading dose, followed by 80 mg daily for 6 more doses	No adverse events
Tran Hien, et al., 1996	276	20 mg/kg IM loading dose; then 10 mg/kg every 8 hours for minimum of 3 days †	Hemoglobinuria (blackwater) (4); hypoglycemia (69/276, 25%); QTc prolonged > 500 msec (60/133 45%) patients with ECG monitoring; QTc prolonged > 25%	Artemether 284	4 mg/kg IM loading dose; followed by 2 mg/kg every 8 hours for minimum of 3 days †	Hemoglobinuria (blackwater) (7); hypoglycemia (31/284, 11%); QTc prolonged > 0.5 second 38/152 patients with ECG monitoring, 25%); QTc

			(12/133, 9%)			prolonged > 25% (11/152, 7%)
Van Hensbroek, et al., 1996	288	20 mg/kg IM loading dose; then 10 mg/kg every 12 hours for 5 days#	Hypoglycemia (42/288, 14.6%); injection site reactions (17/88, 5.9%); sterile abscess at injection site (5/288, 1.7%)	Artemether 288	3.2 mg/kg IM initial dose, followed by 1.6 mg/kg daily for 4 days#	Hypoglycemia (29/288, 10.1%); injection site reactions (2/288, 0.7%); sterile abscess at injection site (1/288, 0.3%)

NR= not reported; N= number of patients in treatment group

*oral quinine substituted when patient was able to swallow tablets

** Patient switched to oral artesunate or oral artesunate plus mefloquine or tetracycline or doxycycline

SP= sulfadoxine-pyrimethamine

†When patient could take oral medication, a second randomization was performed to either single oral dose of mefloquine (15 mg/kg) or to oral quinine 10 mg/kg three times daily for up to 4 days. Treatment with quinine was followed by 2 tablets of SP.

#In year 2 and 3 of the study, patients also received a single oral dose of SP after randomized treatment.

‡ Adverse events reported with quinine in this pediatric studies included weakness (2), aphasia (8), deafness (2), fevers/rigors (2), anorexia (6), nausea/vomiting (2), diarrhea (5), cough (7), pneumonia (7), conjunctivitis (2), other infections (e.g. skin) (5).

Medical officer Comments: Although actual quantification of adverse events by combining studies is not possible due to significant differences in study design, patient populations, and adverse event reporting, some patterns of adverse events with intravenous quinine emerged upon review. Hypoglycemia, dizziness or vertigo, tinnitus, and cinchonism were reported as adverse events more frequently in the quinine group than in comparator groups. QTc prolongation was reported more commonly with quinine than with comparators, except in the study reported by Murphy, et al. (1996), in which the incidence of significant QTc prolongation was higher in the artemether than the quinine treatment group. Hypotension was reported as an adverse event in quinine-treated patients in only one study (Singh, et al., 2000). These data were pooled across studies in an attempt to estimate incidence of specific adverse events in patients who received quinine and those who received the comparator, as discussed below.

In an attempt to quantify the adverse events reported in adult patients with parenteral quinine or the comparator (artemether and artesunate), the total number of patients for each treatment arm, and the number of patients with specific adverse events were combined across studies. Because adverse events were not reported systematically reported in all of the studies, only a rough estimate (possibly an underestimate) of incidence can be determined, as shown in the table below.

Table 58: Estimate of Incidence of Adverse Events in pooled Studies of Adult Patients* treated with parenteral Quinine or Comparator (calculated from table above)

Adverse Event	Quinine N=822 n (%)	Comparator** N=830 n (%)
Hypoglycemia	132 (16.1)	60 (7.2)
QTc prolongation > 500 msec	60 (7.3)	38 (4.6)
Vomiting	21 (2.6)	18 (2.2)
Convulsions	17 (2.1)	21 (2.5)
Injection site reactions	17 (2.0)	2 (0.2)
Neutropenia	8 (1.0)	10 (1.2)
Neuropsychiatric symptoms	8 (1.0)	14 (1.7)
Gastrointestinal intolerance	7 (0.9)	2 (0.2)
Diarrhea	7 (0.9)	8 (1.0)
Sterile abscess at injection site	5 (0.6)	1 (0.1)
Dizziness/vertigo	4 (0.5)	0
Hemoglobinuria	4 (0.5)	7 (0.8)
Cinchonism	2 (0.2)	0

*Studies with adult patients included Singh, et al., 2002; Newton, et al., 2003; Satti, et al., 2002; Adam, et al., 2002; Faiz, et al., 2001; Karbwang, et al., 1995; Karbwang, et al., 1992; Tran, et al., 1996; van Hensbroek et al., 1996).

** Comparators were artemether (1055 patients), and artesunate (59 patients).

Medical Officer Comments: Patients with severe malaria could be obtunded and unable to report many of the adverse events noted in studies with oral quinine, such as hearing or visual loss. Because of the differences in study design, as well as in collection and reporting of adverse events, these data can only serve as a very rough snapshot of adverse events observed in patients treated for severe malaria. It is notable that hypoglycemia, QTc prolongation, dizziness/ vertigo and, cinchonism were reported more frequently in patients who received quinine than the artemisinin comparator. It should also be noted that injection site reactions and sterile abscesses at the injection site were noted only in studies with intramuscular quinine rather than intravenous.

Adverse Events Reported in Postmarketing Databases

The most common adverse events from the FDA AERS postmarketing databases from 1969 through December 31, 2003 were summarized by the applicant, as shown in the table below, from 487 adverse event listings, some of which may have been duplicates and follow-up reports not linked to the initial report. From 1969 to October, 1997, thrombocytopenia was the most common adverse event reported, with 66 reports. Similarly, in the time period from November, 1997 through 31 December, 2003, thrombocytopenia was the most commonly reported adverse event, with 44 total reports. After thrombocytopenia, the most common adverse reactions reported in the latter time frame were vomiting (22 reports), nausea (19 reports). Interestingly in the earlier time frame (1969 to October, 1997), the most common adverse events after thrombocytopenia were rash (18 reports), dyspnea (16 reports) and thrombocytopenic purpura (14 reports).

Table 59: Most Common Adverse Events Reported in FDA Postmarketing Databases from 1968 through December 31, 2003 (Applicant's Table 8, 120-day Safety Update)

The 20 Most Common Adverse Events by Database Reported in Association with Quinine (Suspect Drug) During FDA's Postmarketing Experience

Adverse Event Term (COSTART Data) 1969 – 31 Oct. 1997	Count ¹	Adverse Event Term (MedDRA Data)	Count	
			NDA 21-799 1 Nov. 1997 – 30 Jun 2003 ²	Update 1 Nov. 1997 – 31 Dec 2003 ³
Thrombocytopenia	66	Thrombocytopenis	35	44
Rash	18	Vomiting NOS	22	22
Thrombocytopenic Purpura	14	Nausea	15	19
Chills	9	Medication Error	11	17
Dyspnea	16	Drug Interaction NOS	16	16
Coagulation Disorder	9	Pyrexia	11	15
Leukopenia	13	Ecchymosis	13	13
Hypotension	12	Petechiae	13	13
Epistaxis	11	Diarrhea NOS	11	11
Acute Kidney Failure	10	Dyspnea NOS	11	11
Gum Hemorrhage	9	Epistaxis	9	10
Deafness	9	Deafness NOS	9	9
Fever	9	Drug Maladministration	9	9
Headache	9	Hemoglobin Decreased	9	9
Nausea and Vomiting	9	Overdose NOS	9	9
Pruritus	9	Tinnitus	9	9
Chills and Fever	8	Platelet Count Decreased	–	9
Tinnitus	9	Hematoma NOS	8	8
Asthenia	8	Liver Function Tests NOS Abul	8	8
Coma	8	Rigors	–	8

1. Source: FOI Spontaneous Reporting System with Quinine, 1968 through October 1997; included in NDA 21-799
2. Source: FOI Report of Adverse Events with Quinine through 30 June 2003, the most current information available publicly as of 9 June 2004; included in NDA 21-799
3. Source: FOI Report of Adverse Events with Quinine Reaction Summary through 31 December 2003, the most current information available publicly as of 31 December 2004

Medical Officer Comments: Postmarketing reports do not permit estimation of adverse event incidence. These reports are collected voluntarily from physicians, other health care providers, the sponsor, and consumers, and the denominator (number of patients who received the medication) is not known. Additionally, because the terms (COSTART vs. MedDRA) for adverse events differed across the time periods reported, pooling of adverse events across the time periods is not feasible. However, thrombocytopenia was the most common adverse event for all time periods reported.

In the WHO postmarketing database for quinine, there were a total of 1908 reports of 4191 adverse events (an average of 2.2 events per report) from 27 countries, reported from 1968 through December, 2004 for any quinine product. For oral quinine, there were 504 reports of 1195 adverse events (an average of 2.4 events per report) from 15 countries, from 1968 through March, 2004. The most common adverse events reported were summarized by the sponsor, as shown in the table below.

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Table 60: Most Common Adverse Events Associated with Quinine in WHO Database from 1968 through December, 2004 (from Applicant's Table 9, 120-day safety update)

World Health Organization Data: The Most Commonly Reported Adverse Events Associated with Quinine

Adverse Event	Count	
	NDA 21-799 ¹ Oral Quinine Sulfate 1968 through March 2004	All Quinine Products 1968 through December 2004 ²
Total No. of Reports	504	1908
Thrombocytopenia	94	409
Tinnitus	66	361
Vomiting	51	171
Purpura	50	169
Nausea	50	158
Fever	47	127
Rash	30	111
Pruritus	31	103
Headache	35	94
Rigors	27	76
Diarrhea	23	74
Dizziness	20	67
Rash erythematous	15	64
Urticaria	15	54
Epistaxis	14	52
Photosensitivity reaction	13	41
Dyspnea	11	40
Deafness	0	39
Rash maculo-papular	17	39

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1. Source: WHO Report of Adverse Events with Oral Quinine Sulfate through March 2004.
2. Source: WHO Report of Adverse Events with Quinine through 2 November 2004, the most current information available publicly as of 31 December 2004 for quinine, regardless of the salt or route of administration.

Medical Officer Comments: Similar to the FDA AERS postmarketing database, thrombocytopenia was the most frequent adverse event reported overall. Aside from thrombocytopenia, the most frequently reported adverse events were tinnitus and vomiting. There was little difference in the relative frequency of specific adverse event reports for oral quinine compared to all quinine products, except for deafness which was not reported with oral quinine in this database. Deafness, however, was reported to the AERS database, as shown in Table 52 above. The nature of the postmarketing data is such that a true incidence cannot be calculated from adverse event reports given lack of denominator data (number of patients who received the drug). Additionally, postmarketing data reporting is voluntary, and is generally considered underreported.

7.1.5.5 Identifying common and drug-related adverse events

In most of the randomized, controlled studies provided by the applicant with this NDA submission, drug-related adverse events were not distinguished from those considered unrelated. In the bioequivalence studies sponsored by the applicant, however, adverse events considered possibly or probably related to study drug by the investigator were reported, and are shown in the tables below.

Table 61: Drug-Related Adverse Events in Pharmacokinetic Study R040376 Dose-Proportionality Study (Data obtained from adverse events dataset)

Adverse Event	Quinine 1 x 324 mg capsule N=24	Quinine 2 x 324 mg capsule N=24	Total events* N=24
Headache	2	0	2
Night sweats	1	0	1
Myalgias	1	0	1
Nausea	0	3	3
Light-headedness	0	1	1
Diarrhea	0	1	1
Dizziness	0	1	1
Tinnitus	0	1	1
Total Drug-Related Adverse Events	4	7	11
Number (%) of subjects with a drug-related AE	3 (12.5%)	5 (20.8%)	8 (33.3)

N= number of subjects subjects were the same for each treatment group

Medical Officer Comments: In this study, the most common drug-related adverse events were nausea, which occurred in 3/24 (12.5%) subjects who received a 648 mg dose of quinine, and headache, which occurred in 2/24 (8.3%) subjects who received a 324 mg dose of quinine. Although the incidence of dru-related adverse events was higher in subjects who received the higher (648 mg) dose of quinine sulfate, the number of subjects tested was too small to draw conclusions regarding any dose relationship between adverse events and quinine.

Table 62: Drug-Related Adverse Events in Pharmacokinetic Bioequivalence Study RA3085 (data obtained from adverse events dataset)

Adverse Event	Mutual Pharma Quinine capsule 324 mg (fasted) N=27	GPO Quinine capsule 300 mg (fasted) N=27	Mutual Pharma Quinine Capsule 324 mg (fed) N=27	Total events N=27
Headache	3	3	3	9
Stiff neck	1	0	0	1
Nausea	0	2	1	3
Vomiting	0	1	1	2
Heartburn	0	0	1	1
Total drug-related adverse events	4	6	7	17
Total subjects (%) with a drug-related adverse event	4 (14.8)	3 (11.1)	5 (18.5)	12 (44.4)

N= number of subjects.

This study had a three-way crossover design, so subjects are the same for each group

Medical Officer Comments: No significant difference was seen in drug-related adverse events in subjects who received quinine sulfate in fed or fasted state, or those who received the Thailand-GPO formulation in comparison to Mutual's 324 mg capsule. In this study, headache was the most common adverse event considered possibly or probably related to study drug, occurring in 3/27 (11.1%) subjects in each treatment period.

Drug-Related Adverse Events Reported in Randomized, Controlled Studies of Quinine Monotherapy

This section describes only studies which reported adverse events considered drug-related by the investigators.

Study 1: McGready, et al. (2000)

In this randomized, controlled study performed in Thailand in pregnant women (second or third trimester), adverse events considered possibly drug-attributable were compared for the 2 treatment groups. There were no drug-related adverse events considered serious in this study. Drug-attributable adverse events reported in this study are shown in the following table. For full details of the study, see Appendix, section 10. 1.

Table 63: Incidence of Drug-Attributable Adverse Events Reported in McGready, et al. (2000)

Adverse Event	Quinine N=66	Mefloquine-artesunate N=42
	%	%
Headache	50	21
Muscle/joint pain	28	32
Abdominal pain	50	29
Anorexia	48	34
Nausea	50	47
Vomiting	2	0
Dizziness	87	45
Tinnitus	66	17
Abnormal neuro*	5	1

*authors did not state if this meant neurological sign or symptom

Medical Officer Comments: In this study which included only women in the second or third trimester of pregnancy, adverse events significantly (approximately 2-fold higher) more common in patients who received quinine than the comparator were headache, tinnitus, and dizziness. These findings are consistent with the known adverse event profile of quinine.

Study 2: Bich, et al. (1996)

This study was performed in Vietnam in patients ages 8-65 years old with uncomplicated *P. falciparum* malaria. For full details, see study report in Appendix, section 10.1. Patients were

randomized to oral quinine monotherapy (10 mg/kg 3 times daily for 7 days) (N=59), artemisinin (20mg/kg single dose) plus quinine (10 mg/kg 3 times daily for 3 days) (N= 45), or artemisinin (20mg/kg single dose) plus doxycycline (4 mg/kg for 3 days) (N=53). Drug-related adverse events reported in this study are shown in the table below.

Table 64: Incidence of Drug-Related Adverse Events Reported by Bich, et al. (1996)

Adverse Event (AE)	Quinine N=59	Quinine +artemisinin N=45	Doxycycline+ artemisinin N=53
	n (%)	n (%)	n (%)
Any drug-related AE	18 (30.5)	9 (20)	8 (15.1)
Dizziness	9 (15.3)	4 (8.9)	4 (7.5)
Tinnitus	13 (22.0)	5 (11.1)	1 (1.9)
Impaired hearing	6 (10.2)	4 (8.9)	0
Excess salivation	2 (3.4)	0	0
Dry mouth	4 (6.8)	1 (2.2)	1 (1.9)
Hemoglobinuria	0	0	1 (1.9)
Skin rash	0	1 (2.2)	0

Medical Officer Comments: Not unexpectedly because of the longer duration of treatment, the quinine monotherapy group had the highest incidence of drug-related adverse events. Tinnitus and impaired hearing were observed more frequently in patients who received one of the two quinine-containing regimens.

Study 3: De Vries, et al. (2000)

This study was a continuation of the study published by Bich, et al. (1996) discussed above. For full details see study report in Appendix, section 10.1. This study was performed in Vietnam, and included patients ages 8-65 years old with uncomplicated *P. falciparum* malaria, 84 patients were randomized to 7-day quinine monotherapy (10 mg/kg 3 times daily) 96 patients were randomized to artemisinin (20 mg/kg single dose) plus quinine (10 mg/kg 3 times daily for 3 days), or to artemisinin (20 mg/kg single dose) plus quinine (10 mg/kg 3 times daily for 5days). The authors reported 2 cases of hemoglobinuria observed after 24 hours of treatment, and regarded these events as adverse effects of quinine, although it was not specifically stated to which treatment group the patients who experienced hemoglobinuria had been randomized. Both patients, however, were withdrawn from the study due to hemoglobinuria and were treated with artesunate. One of these cases was reported previously in the study by Bich, et al. (1996).

Medical Officer Comments: Hemoglobinuria has also been described in the published literature, in association with severe malaria, with blackwater fever in malaria patients treated with quinine, with hemolysis related to G6PD deficiency, or to quinine hypersensitivity. The authors of the study attributed hemoglobinuria to quinine in both cases.

Drug-Related Adverse Events Reported in Randomized, Controlled Studies of Quinine Combination Therapy

This section describes the only study submitted of quinine combination therapy which reported adverse events considered drug-related by the investigators/authors.

Study 1: Karbwang, et al. (1994)

This study was performed in Thailand and enrolled only males ages 15-35 years old. For full details see study report in the Appendix, section 10.1. Patients were randomized to quinine (600 mg orally 3 times daily) plus tetracycline (250 mg orally every 6 hours) for 7 days (N=33), or to artesunate (200 mg orally initial dose, then 100 mg 12 hours later, then daily for 4 days) (N=31). The incidence of drug-related adverse events in this study is shown in the table below.

Table 65: Incidence of Drug-Related Adverse Events Reported by Karbwang, et al. (1994) (from author's Table 3)

Drug-Related Adverse Event	Artesunate N=31	Quinine + tetracycline N=33
	n (%)	n (%)
Nausea	14 (45)	20 (60)
Dizziness	16 (52)	16 (48)
Vomiting	8 (26)	30 (91)
Tinnitus	0	29 (88)
Convulsions	1 (3)	0
Bradycardia	7 (23)	NE

Medical Officer Comments: The authors note that the incidence of nausea, and dizziness were not significantly different in the two groups; while the incidence of vomiting and tinnitus were significantly higher in the quinine+tetracycline group than in the comparator group. ECGs were not performed in the quinine-tetracycline group, so the incidence of cardiac arrhythmia or QTc prolongation could not be determined for that regimen.

Drug-Related Adverse Events Conclusions

The most common adverse events determined to be drug-related (for quinine mono- or combination therapy) by study investigators/authors were headache and nausea in the pharmacokinetic studies, headache, tinnitus and dizziness (McGready, et al., 2000), tinnitus and hearing impairment (Bich, et al., 1996), hemoglobinuria (De Vries, et al., 2000), and tinnitus and vomiting (Karbwan, et al., 1994).

7.1.5.6 Additional analyses and explorations

Foreign labels for oral quinine were compared for inclusion of adverse events. Although inclusion of an adverse event in a label, does not necessarily imply its relative incidence, adverse events noted almost universally in the foreign quinine labels included cinchonism (10/10), headache (9/10), cutaneous rashes and urticaria (10/10), and tinnitus (9/10) (section 7.1.4).

7.1.6 Less Common Adverse Events

Because the actual incidence of adverse events with oral quinine could not be determined from published studies, we have relied heavily on reviews of quinine toxicity to ascertain relative frequency of adverse events. Additionally, adverse events associated with quinine use identified only from case reports or case series were considered uncommon or rare.

Some of the less common adverse events reported with quinine include asthma, blackwater fever, with massive hemolysis, hemoglobinemia, and hemoglobinuria, TTP, hypoprothrombinemia, leukopenia, agranulocytosis (as reviewed by Tracy and Webster, 2001) Other rare or uncommon adverse events reported with quinine include transient or permanent blindness, thrombocytopenia, leukopenia, acute intravascular hemolysis, HUS, and DIC, and cardiovascular adverse effects, including arrhythmias, photosensitivity rashes, cutaneous vasculitis, lichen planus, lichenoid photosensitivity, and granulomatous hepatitis (as reviewed by Taylor and White, 2004).

Adverse events for which only one or a few case reports of quinine-associated adverse events were provided by the applicant, or found upon literature search include lupus-like syndrome, lupus anticoagulants, toxic epidermal necrolysis, Steven's Johnson syndrome, acral necrosis, renal failure, acute interstitial nephritis, pulmonary edema, ARDS, pulmonary infiltrates, blindness, deafness, as reviewed in section.7.1.3.3 above.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Pharmacokinetic Studies

In the two pharmacokinetic studies submitted by the applicant, laboratory evaluations were performed at screening, and selected laboratory evaluations were performed on study exit. The applicant states that laboratory test results showed no clinically significant changes, or changes considered by the investigator to be related to study drug. Laboratory data was not summarized or presented in the datasets for these studies, and thus was not reviewed. Some of the published studies submitted in support of this application were reviewed to evaluate changes in laboratory values associated with quinine.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The randomized, controlled trials which studied oral quinine in the treatment of uncomplicated malaria, and those which evaluated parenteral quinine for treatment of severe malaria were reviewed for laboratory analyses. Some of the studies reported monitoring laboratory values, but most (8/11) did not report the results, as summarized in the table below. Of the 3 studies that reported laboratory results, only 1 reported substantial laboratory data.

Table 66: Laboratory Evaluations in Randomized Controlled Trials of Oral Quinine Monotherapy for treatment of Uncomplicated Malaria (adapted from Applicant's Table 18, ISS)

Study	N	Patient Population	Laboratory Evaluation	Results of Laboratory Evaluation
Watt, et al., 1988	10	Males ≥ 16 years old	Admission hematology and biochemistry only	NA
Pukrittayakamee, et al., 2004	30	Adult males	Routine biochemistry and hematology at baseline, 7, 14, 21 and 28 days	NR
Mueller, et al., 2004	48	Age ≥ 18 years old	Not reported	NA
Ache, et al., 2002	48	> 6 months old	Hemoglobin and hematocrit at baseline	NA
Rahman, et al., 2001	49	12-60 years old	Hemoglobin at baseline	NA
Pukrittayakamee, et al., 2000	68	Adult males	Routine biochemistry and hematology at baseline, days 7, 14, 21, and 28	No patient developed a serious laboratory abnormality
McGready, et al., 2000	42	Pregnant women	Hematocrit every 2 weeks	Mean hematocrits were 29.4 % (17.5-39.0) for MAS group and 28.7% (21.0-37.2) for Q group at baseline, and 27.6% and 29.5% for MAS and Q groups, respectively, day 7 (p=0.043)
De Vries, et al., 2000	84	8-65 years old	CBC and "liver tests" at baseline and day 3	NR
Bich, et al., 1996	59	8-65 years old	Hemoglobin, hematocrit, WBC, glucose, AST, ALT, creatinine, BUN at baseline and day 3	All treatment groups (Q, AQ, and AD) had small decrease in hemoglobin and hematocrit on day 3. Mean WBC decreased from 7.6 x 10 ⁹ /L to 7.2 x 10 ⁹ /L on day 3; BUN and AST decreased slightly in all groups; AST decreased slightly in AQ and AD groups
Metzger, et al., 1995	40	> 15 years old	Not reported	NA
Segal, et al., 1974	26	Males > 15 years old	Hematocrit, WBC, bilirubin, alkaline phosphatase, AST, and creatinine at baseline, days, 3,6, and 18	See table 60 below.

N= number of patients who received quinine

NA= not applicable;

NR= not reported

Medical Officer Comments: Only 1 of these studies provided any substantial laboratory data relevant to safety (Segal, et al., 1974), and in that case only the mean and range of laboratory values was provided for the quinine group and comparator over time, as summarized in the table below.

Table 67: Laboratory Evaluations Reported in Segal, et al. (1974) Study

Laboratory Test	Study Day	Quinine N=26	WR33063 N=25
		Mean (range)	Mean (range)
Hematocrit (%)	0	33.0 (20-46)	33.3 (12-47)
	3	30.6 (16-45)	32.2 (19-44)
	6	33.6 (18-46)	32.4 (23-44)
	28	39.6 (30-47)	37.9 (30-44)
WBC (count/mm ³)	0	6,256 (3,080-13,420)	5,895 (3,450-11,330)
	3	6,561 (3,190-10,120)	5,918 (2,970-9,990)
	6	7,297 (4,400-14,300)	7,085 (3,050-11,000)
	28	9,295 (5,280-15,840)	9,638 (4,840-25,410)
Bilirubin (direct) mg/dL	0	0.69 (0.1-5.1)	0.56 (0.1-3.0)
	3	0.64 (0.1-4.2)	0.44 (0-1.2)
	6	0.46 (0-3.4)	0.32 (0-0.9)
	28	0.23 (0-0.6)	0.25 (0-0.9)
Bilirubin (total) mg/dL	0	1.34 (0.3-6.1)	1.29 (0.3-3.8)
	3	0.9 (0.2-4.9)	0.8 (0.1-1.7)
	6	0.7 (0.1-3.7)	0.8 (0.1-1.2)
	28	0.5 (0.1-1.1)	0.6 (0.1-1.5)
Alkaline phosphatase (sigma units???)	0	2.1 (1.0-4.7)	2.5 (0.8-6.1)
	3	1.9 (0.8-4.2)	2.5 (1.1-5.1)
	6	1.9 (0.9-3.9)	2.4 (1.1-4.7)
	28	2.5 (1.4-5.7)	2.9 (1.3-7.0)
AST (S-F units)	0	29 (14-75)	39 (15-97)
	3	25 (3-38)	30 (11-72)
	6	24 (14-55)	32 (11-105)
	28	26 (17-41)	26 (13-59)
Creatinine (mg/dL)	0	1.4 (0.5-6.8)	1.3 (0.6-6.5)
	3	1.2 (0.5-5.3)	1.2 (0.6-8.5)
	6	1.0 (0.6-3.2)	1.0 (0.5-5.5)
	28	0.8 (0.5-1.2)	0.8 (0.5-1.3)

Medical Officer Comments: There were no apparent differences in the mean laboratory values during the course of treatment or at 28 days in the above study; however, statistical analysis was not provided by the investigator. Normal laboratory values were not provided, but the range of values indicates that there were likely some outliers with laboratory abnormalities, although these were not described in the study.

Laboratory Evaluation in Published Randomized, Controlled Trials of Combination Quinine Therapy for Treatment of Uncomplicated *P. falciparum* Malaria

Laboratory testing was performed in 10 of the 16 randomized studies which evaluated quinine combination therapy. However, no laboratory data was provided in 2 of these studies. Additionally, six of the studies reported only that no laboratory abnormalities were seen. Laboratory abnormalities with a quinine combination regimen were reported in 3 studies (De Vries, et al., 2000, De Alencar, et al., 1997, and Looaresuwan, et al., 1994) as described in the following table.

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Table 68: Laboratory Data in Randomized, Controlled Trials of Oral Quinine Combination Treatment of Uncomplicated *P. falciparum* Malaria (Applicant's Table 20, ISS)

Study	N (Treatment/Duration Code) ¹	Abnormal Laboratory Finding(s)
Duarte <i>et al.</i> , 1996(Brazil)	88 (Q3T7)	Selected biochemical and hematological tests and urinalysis were performed on admission and follow-up visits. No results or conclusions are, however, provided.
Pukrittayakamee <i>et al.</i> , 2004(Thailand)*	30 (Q7T7)	Routine biochemical and hematological tests were obtained on admission and repeated on Days 7, 14, 21, and 28 after admission. No results or conclusions are, however, provided.
Pukrittayakamee <i>et al.</i> , 2000(Thailand)*	(Q7C7 and Q7T7)	Routine biochemical and hematological tests were obtained on admission and repeated on Days 7, 14, 21, and 28 after admission. None developed a serious laboratory test abnormality.
de Vries <i>et al.</i> , 2000(Vietnam)*	184 (A1Q3 and A1Q5)	Two patients had hemoglobinuria after 24 hours of quinine treatment and were discontinued (regimen not specified).
Salcedo <i>et al.</i> , 1997 (Brazil)	14 (Q3T7)	Routine biochemical and hematological tests were obtained on admission and repeated on Days 7, 14, 21, and 28 of follow-up. Analysis of pre- and post-treatment values did not show a statistically significant difference ($P > 0.05$, student's t test)
de Alencar <i>et al.</i> , 1997(Brazil)	77 (Q7T7)	Routine biochemical and hematological tests were obtained on admission and repeated on Days 7, 14, 21, and 28 of follow-up. No patient with normal laboratory values on admission developed abnormal values on treatment, except for eosinophilia (number of patients not specified), which was attributed to intestinal parasites.
Vanijanonta <i>et al.</i> , 1996(Thailand)	50 (Q7T7 and Q7CQ3)	Routine biochemical and hematological tests were obtained on admission and repeated weekly thereafter. There were no significant changes in the laboratory test results.
Bich <i>et al.</i> , 1996(Vietnam)*	45 (A1Q3)	Selected biochemical and hematological tests and urinalysis were performed on admission and after 3 days of treatment. No results were significantly different for quinine <i>versus</i> artemisinin/quinine.
Looareesuwan <i>et al.</i> , 1994(Thailand)	52 (Q7T7)	Selected biochemical and hematological tests and urinalysis were performed on admission and on Days 7, 14, 21, and 28 of follow-up. Two patients who had normal transaminases on admission had increased values (range 103 to 154 IU) 2 to 3 weeks after treatment; values returned to within normal limits in 3 to 6 weeks.
Karbwang <i>et al.</i> , 1994(Thailand)	33 (Q7T7)	Routine biochemical and hematological tests were obtained on admission and on Days 2, 4, and 7 and then weekly until Day 28. No significant drug-related abnormalities occurred.

Q=quinine; T=tetracycline; C=clindamycin; A=artemisinin or artesunate; CQ=chloroquine *Also reviewed in Monotherapy ¹Treatment/Duration codes = drug abbreviation followed by duration of treatment in days. Combination therapy is represented as first drug abbreviation, duration, second drug abbreviation, duration

Medical Officer Comments: These studies provided very limited data on laboratory abnormalities which occurred in patients who received quinine combination therapy. The abnormalities which were reported include hemoglobinuria, which was discussed

previously (section 7.1.5.5), and mild-moderate transient transaminase elevation noted in 2 patients by Looareesuwan et al., 1994.

Laboratory Evaluation in Randomized, Controlled Trials of Parenteral Quinine for Treatment of Severe *P. falciparum* Malaria

Among the randomized trials of parenteral quinine for treatment of severe malaria, 13/14 performed some routine laboratory monitoring, as summarized by the applicant in the table below. Patients with severe malaria often have significant laboratory abnormalities at baseline, including anemia, leukopenia, thrombocytopenia, hypoglycemia, lactic acidosis, hyponatremia, elevated bilirubin, creatinine, and transaminases, and others. Thus, attributing laboratory abnormalities to quinine in patient with severe malaria could be difficult, and most of the studies summarized below did not report laboratory values during treatment, or treatment-related abnormal laboratory abnormalities.

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Table 69: Summary of Laboratory Data from Clinical Trials of Parenteral Quinine (Applicant's Table 19, ISS)

Abnormal Laboratory Findings in Published Randomized Studies of Parenteral Quinine for Treatment of Severe *P. falciparum* Malaria, Including Cerebral Malaria

Study	(Treatment/ Duration Code ¹)	Abnormal Laboratory Finding(s)
Intravenous		
<u>Newton et al., 2003</u> (Thailand)	54 (Q7 ²)	Glucose and lactate were evaluated at frequent intervals during treatment for an unspecified period of time: 28% developed hypoglycemia.
<u>Satti et al., 2002</u> (Sudan)	39 (Q7)	Hematological and biochemical tests were performed on admission and repeated on Day 3 of treatment. Hypoglycemia was observed in 1 patient (3%).
<u>Adam et al., 2002</u> (Sudan)	21 (Q7)	Capillary blood glucose was measured on admission and "estimated" 2 hours after drug administration. Hypoglycemia was observed in 1 patient (5%).
<u>Faiz et al., 2001</u> (Bangladesh)	54 (Q7)	Hematological and biochemical tests were performed at admission and repeated only as clinically warranted. No comment was made on abnormal laboratory test results associated with quinine.
<u>Thuma et al., 2000</u> (Zambia)	44 (Q7)	Hematological and biochemical tests were performed on admission and repeated on Days 3, 7, 14, 21, and 28. There was no difference between treatment with artemether and quinine treatment groups. No specific reference was made to abnormal laboratory test results attributed to quinine.
<u>Moyou-Somo et al., 2001</u> (Cameroon)	51 (Q7)	Hematological and biochemical tests were performed on admission and repeated on Days 3, 7, 14, and 28. There was no difference between treatment with artemether and quinine treatment groups. No specific reference was made to abnormal laboratory test results attributed to quinine.
<u>Taylor et al., 1998</u> (Malawi)	88 (Q5 ²)	Hematological and biochemical tests were performed on admission and repeated on Days 3, 7, and 28. No abnormal laboratory test results attributed to quinine were reported.
<u>Ohumare et al., 1999</u> (Nigeria)	49 (Q7)	Hematological and biochemical tests were performed on admission and Days 3 and 7 and then weekly at follow-up to Day 28. No abnormal laboratory test results attributed to quinine were reported.
<u>Murphy et al., 1996</u> (Kenya)	71 (Q5 ²)	Hematological and biochemical tests were performed at admission and repeated only as clinically warranted. No abnormal laboratory test results attributed to quinine were reported.
<u>Karbwang et al., 1993</u> (Thailand)	52 (Q7)	Hematological and biochemical tests were performed on admission and repeated on Days 2, 4, and 7. No abnormal findings were associated with quinine treatment.
<u>Karbwang et al., 1992</u> (Thailand)	12 (Q7)	Hematological and biochemical tests were performed on admission and repeated on Days 2, 4, and 7. There were no significant drug-related changes in laboratory test results.
Intramuscular		
<u>Tran et al., 1996b</u> (Vietnam)	276 (Q3)	Glucose and lactate were evaluated at 4, 8, 12, and 24 hours after admission: 25% developed hypoglycemia.
<u>Van Hensbroek et al., 1996</u> (Gambia)	288 (Q5)	Blood glucose was measured on admission and repeated after 4 and 12 hours and then when clinically indicated. Hypoglycemia occurred in 14.6% of patients.

Q=quinine

¹Treatment/Duration codes = drug abbreviation followed by duration of treatment in days.

²Intravenous treatment was followed by treatment with one other oral antimalarial drug

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Medical Officer Comments: Review of these studies confirmed the results shown in the applicant's table above. In Tran, et al. (1996), hypoglycemia was noted in 25% quinine-treated patients (adults) in comparison to 11% of those who received artemether. The relative risk as determined by the investigators was 2.3, with a 95% confidence interval of 1.6 to 3.4, and p value = < 0.001). In Van Hensbroek et al., (1996), hypoglycemia was reported in 10.1% of patients (children) who received artemether in comparison to 14.6% of children who received quinine. This difference was not statistically significant

after stratification for the presence of hypoglycemia on admission. In Karbwang, et al. (1995), the authors noted that 10 of 47 (21.3%) patients in the artemether group, and 8 of 50 (16%) patients in the quinine group developed neutropenia, defined as a absolute neutrophil count < 3000 cells on the third treatment day, although some patients were neutropenic prior to treatment. In some of these patients (treatment group not specified), neutropenia persisted at day 7, but was not followed further.

Laboratory Adverse Events Reported in Postmarketing Safety Databases

The applicant provided a summary of common laboratory adverse events in patients who received quinine reported to AERS from January, 1969 to 30 June, 2003. These events were not reviewed for possible causal relationship to quinine. For both time periods reported, thrombocytopenia was the most frequent laboratory adverse event, as shown in the following table.

Table 70: Laboratory Adverse Events Reported in 5 or more Patients who received Quinine in AERS Database (Applicant’s Table 21, ISS)

Adverse Event Term	Counts	
	1 Jan 1969 – 31 Oct. 1997 ¹	1 Nov. 1997 – 30 June 2003 ²
Hematology		
Thrombocytopenia	66	35
Platelet Count Decreased	–	6
Leukopenia	13	–
Hematocrit Decreased	–	5
Hemoglobin Decreased	–	9
International Normalized Ratio Increased	–	5
Coagulation Disorder	9	–
Biochemistry		
Liver Function Tests NOS Abnormal	8	3
Renal Impairment NOS	–	6
Blood Creatine Increased	–	5
Blood Potassium Increased	–	5
Leukocytosis	5	–

Source: FOI Report of Adverse Events with Quinine, 9 June 2004
¹Costart Terminology / Spontaneous Reporting System (SRS) database
²MedDRA Terminology / Adverse Event Reporting System (AERS) database

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Medical Officer Comments: As noted previously, postmarketing adverse event data cannot be used to determine incidence unless a denominator (number of patients who received the drug in question) is available. The Medwatch reports for these events were not reviewed, so although they were associated with quinine use, a causal relationship has not been established.

The applicant also provided a summary of laboratory adverse events from the WHO postmarketing database which included 504 reports from 15 countries. This summary is provided in the table below.

Table 71: Laboratory Adverse Events in Patients who received Quinine Reported to WHO Database from 1968 to March 2004 (Applicants' Table 22, ISS)

Adverse Event Terms	Count
Hematology	
Thrombocytopenia	94
Granulocytopenia	11
Leucopenia	6
Agranulocytosis	5
Pancytopenia	4
Anemia aplastic	3
Anemia hemolytic	3
Leukocytosis	3
Prothrombin decreased	2
Biochemistry	
Hepatic function abnormal	5
NPN increased	4
Hypoglycemia	3
LDH increased	3
Renal function abnormal	3
Urinalysis	
Hematuria	11

Medical Officer Comments: Thrombocytopenia was the most common laboratory adverse event, followed by granulocytopenia and hematuria for this time period. The term, "NPN" increased was not clarified by the applicant.

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were performed to evaluate laboratory abnormalities from the data provided.

7.1.7.5 Special assessments

Not applicable

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Pharmacokinetic Studies

In the two pharmacokinetic studies submitted with this NDA, vital signs were routinely obtained at baseline and at specified times post-dosing. The applicant concluded that no clinically significant changes were observed in the vital signs measurements, and that no changes were considered related to the study medication by the investigator. The applicant did not provide any statistical analysis for vital signs measurements in these studies. The vital signs databases

provided by the applicant for these two studies were reviewed and no significant abnormalities in vital signs were identified by the Medical Officer.

Medical Officer Comments: *These studies used single doses of quinine sulfate (324mg and/or 648 mg) in healthy subjects, and steady state plasma concentrations of quinine would theoretically not be achieved until 3 days of dosing (648 mg 3 times daily) (see pharmacokinetics section 5.1 above). These data are therefore limited in their predictive value regarding the potential for hypotension and other adverse events in patients receiving quinine for malaria.*

Published Randomized, Controlled Trials of Quinine Monotherapy

The applicant summarized vital signs monitoring in the randomized studies of oral quinine in patients with uncomplicated malaria, as shown in the table below. Eight of the 11 studies monitored vital signs (temperature, blood pressure and heart rate). In some of these studies, fever clearance time was determined as a measure of treatment efficacy, and is discussed in the Integrated Summary of Efficacy in this review (section 6). Notably, there were no reports of hypotension in these studies with oral quinine monotherapy.

Table 72: Evaluation of Vital Signs in Randomized, Controlled Trials of Oral Quinine Monotherapy (Applicant's Table 23, ISS)

Abnormal Vital Sign Measurements in Published Randomized Studies of Oral Quinine Monotherapy for Treatment of Uncomplicated *P. falciparum* Malaria

Study	N (Treatment/ DurationCode ¹)	Abnormal Vital Sign Measurement(s)
<u>Pukrittayakamee et al., 2004</u> (Thailand)	30 (Q7)	Vital signs (not further described) were recorded every 4 hours until resolution of fever and thereafter every 6 to 12 hours. No abnormal vital sign measurements were reported.
<u>Mueller et al., 2004</u> (Congo)	48 (Q7)	On Days 3 and 7, pulse, blood pressure, and axillary body temperature were recorded. No abnormal vital sign measurements were reported.
<u>Pukrittayakamee et al., 2000</u> (Thailand)	68 (Q7)	Vital signs (not further described) were recorded every 4 hours until resolution of fever and thereafter every 6 to 12 hours. No abnormal vital sign measurements were reported.
<u>McGready et al., 2000</u> (Thailand)	42 (Q7)	Weekly physical examination included oral temperature, blood pressure, and pulse. No results or adverse outcomes were reported for vital sign measurements.
<u>de Vries et al., 2000</u> (Vietnam)	84 (Q7)	Vital signs (not further described) were recorded every 8 hours during hospitalization. No abnormal vital sign measurements were reported.
<u>Bich et al., 1996</u> (Vietnam)	59 (Q7)	Vital signs (not further described) were recorded every 8 hours until at least three normal temperature readings were obtained. No abnormal vital sign measurements were reported.
<u>Metzger et al., 1995</u> (Gabon)	40 (Q1.5)	Clinical "signs" were recorded every 12 hours until the patient "was free of symptoms". Apparently, axillary temperatures were measured. No abnormal vital sign measurements were reported.
<u>Seegal et al., 1974</u> (Thailand)	26 (Q6)	Oral temperature was taken every 6 hours. Additional vital sign measurements are not described.

Q=quinine

¹Treatment/Duration codes = drug abbreviation followed by duration of treatment in days.

Medical Officer Comments: *As discussed previously, there may have been reporting bias in some of these studies; and the absence of reports on abnormal vital signs does not rule out their occurrence.*

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Published Randomized, Controlled Trials of Quinine Combination Therapy

Seven of the 16 studies of quinine combination therapy monitored vital signs, and 4 of these studies had a quinine monotherapy arm and were shown in the previous table. No abnormal vital sign measurements were reported as shown in the table below.

Table 73: Evaluation of Vital Signs in Randomized, Controlled Trials of Quinine Combination Therapy for Uncomplicated P. falciparum Malaria (Applicant's Table 25, ISS)

Study	N (Treatment/Duration Code ¹)	Abnormal Vital Sign Measurement (s)
<u>Pukrittayakamee et al. 2004</u> (Thailand)*	30 (Q7T7)	Vital signs (not further described) were recorded every 4 hours until resolution of fever and thereafter every 6 to 12 hours. Abnormal vital sign measurements are not reported.
<u>Pukrittayakamee et al. 2006</u> (Thailand)*	136 (Q7C7 and Q7T7)	Vital signs (not further described) were recorded every 4 hours until resolution of fever and thereafter every 6 to 12 hours. Abnormal vital sign measurements are not reported.
<u>de Vries et al. 2006</u> (Vietnam)*	184 (A1Q3 and A1Q5)	Vital signs (not further described) were recorded every 8 hours during hospitalization. Abnormal vital sign measurements are not reported.
<u>Vandisornsa et al. 1996</u> (Thailand)	50 (Q7T7) and (Q7CQ3)	Vital signs (not further described) were recorded every 4 hours until resolution of fever and thereafter every 6 to 12 hours. Abnormal vital sign measurements are not reported.
<u>Bich et al. 1996</u> (Vietnam)*	45 (A1Q3)	Vital signs (not further described) were recorded every 8 hours until at least three normal temperature readings were obtained. Abnormal vital sign measurements are not reported. There was no evidence of iatrogenic hypotension.
<u>Metzger et al. 1995</u> (Gabon)*	80 (Q1.5C3 and Q1.5D3)	Clinical "signs" (not further described) were recorded every 12 hours until the patient "was free of symptoms". Apparently, axillary temperature was measured. Abnormal vital sign measurements are not reported.
<u>Loaareesuwan et al. 1994</u> (Thailand)	52 (Q7T7)	Body temperature, pulse, and respiratory rate were measured every 4 hours. Abnormal vital sign measurements are not reported.

Q=quinine; T=tetracycline; C=clindamycin; D=doxycycline; A=artemisinin or artesunate; CQ=chloroquine

*Also reviewed in Monotherapy

¹Treatment/Duration codes = drug abbreviation followed by duration of treatment in days. Combination therapy is represented as first drug abbreviation, duration, second drug abbreviation, duration

Medical Officer Comments: As discussed previously, there may have been reporting bias in some of these studies; and the absence of reports on abnormal vital signs does not rule out their occurrence.

Published Randomized Controlled Trials of Parenteral Quinine Therapy

In the randomized studies of parenteral quinine, vital signs were measured routinely in 10 of the 16 studies provided by the applicant. Results of vital signs measurements in these studies were summarized by the applicant, as shown in the table below. None of these studies reported drug-related abnormal vital sign measurements in patients treated with quinine.

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Table 74: Evaluation of Vital Signs in Randomized, Controlled Trials of Parenteral Quinine Treatment for Severe *P. falciparum* malaria (Applicant's Table 24)

Abnormal Vital Sign Measurements in Published Randomized Studies of Parenteral Quinine for Treatment of Severe *P. falciparum* Malaria, Including Cerebral Malaria

Study	N (Treatment/ Duration Code ¹)	Abnormal Vital Sign Measurement (s)
Intravenous		
<u>Newton et al., 2003</u> (Thailand)	54 (Q ²)	Pulse, respiratory rate, blood pressure, and axillary body temperature were measured every 15 minutes for the first 2 hours, at 4, 6, 8, 10, and 12 hours, and then every 6 hours until parasitemia had cleared for 24 hours. No drug-related abnormal vital sign measurements were reported.
<u>Faiz et al., 2001</u> (Bangladesh)	54 (Q7)	Temperature, pulse, blood pressure, and respiratory rate were monitored every 6 hours during the period of coma and every 12 hours thereafter. No drug-related abnormal vital sign measurements were reported.
<u>Thuma et al., 2000</u> (Zambia)	44 (Q7)	Vital signs (not further described) were measured every 4 hours. No drug-related abnormal vital sign measurements were reported.
<u>Meyou-Somo et al., 2001</u> (Cameroon)	51 (Q7)	Pulse and respiratory rate were measured every 4 hours and blood pressure and rectal temperature were measured every 8 hours until Day 7, and then weekly on Days 14, 21, and 28. No drug-related abnormal vital sign measurements were reported.
<u>Taylor et al., 1998</u> (Malawi)	88 (Q3 ²)	Vital signs were measured hourly for the first 6 hours, 2-hourly until the patient regained consciousness, and then 4-hourly until discharge. No reference was made to abnormal vital signs.
<u>Murphy et al., 1996</u> (Kenya)	71 (Q3 ²)	Temperature, pulse, and blood pressure were measured every 4 hours. No drug-related abnormal vital sign measurements were reported.
<u>Karuwang et al., 1995</u> (Thailand)	52 (Q7)	Vital signs were measured every 6 hours. No drug-related abnormal vital sign measurements were reported.
<u>Karuwang et al., 1992</u> (Thailand)	12 (Q7)	Vital signs were measured every 6 hours. No drug-related abnormal vital sign measurements were reported.
Intramuscular		
<u>Tran et al., 1996b</u> (Vietnam)	276 (Q3)	Detailed clinical observations were recorded at least every 4 hours for the first 24 hours and every 6 hours thereafter. No drug-related abnormal vital sign measurements were reported.
<u>Van Hensbruek et al., 1996</u> (Gambia)	288 (Q5)	Temperature, pulse, and respiratory rate were measured every 4 hours for the first 24 hours and then every 6 hours until discharge. No drug-related abnormal vital sign measurements were reported.

Q=quinine

¹Treatment/Duration codes = drug abbreviation followed by duration of treatment in days.

²Intravenous treatment was followed by treatment with one other oral antimalarial drug

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Medical Officer Comments: In the study by Newton, et al. (2003) shown above, one patient initially randomized to artesunate developed a widespread, erythematous, urticarial rash and was switched to quinine therapy. The patient died 52 hour later with pulmonary edema, oliguria, hypotension and electromechanical dissociation. The authors attributed these events to severe malaria. As such, it would be difficult to attribute hypotension to quinine or other treatment in patients with severe malaria, because significant hypotension is often present as a disease manifestation.

Reports of hypotension with intravenous quinine were identified in the literature as reviewed in section 7.1.3.3 above. Some, but not all of those reports were in patients who received a bolus (rapid) intravenous infusion of quinine. In one published randomized, controlled study (not shown in the table above) which evaluated intravenous quinine for treatment of severe malaria, hypotension was reported as an adverse event in 3 of 26 (11.5%) patients who

received intravenous quinine (10 mg/kg daily for 7 days), and in none of the 26 patients treated with artemether in Singh, et al. (2000). Additionally, hypotension in conjunction with pulmonary edema was reported in a patient who received a single 300 mg dose of quinine sulfate for leg cramps (Everts, 2004).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable

7.1.8.4 Additional analyses and explorations

No additional analyses were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

For this 505 (b)2 NDA, the applicant submitted 2 bioequivalence studies which also evaluated ECG data up to 24 hours after a single dose (324 mg or 648 mg) of quinine sulfate. Additionally, the applicant provided published literature, including clinical studies which did ECG testing in patients with malaria, as previously reviewed in section 7.1.3.3. The preclinical information on cardiovascular toxicity of quinine was reviewed briefly above in section 7.1.3.3. See Dr. Steven Kunder's Pharmacology/Toxicology review for full details.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

In both of the pharmacokinetic studies submitted with this NDA, electrocardiograms were obtained in subjects at baseline, and at 2, 4, 6, 12, and 24 hours after the quinine sulfate dose. A summary of the ECG data regarding QTc intervals from these studies follows below. The applicant also provided an ECG dataset which contained values for heart rate, PR interval, QRS interval, QT and QTc intervals for each subject at specified time points.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.1.1.1 Analyses focused on measures of central tendency

ECG Data from Quinine Dose Proportionality Study R04-0376

This was a randomized, open-label, two-way crossover study, in which 24 healthy (non-smoking) subjects (13 males and 11 females) were enrolled. Mean age was 33.0 (\pm 13.9 years),

ranging from 19-61 years, 23 were Caucasian, and 1 was a Native American. Twenty three subjects completed the study; and one subject withdrew for personal reasons.

A single oral dose of quinine sulfate 324 mg (one capsule), or 648 mg (2 capsules) was administered under fasting conditions on two separate occasions, with a 7 day wash-out period between the first and second dose. ECG data were obtained at 2, 4, 6, 12, and 24 hours after each dose, and mean QTc and change from baseline for each of the timepoints is shown in the following table.

Table 75:

Mean QTc Measurements and Change from Baseline Over 24-hours Following a Single Oral Dose in Patients in Mutual-Sponsored Dose Proportionality Study R04-0376 (Applicant's table 2, 120-day safety update)

Statistic	QTc (msec)					
	Baseline	2 hr	4 hr	6 hr	12 hr	24 hr
Quinine Sulfate Capsules USP, 1 × 324 mg						
Mean ± SD N=23 ¹	404 ± 20	415 ± 26	414 ± 26	411 ± 21	411 ± 24	409 ± 24
Change from Baseline ¹ ± SD	--	10.4 ± 18.8	9.1 ± 17.4	6.4 ± 13.9	5.2 ± 15.3	4.8 ± 11.9
Quinine Sulfate Capsules USP, 2 × 324 mg						
Mean ± SD N=24	410 ± 26	422 ± 29	422 ± 30	419 ± 25	417 ± 24	412 ± 23
Change from Baseline ± SD	--	12.3 ± 17.7	12.0 ± 14.8	9.3 ± 14.8	7.5 ± 14.4	2.8 ± 14.4

Source: ECG data for R04-0376

¹Subject 10 has no baseline value, thus 22 subjects contributed data to the baseline mean and change from baseline

Medical Officer Comments: The mean maximum change of QTc was 10.4 ± 18.8 msec and 12.3 ± 17.7 msec after a single 324 mg or 648 mg dose of quinine sulfate, respectively. This change is probably not clinically significant. However, these data may not reflect changes in QTc intervals after repeated doses of quinine as in those used for treatment of malaria.

In this study, a total of 7/24 (29.2%) subjects had significant QTc prolongation (≥ 450 msec) post-quinine dosing, as shown in the following table. No subjects had QTc prolongation > 470 msec.

Table 76: QTc Intervals in Individual Subjects with a measured QTc > 450 msec (Applicant's Table 3, 120-day safety update)

Patients with QTc > 450 Msec and Baseline and Within 24 hours Following a Single Oral Dose in Patients in Mutual-Sponsored Dose Proportionality Study R04-0376

Subj. No.	Dose (mg)	QTc					
		Baseline	2 Hours	4 Hours	6 Hours	12 Hours	24 Hours
3	648	454	449	453	442	441	433
7	324	411	448	454	427	421	436
11	648	398	456	430	439	445	431
15	324	402	459	434	443	435	401
	648	431	444	460	442	442	437
16	324	437	432	436	441	421	463
	648	439	463	461	453	443	435
19	648	403	463	405	405	420	416
20	324	439	445	458	434	441	432
	648	437	458	470	463	458	438

Source: ECG data for R04-0376

In the following table, pharmacokinetic parameters data were compared to the QTc data for patients shown in the table above to assess whether QTc prolongation occurred at the quinine Tmax in individual patients.

Table 77: Correlation of pharmacokinetic data with maximum QTc interval (from Pharmacokinetics dataset, NDA-21-799)

Subject	Dose (mg)	Maximum QTc (msec)	Quinine concentration At time of maximum QTc (ng/mL)	Cmax (ng/mL)	Tmax (Time of Cmax)
3	648	454 (baseline), and 453 (4 hours)	3390.38	3554.03	2.5 hours
7	324	454 (4 hours)	4799.84	5500.75	2.0 hours
11	648	456 (2 hours)	3528.04	3605.67	2.5 hours
15	324	459 (2 hours)	3331.95	3438.53	3.5 hours
15	648	460 (4 hours)	2744.50	2863.91	3.5 hours
16	324	463 (24 hours)	599.73	3202.72	2.0 hours
16	648	463 (2 hours)	2011.53	2100.37	3.5 hours
19	648	463 (2 hours)	1827.01	2522.87	2.5 hours
20	324	458 (4 hours)	2711.35	2903.90	3.0 hours
20	648	470 (4 hours)	2912.70	3071.50	2.5 hours

Medical Officer Comments: With the exception of subject 16, whose maximum QTc occurred 24 hours after the quinine dose, these data suggest a relationship between maximum QTc and quinine Tmax. In most cases the quinine concentration at the time of maximum QTc prolongation was slightly lower than the Cmax; however ECG data was only collected at 2, 4, 6, 12, and 24 hours post-quinine dose, so the actual maximum QTc may have been missed.

A linear regression analysis was performed with data from both pharmacokinetic studies by the Clinical Pharmacology Reviewer, Dr. Gerlie Gieser to determine if there was a

relationship between QTc and plasma quinine concentration. These data were discussed in Clinical Pharmacology (section 5.2) section of this review. In brief, a slightly positive correlation was found between QTc and plasma quinine concentration. This correlation was more obvious with females than males.

Demographic data for the 7 subjects in this study who had a measured QTc >450 msec are shown in the table below.

Table 78: Demographic data for Subjects with QTc \geq 450 msec (from Applicant's Demographics dataset)

Subject ID	Age	Gender	Race
3	21	F	C
7	52	F	C
11	52	F	C
15	42	F	C
16	20	M	C
19	37	M	C
20	58	F	C

F= female; M= male; C= caucasian

Medical Officer Comments: QTc interval prolongation > 450 msec (post-baseline) was observed in 5 of 11 (45.5%) females, and in 2 of 13 (15.4%) male subjects in this study. Four of the five women with QTc prolongation were older than 40 years; while most of women, 3/6 (50%) without significant QTc prolongation were younger than age 25. Interestingly, most of the males in the study were younger than age 40 years (92%); while 6 of 11 (54.5%) of females were over the age of 40. However, too few subjects were enrolled to draw firm conclusions regarding age, gender and QTc interval changes in this study.

ECG Data from PK Study RA3085

This was a randomized, open-label, single-dose, three-way crossover study comparing the Mutual Pharmaceutical Company's quinine sulfate 324 mg capsule formulation (under fed and fasted conditions), with the 300 mg quinine sulfate tablet formulation manufactured by the GPO, Bangkok, Thailand. Twenty seven healthy, non-smoking subjects, 12 males and 15 females were enrolled. Mean age was 24.2 years (range 18-47 years), and 26 subjects were Caucasian, and one was Hispanic. Twenty five of 27 (92.6%) subjects completed all three treatment periods of the protocol. One subject was discontinued due to a positive pregnancy test; and a second withdrew for personal reasons.

An ECG was obtained at baseline, and at 2, 4, 6, 12, and 24 hours after each dose. No subject had a QTc interval exceeding 450 msec post-dosing; and the mean QTc interval change from baseline was not significant, as shown in the table below.

Table 79: Mean QTc Measurements and Change from Baseline Over 24-hours Following a

Single Oral Dose in Patients in Mutual-Sponsored Bioequivalence Study RA3-085 (Applicant's Table 26, ISS)

	Study RA3-085 QTc (msec)					
	Baseline	2 hr	4 hr	6 hr	12 hr	24 hr
Mutual Pharma's 324 mg Capsule (Fasting)						
Mean ± SD N=26	399 ± 18	402 ± 23	399 ± 20	400 ± 22	398 ± 20	399 ± 23
Change from Baseline	--	2.5	-0.5	1.0	-1.6	-0.3
GPO's 300 mg Tablet (Fasting)						
Mean ± SD N=25	399 ± 15	406 ± 24	400 ± 24	400 ± 19	396 ± 17	394 ± 20
Change from Baseline	--	7.1	1.3	1.0	-3.0	-5.24
Mutual Pharma's 324 mg Capsule (Fed)						
Mean ± SD N=27	397 ± 18	397 ± 19	396 ± 25	402 ± 22	400 ± 19.6	400 ± 20
Change from Baseline	--	-0.0	-1.7	4.4	2.3	3.0

Medical Officer Comments: In this study, no significant mean QTc prolongation was observed after a single dose of Mutual's 324 mg capsule in fed or fasting subjects, or after a single dose of the GPO 300 mg capsule in fasting subjects. The maximum change in QTc over baseline was 2.5 msec in fasted subjects who received Mutual's 324 mg quinine sulfate capsule, and 4.4 msec in fed subjects who received a 324 mg capsule; while the maximum change in QTc was 7.1 msec in fasted subjects who received Thailand-GPO's 300 mg tablet. These data must be interpreted cautiously however, because changes in QTc intervals may differ after repeated quinine dosing.

Overall Conclusions Regarding QTc Data from Mutual Pharmaceutical's Pharmacokinetic Studies

I. There were only minimal changes in overall mean QTc interval in both studies after a single dose of quinine sulfate (324 mg or 648 mg). The mean changes in QTc were similar with the Mutual Pharmaceutical Co. formulation and the GPO formulation of quinine sulfate 324 mg, and in fed or fasting subjects. Whether similar results would be observed in patients with malaria who received multiple doses of quinine sulfate is not known.

2. In study R04-0376, 7/24 (29.2%) subjects had a maximum QTc interval of > 450 msec (470 msec was the maximum QTc interval recorded) during the 24 hour post-dose monitoring period. No cardiac arrhythmias or other adverse events potentially due to an arrhythmia were reported in these subjects. Syncope was reported in 1 subject in each study; however, neither patient had a prolonged QTc interval or cardiac arrhythmia on ECG.

3. As shown in section 5.2 of this review, a temporal relationship was seen between total plasma quinine concentration and Δ QTc, with the greatest increase in mean Δ QTc around the time of Tmax (2-4 hours). Additionally, a weak correlation was shown between Δ QTc and time matched individual plasma quinine concentrations, in female > male subjects, when a linear regression analysis was performed combining data from both pharmacokinetic studies.

4. ECG data was obtained from a relatively small number of healthy subjects (49 for both studies), so the data cannot necessarily be extrapolated to a larger, non-homogeneous population. Additionally, patients with electrolyte abnormalities (hypokalemia, hypocalcemia, and hypomagnesemia), congestive heart failure, renal or hepatic impairment, those < 16 years old or > 65 years old may be at higher risk for drug-related QT/QTc interval prolongation and torsades de pointes, and were not evaluated in these phase I studies. Female patients may also be at higher risk for drug-related QTc prolongation, and although 5/7 (71.4%) subjects who had a QTc interval of > 450 msec in study R04-0376 post quinine dosing, were female, too few subjects were enrolled in the study to draw firm conclusions regarding any gender-related effects of the drug.

ECG Data from Randomized, Controlled Trials of Oral or Parenteral Quinine

See section 7.1.3.3.

7.1.9.4 Additional analyses and explorations

Please refer to section 5.2, Clinical Pharmacology for linear regression analysis of QTc interval data obtained from the pharmacokinetic studies.

7.1.10 Immunogenicity

The applicant did not submit any preclinical data regarding immunogenicity of quinine. Quinine itself is not immunogenic, but probably acts as a hapten, and induces immunogenicity after binding protein. However, in humans, quinine has been shown to elicit specific antibodies directed against platelets, red blood cells, leukocytes, causing thrombocytopenia, anemia and leukopenia, and possibly other cell types, as reviewed in section 7.1.3.3 above.

7.1.11 Human Carcinogenicity

Carcinogenicity studies have not been performed in animals. For this indication, treatment of acute malaria, which generally requires 7 days of antimalarial therapy, human carcinogenicity studies are not required.

Medical Officer Comments: For other indications, such as malaria prophylaxis, which could be long-term, carcinogenicity studies in animals would likely be required for this drug.

7.1.12 Special Safety Studies

No special safety studies were submitted. See sections 5.2 and 7.1.9 for review of the ECG data, with respect to the potential for QT prolongation with quinine sulfate.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no literature reports of abuse potential or withdrawal phenomena associated with quinine.

7.1.14 Human Reproduction and Pregnancy Data

Quinine has known teratogenicity in humans. Some of the malformations reported include auditory nerve hypoplasia and deafness, limb anomalies, visceral defects, and visual changes (Dannenberg, et al., 1983). At high doses, quinine may also have weak abortifacient properties. In a case series by Dannenberg, et al. (1983), 11 of 70 (16%) women who used quinine in an attempted self-abortion died, 41 offspring in this series had congenital anomalies for which quinine was the suspected etiologic agent, and abortion without maternal death was achieved in only 3/70 (4%) of cases. The quinine dose (where known) used in these cases varied from < 1 gram to 30 grams.

It is not known whether quinine is teratogenic at the doses used for treatment of malaria; although standard doses of quinine apparently do not increase the risk of abortion or pre-term delivery. In a descriptive, non-randomized study of malaria treatment of pregnant women in Thailand, there was no significant difference between treatment groups (quinine, mefloquine, quinine plus mefloquine, and artemisinin for mean birthweight or mean gestational age; and no congenital abnormalities were reported among the children born in the study (McGready and Nosten, 1999). In a randomized, open-label study of quinine vs. mefloquine-artesunate, in 108 evaluable pregnant women with drug-resistant malaria, there were 2/108 (1.9%) mid-trimester abortions in the mefloquine-artesunate arm, and none in the quinine arm. No stillbirths were reported, and no congenital abnormalities occurred among the 92 documented births. Blindness was reported in one infant born to a mother who received quinine. However, the blindness in this child, with an estimated gestation age of 31 weeks, was attributed to retinopathy of prematurity. There were also no differences in birthweight or estimated gestational age between the treatment groups. Patients in this study received the standard doses of quinine for treatment of malaria (10 mg/kg every 8 hours) for 7 days.

In an epidemiological study performed from July, 1991 through June, 1994, a total of 655 Thai women diagnosed with *P. falciparum* malaria during pregnancy were treated at some time during pregnancy with quinine sulfate (10 mg/kg orally 3 times daily for 7 days) alone (Nosten, et al. (1999). As reviewed by Dr. Gerard Nahum, of the Pregnancy and Lactation Team, there was no

clinically relevant or statistically significant difference in the rate of stillbirths (odds ratio = 0.87) or in the rate of congenital malformations (odds ratio = 0.82) between women with malaria treated with quinine and 2,470 pregnant women without malaria or antiparasitic treatment. There was a statistically significant difference in the rate of low birth weight, 17.8% in pregnant women with malaria who were treated with quinine, and 12.7% in the control group (odds ratio=1.4, 95% CI 1.1-1.9). However, this difference could be attributed to malaria alone, and the difference in birthweights was small (-31 to -209 grams), and not considered clinically significant.

In another epidemiological study which was part of the Collaborative Perinatal Project (USA), in a cohort of 50,282 mother-child pairs, 3,248 (6.5%) children with drug exposures during pregnancy had congenital malformations. Among 104 mother-child pairs who were exposed to quinine (unknown dose or duration) during the first 4 months of pregnancy, 2 children (1.9%) had congenital malformations (Heinonen, et al., 1977).

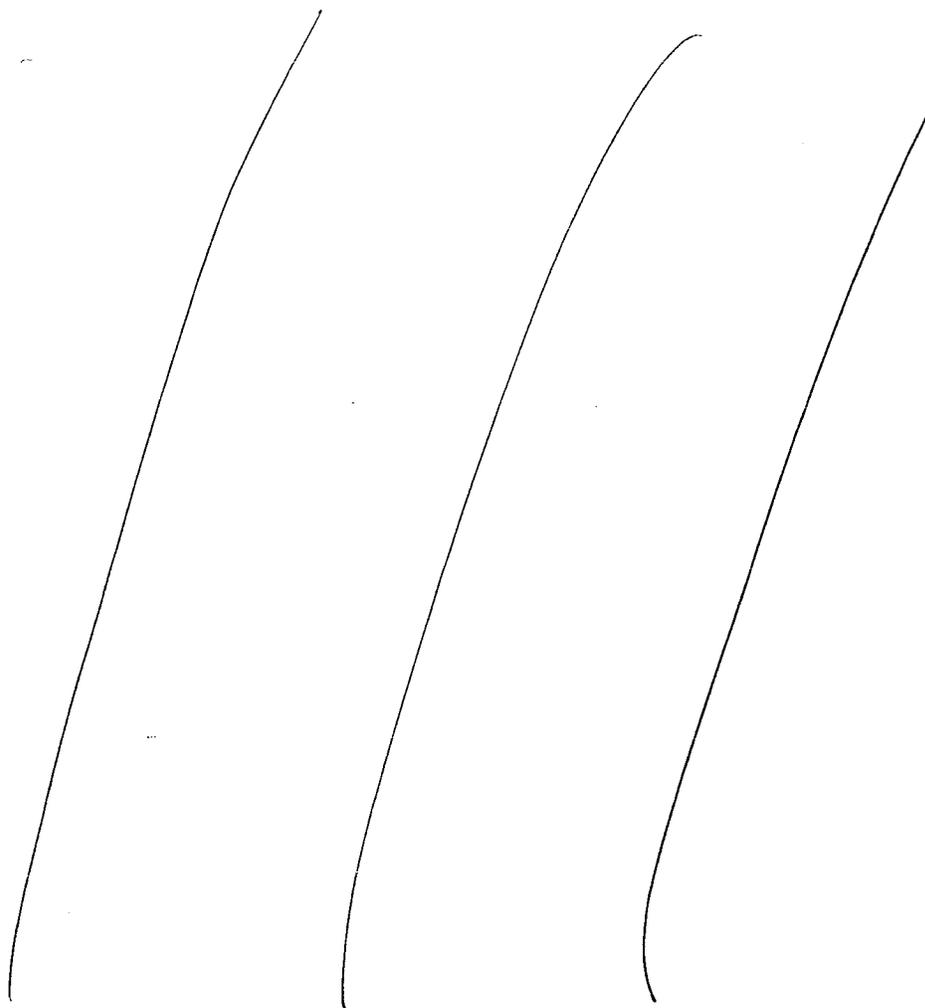
In the postmarketing AERS safety database, one case of congenital abnormalities was considered was reported in a patient who had a serious outcome. As reviewed by ODS, cerebellar hypoplasia was reported in a premature (32-week) French infant who had been exposed to quinine (in addition to 4 other medications taken by the mother) during gestation. The reporting physician did not attribute the congenital abnormality to quinine or any of the other drugs. Sufficient information was not provided to determine if this abnormality was related to quinine use.

Medical Officer Comments: *Maternal and fetal morbidity and mortality is high in untreated severe falciparum malaria, and few treatment options may exist, particularly in pregnant women with malaria acquired in Southeast Asia, where P falciparum may be resistant to multiple antimalarial drugs. Although teratogenic effects of quinine have been reported, particularly with high doses of quinine, the benefit of quinine therapy probably outweighs the risk of quinine use in a pregnant woman with P. falciparum malaria.*

Other antimalarial agents available for use in pregnancy in areas of chloroquine-resistant P. falciparum malaria, include mefloquine (pregnancy category C), and atovaquone-proguanil (pregnancy category C). Despite the pregnancy category C ratings, mefloquine and atovaquone-proguanil are generally not recommended by the CDC or the WHO for treatment of malaria in pregnant women, because adequate and well-controlled studies to support their safety and efficacy in pregnant women have not been performed. The CDC recommendations advise use of quinine plus clindamycin for treatment of chloroquine-resistant P. falciparum malaria in pregnant women (CDC 2004 Guidelines for Treatment of Malaria in the U.S.). Clindamycin has a pregnancy category B rating, but cannot be used alone for treatment of malaria. Other antimicrobials recommended by the CDC for use in conjunction with quinine for treatment of chloroquine-resistant P. falciparum, are tetracycline and doxycycline, which are both pregnancy category D.

Recommendations of the Pregnancy and Lactation Team

The DSPIDP consulted the Pregnancy and Lactation Team for review of this information and recommendations regarding the pregnancy section of the final product labeling. Their major recommendation was to change the proposed Pregnancy category ____ to C, based on a risk/benefit assessment in favor of quinine, i.e. *P. falciparum* malaria is a potentially life-threatening illness in pregnant women associated with adverse pregnancy outcomes, and the benefit of treatment with quinine sulfate may outweigh the risk. Additional recommendations were made regarding the sections on Labor and Delivery and Nursing Mothers in the proposed label. The following labeling recommendations were provided and have been incorporated into the proposed final product labeling for quinine sulfate:





7.1.15 Assessment of Effect on Growth

No published studies were submitted which evaluated the effect of quinine sulfate on growth.

7.1.16 Overdose Experience

Quinine overdose has been observed in several situations, including self-poisoning, accidental overdose, particularly as the result of heroin or cocaine adulteration with quinine, and attempts at self-abortion. At one time, quinine poisoning was apparently a common cause of death in children under 4 years old, due to consumption of quinine tablets prescribed for a relative, in an epidemiologic study in Australia (Pearn, et al., 1984).

The clinical manifestations of quinine overdose are well-described in the literature. As reviewed by Taylor and White, 2004, cinchonism invariably occurs with overdose; while some of the serious effects of quinine overdose include blurred vision, fixed dilated pupils, visual fields restriction, amblyopia, altered color perception, and blindness, hypoglycemia, cardiac arrhythmias, and death. ECG signs of quinine overdose include sinus tachycardia, prolonged PR interval, bundle branch block, QRS widening, prolongation of QTc interval, ST segment depression, and T-wave inversion. Cardiac arrhythmias include ventricular tachycardia, idioventricular rhythm. CNS features of overdose include impaired consciousness, coma, and seizures, particularly in children.

Bateman and Dyson (1986) extensively reviewed quinine overdose toxicity. These authors noted that moderately elevated quinine levels are associated with cinchonism (auditory symptoms, gastrointestinal disturbances, vasodilatation, sweating, and headache); while higher plasma quinine levels are associated with more severe visual disturbances, cardiac and neurological features. Gastrointestinal symptoms include mild nausea, or with large overdoses, vomiting, abdominal pain, and diarrhea. Vasodilation may be associated with mild hypotension seen in the absence of cardiac dysrhythmia. Auditory symptoms include tinnitus, and with larger overdoses, bilateral nerve deafness and vertigo. According to these authors, auditory symptoms generally resolve within a few days of overdose, and permanent hearing loss after acute quinine overdose has not been reported.

Other toxic effects of quinine discussed by Bateman and Dyson (1986) include allergic reactions associated with quinine include angioedema in aspirin-sensitive patients, anaphylactoid reactions, and drug fever, hematologic reactions, including thrombocytopenia, hemolytic anemia, agranulocytosis, DIC, hepatitis, hypoglycemia, hypokalemia, purpura, erythema multiforme, fixed drug eruption, toxic epidermal necrolysis, ataxia, seizures, coma, respiratory depression, deterioration in patients with myasthenia gravis, oculotoxicity, and cardiac toxicity, including myocardial depression, wide-complex ventricular tachycardias, and electromechanical dissociation. Ventricular fibrillation and torsades de pointes have also been reported (Bodenhamer and Smilkstein, 1992; Morrison, et al., 2003).

The clinical features of quinine overdose were reviewed by Jaeger, et al (1987), who compared two published case series for adverse events, as shown in the table below.

Table 80: Clinical features of quinine overdose (adapted from Jaeger, et al., 1987)

Clinical Features of Overdose	Dyson, et al (1985) N=48	Boland, et al., 1983 N=165
	% patients	% patients
Asymptomatic	17	21
Unconscious from other drugs	8	--
Symptomatic	75	79
Nausea	54	47
Vomiting	40	--
Tinnitus	56	38
Deafness	50	23
Vasodilatation	15	--
Hyperventilation	6	--
Mild impairment of consciousness	--	14
Coma	--	2.5
Visual Symptoms	17	42
Blurred vision (only)	--	19
Altered color perception (only)	2	--
Visual field constriction (only)	2	--
Blindness	13	23.6
Cardiovascular symptoms	50	--
Tachycardia > 100	46	23
Hypotension (SBP< 90 mm)	10	--
Pulmonary edema	2	--
Ventricular tachycardia	2	2.5
ECG abnormalities	35*	8
Increased PR interval	8	5
Widening of QRS interval	--	3
Fatalities	0	3**

*ECG changes occurred in 17/48 (35.4%) patients, and included atrial repolarization changes in 4, prolongation of PR interval in 3, QT interval prolongation > 420 msec in 15, minor ST segment depression in 6, T wave flattening or inversion in 6, and prominent U waves in 6 patients.

** Death was reported in 5/165 (3.0%), including 4 patients with intractable ventricular arrhythmias, and one with "Jacksonian fit" followed by cardiac arrest.

Medical Officer Comments: In a case review of 48 patients admitted to a regional poison center for quinine overdose (Dyson, et al., 1985), one patient developed ventricular tachycardia and had a plasma quinine concentration of 23.5 mg/L. This arrhythmia ended spontaneously 8 hours after ingestion. The patient reportedly went on to develop pulmonary edema, unresponsive to diuretics, but cleared slowly after the next 3 days. In the same study, visual loss occurred in every patient that had a quinine plasma concentration ≥ 10 mg/L.

Quinine toxicity appears to be related to plasma concentration. As reviewed by Jaeger, et al., (1987), in general, the toxic effects of quinine occur at plasma concentrations ≥ 10 mg/L. In one study, cardiac arrhythmias were reported at plasma quinine concentrations above 15 mg/L (Bateman, et al., 1985); while in one case series, blindness was associated with plasma quinine concentrations > 15 mg/L less than 10 hours after ingestion (Boland, et al., 1985).

The lethal dose of quinine is between 2 and 8 grams in adults, but has not been further defined (Jaeger, et al., 1987; Taylor and White, 2004).

Serious adverse events associated with accidental or intentional quinine overdose reported in the AERS postmarketing safety database included anuria, cardiac arrest, hypotension, arrhythmia, cinchonism, visual disturbance, increased AST, increased creatinine, increased ALT, increased ammonia, increased bilirubin, increased INR, prolonged prothrombin time, increased thromboplastin time, decreased platelet count, decreased hematocrit, dehydration, myalgia, thrombocytopenia, vomiting, blindness, atherosclerosis, hepatic cirrhosis, apnea, brain edema, cardiomegaly, coma, confusional state, intestinal infarction, ileal perforation, peritonitis, pulmonary edema, absent pulse, respiratory arrest, congestive cardiomyopathy, hyperhidrosis, depressed level of consciousness, acidosis, hemodialysis, mental status changes, multi-organ failure, renal failure, azotemia, bronchitis, Coombs test positive, hematuria, myocardial infarction, normochromic normocytic anemia, oliguria, prolonged prothrombin time, superinfection, acute renal failure, asthenia, nausea, impaired hearing, tinnitus, increased creatine phosphokinase, grand mal convulsion, leukocytosis, asphyxiation, pulmonary edema, nephrogenic diabetes insipidus, polyuria, hypokalemia, supraventricular tachycardia, cardiogenic shock, and death.

Medical Officer's Comments: in many of these cases, the drug overdose was due to multiple drugs, so attribution to quinine is difficult. These cases were not further reviewed to determine causality.

Management of quinine overdose

Quinine overdose is managed by supportive therapy, including inotropic support for circulatory failure. Activated charcoal to decrease absorption in the stomach may be useful (Taylor and White, 2004). Activated charcoal has been recommended by the American Academy of Clinical Toxicology to increase quinine clearance in the setting of overdose (American Academy of Clinical Toxicology, 1999). In one study of 7 healthy adult volunteers, multiple-dose activated charcoal (50 grams administered 4 hours after quinine dose (single 600 mg dose), then 3 doses over the next 12 hours) decreased the elimination half life from 8.23 to 4.55 hours, and increased the mean quinine clearance by 56% from 11.8 L/h to 18.4 L/h (Lockey and Bateman, 1989).

Attempted methods to increase quinine elimination, including hemodialysis, peritoneal dialysis, charcoal hemoperfusion, phasmapheresis, exchange transfusion, and forced acid diuresis are not considered useful (Bateman and Dyson, 1986).

Medical Officer's Comments: In the proposed label,

Additionally, the American Academy of Pediatrics changed its recommendation in 2003, such that the use of syrup of ipecac to induce vomiting is no longer routinely recommended for emergency use because it has not been shown to be beneficial in improving clinical outcomes in cases of accidental poisoning. We have proposed wording in the final product labeling regarding management of quinine overdosage as follows:

*“Quinine is rapidly absorbed, and attempts to remove residual quinine sulfate from the stomach by gastric lavage may not be effective. Multiple-dose activated charcoal has been shown to decrease plasma quinine concentrations (See **CLINICAL PHARMACOLOGY/ Extracorporeal elimination**).*

Forced acid diuresis, hemodialysis, charcoal column hemoperfusion, and plasma exchange were not found to be effective in significantly increasing quinine elimination in a series of 16 patients.”

7.1.17 Postmarketing Experience

Postmarketing safety data is available for this NDA because quinine has been available in the U.S. since before the 1938 Food, Drug, and Cosmetic Act. Quinine sulfate was switched from over-the-counter to prescription only use in 1998 (FR No. 13528, March, 1998 and 21 CFR 310.547) and marketing for treatment of nocturnal leg cramps was no longer permitted since 1994 (FR notice, and 21 CFR 310.546).

Section 7.1.17 above describes the most common postmarketing adverse events reported to the FDA since 1969 and to the WHO since 1968. Specific adverse events in the AERS database were reviewed by the ODS, at the request of the DSPIDP, specifically with regard to cardiovascular, renal, and hematological adverse events. Most reported adverse events with quinine were from oral administration for the indication of leg (or muscle) cramps, when the indication was provided. See attached consultation from ODS in Appendix (section 10.3)

***Medical Officer Comments:** Most postmarketing adverse events reported to the FDA are in patients who used oral quinine for treatment of nocturnal leg cramps. This may be due to the fact that quinine was (and is) used more frequently in this country for treatment of leg cramps than for treatment of malaria. An alternative explanation may be that the use of quinine for malaria is associated with fewer adverse events, possibly due to the different pharmacokinetics of quinine in patients with malaria.*

Summary of ODS Review of Quinine Postmarketing Data

ODS was consulted by DSPIDP to evaluate specific postmarketing events in the AERS postmarketing database for quinine. The full consultation is attached in the Appendix, section 10.3. Additionally, information regarding specific postmarketing events has been included in the systems review of safety. ODS also provided data mining profiles for both quinine and quinidine

for adverse events reported at an incidence at least twice that expected. These profiles are attached in the Appendix, section 10.3.

In brief, AERS cases which reported a serious outcome through 31 March, 2005 were reviewed. A total of 537 unique cases were identified, most were from the U.S. (82%), 57% were in females, and most reports were in patient 51-60 years old. A sample (400/537) reports was reviewed to determine the indication for quinine use. Most patients (56%) used quinine for leg cramps (or related indications such as spasms, muscle pain, and restless leg syndrome); while only 4% patients used quinine for malaria. Other indications included malignant melanoma (3%), accidental or intentional overdose (11%), and no indication was listed in 19% of cases. A total of 313 cases were reviewed to determine an association between quinine use and adverse event. Positive associations with quinine, determined by a temporal association, a positive de-challenge, or by reporter assessment, were found in the majority of cases reviewed.

ODS reviewed specific adverse events, selected in discussion with DSPIDP. Reports from these adverse events were reviewed to determine possible association with quinine. The specific adverse events of interest, and the number of unique cases reviewed are shown in the following table.

Table 81: Number of AERS Unique Adverse Events Reports Reviewed by ODS (from Dr. Farinas' consultation report, Table 1)

Event of Interest	Number of AERS Cases
Fatalities	81
Teratogenic events	1
Cardiac Events	63
Torsade de pointes	11
Chest Pain	7
Palpitations	5
Arrhythmia	6
Tachycardia	5
Worsening CHF	4
Ventricular tachycardia	3
Syncope	4
Heart arrest, abnormal EKG, atrial fibrillation	2 each
Bradycardia	1
Thrombocytopenia	173
HUS/TTP	25
Agranulocytosis	5
Renal Failure	49
Nephritis	2

Medical Officer Comments: Information from the ODS review of these events was incorporated into section 7.1.3.3 of this review, in the systems review of adverse events associated with quinine, and in section 7.1.1 on deaths.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Safety information for this review was obtained from the two pharmacokinetic studies submitted by the applicant in addition to the published studies submitted in support of this NDA. In addition, the applicant summarized of postmarketing data from the AERS database, and the WHO, and product labeling from a number of foreign countries was provided. Additional literature searches were also performed by the medical reviewer to supplement the information provided by the applicant. Tables 75-79 below describe the studies submitted for safety and efficacy evaluation for this NDA.

Table 82: Pharmacokinetic Studies Submitted for Safety Evaluation

Study	Study Design	N	Study population	Study location	Quinine dose and duration	Comparator(s) dose and duration	Comments
RA3-085	Pharmacokinetic (bioequivalence) 3-way crossover	26	Healthy male and female subjects	U.S.	Mutual's 324 mg quinine sulfate single dose	GPO quinine sulfate 300 mg x 1 dose	Fed and fasting
R04-0376	Pharmacokinetic (dose proportionality) 2-way crossover	24	Healthy male and female subjects	U.S.	Mutual's 324 mg vs. 648 mg single dose	none	Fasted

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Table 83: Published Studies for oral Quinine Monotherapy

Study	Study Design	Total Number of patients enrolled (#Q/#comparator)	Study population	Study location	Quinine dose and duration	Comparator(s) dose and duration	Comments
Watt, et al., 1988	Randomized, double-blinded, double-dummy	20 (10Q/10CQ)	Males ≥ 16 years old	Phillipines	648 mg q8h for 5 days	Chloroquine 25 mg/kg total over 3 days	All AEs reported
Pukrittayakamee, et al., 2004	Randomized, open-label	176 (30Q/30 QT/ 29QP0.25/37QP0.5/ 23A/27AP)	Adult males	Thailand	10 mg/kg 3x daily 7 days	See individual study report	AEs not reported
Mueller, et al., 2004	Randomized, open label	132 (48Q/45ARtea5/ 39ARtea9)	Adults ≥ 18 years	Democratic Republic of Congo	Quinine sulfate 500 mg 3x daily for 7 days	A5: 1 liter/day for 7 days; A9: 1 liter/day for 7 days	AEs not quantified except for tinnitus
Ache, et al., 2002	Randomized, open-label	71 16Q/23CQ (40 mg/kg)/6 CQ (25 mg/kg)/26SP)	Age > 6 months	Venezuela	30 mg/kg per day in 3 doses q8h for 7 days	CQ: 25 mg/kg qd for 3 days; or CQ 40 mg/kg qd for 3 days; or SP 1.25 mg (based on pyrimethamine) as single dose	AEs not reported
Pukrittayakamee, et al., 2000	Randomized, open-label	204 (68Q/68QT/68QC)	Adult males	Thailand	10 mg/kg 3x daily for 7 days	QT:same dose quinine+ tetracycline 4 mg/kg 4 x daily for 7 days; or QC: same dose quinine+ clindamycin 5 mg/kg base 4 x daily for 7 days)	AEs selectively reported
McGready, et al., 2000	Randomized, open-label	115 (108 evaluable) (42 Q/66 MAS)	Pregnant women	Thailand	10 mg/kg q8h for 7 days	MAS: mefloquine 25 mg/kg on day 1 and 10 mg/kg on day 2; artesunate 4 mg/kg/day for 3 days.	Common AEs reported

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De Vries, et al., 2000	Randomized, open-label	268 84 Q/96 ATQ3/88 ATQ5)	8-65 years old	Vietnam	10 mg/kg 3 x daily for 7 days	ATQ3 or QTQ5: artemisinin 20 mg/kg single oral dose +Q 10mg/kg 3x daily for 3 or 5 days.	AEs not reported by treatment group
Bich, et al., 1996	Randomized, open-label	161 (157evaluable) 59 Q/45 ATQ/53 ATD	8-65 years	Vietnam	10 mg/kg 3 x daily for 7 days	ATQ or ATD: artemisinin 20 mg/kg single oral dose, followed by Q 10 mg/kg 3 x daily for 3 days: or doxycycline 4 mg/kd daily for 3 days	Drug-related AEs reported
Metzger, et al., 1995	Randomized, open-label	120 (40 Q/40 QC/40 QD)	Age > 15 years	Gabon	12 mg/kg q 12h for 3 doses	QC and QD: quinine 12 mg/kg q 12 h for 3 doses + clindamycin 5 mg/kg q 12 h for 6 doses; or doxycycline 2 mg/kg q 12 h for 6 doses	AEs not reported individually for each treatment group
Segal, et al., 1974	Randomized, open-label	51 26 Q/25 WR 33063	Males ≥ 15 years old	Thailand	540 mg (base) q 8h for 6 days	WR 33063: 600 mg PO q 8h for 6 days	All AEs reported
Rahman, et al., 2001	Randomized, open-label	413 (49 Q/149 CQ/145 Q3SP/70 M)	12-60 years old	Bangladesh	10 mg/kg q8h for 7 days	CQ: 10 mg/kg on first day, then 7.5 mg/kg qd x 2 days; Q3SP: quinine 10 mg/kg q 8h for 3 days, then SP 25 mg/kg (sulfadoxine) single dose	AEs not reported

AEs= adverse events; Q= quinine; CQ= chloroquine; QT= quinine+tetracycline; QP0.25= quinine+primaquine 0.25 mg/day; QP0.5= quinine+primaquine 0.50 mg/day; A=artesunate; AP= artesunate+primaquine; ARtea5=Artemisia tea 5g/L; ARtea 9=Artemisia tea 9 g/L; SP= sulfadoxine-pyrimethamine; Qc= quinine+clindamycin; MAS=mefloquine+artesunate; AT= artemisinin; ATQ= artemisinin+ quinine; ATD=artemisinin+doxycycline: Q3SP= quinine 3 days+sulfadoxine-pyrimethamine

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Table 84: Published Non-randomized Studies of oral Quinine Therapy

Study	Study Design	Total Number of patients enrolled (#Q/#comparator)	Study population	Study location	Quinine dose and duration	Comparator(s) dose and duration	Comments
Mohaptra, et al., 2003	Non-randomized, non-blinded, prospective study	53 19 Q/53 CQ/43 SPP	> 1 year old	India (near border with Myanmar)	10 mg/kg 3 x daily for 5-7 days	CQ:10mg on day 1 and 2, 5 mg on day 3; SPP: sulfadoxine (25 mg/kg)-pyrimethamine (1.25 mg/kg) single dose, then primaquine (dose not specified)	AEs reported for quinine only
Pineli, et al., 1999	Retrospective study	454 (all quinine)	All patients with confirmed malaria who received quinine	Brazil	10 mg/kg q 8h for 7 days	NA	AEs not reported
Babalola, et al., 1998	Pharmacokinetic study	6 (all quinine)	Patients ages 8-20 years old	Nigeria	10 mg/kg q 8 h for 7 days	NA	No AEs reported in study
Sowunmi, 1996	Pharmacokinetic study	11 (all quinine)	Patients 8-20 years old	Nigeria	10 mg/kg q12 h on day 1, then q8h for 6 more days	NA	AEs not reported
Ringwald, et al., 1995	Prospective study	22 (all quinine)	Patients > 15 years old	Cameroon	500 mg q8h for 3 days	NA	AEs reported
Bhalli and Samiullah, 2001	Prospective (randomized) study (not blinded)	120 59 Q/30 CQ/16 SP/7 QSP/4 QD/4 CQSP	120 consecutive male patients	Pakistan	10 mg/kg q8h for 7 days	CQ: 10 mg/kg single dose, then 5 mg/kg in 6 hours, and qd for 2 days; SP: one tablet	AEs not reported
Giboda and Denis, 1988	Prospective, non-randomized	65 43 Q/22 QT	Males 16-53 years old	Kampuchea	500 mg 3 x daily for 10 days	QT: quinine 500 mg 3 x daily for 10 days + tetracycline	AEs not reported

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						500 mg 3x daily for 7 days	
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* All patients initially received chloroquine, followed by sulfadoxine-pyrimethamine + primaquine if initial regimen failed, then quinine if first 2 regimens failed; NA= not applicable
Q= quinine; CQ=chloroquine; SPP= sulfadoxine-pyrimethamine +primaquine; CQ= chloroquine;
QSP= quinine+sulfadoxine-pyrimethamine; QD=quinine+doxycycline;
CQSP=chloroquine+sulfadoxine-pyrimethamine; QT= quinine +tetracycline

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Table 85: Published Randomized, Controlled Studies with Oral Quinine Combination Therapy

Study	Study Design	N	Study population	Study location	Quinine dose and duration	Comparator(s) dose and duration	Comments
Bunnag, et al., 1996	Randomized, open-label	90 48 Q5T7 42 Q7T7	Males 16-54 years old	Thailand	NA	Q5T7 or Q7T7; quinine 600 mg 3 x daily for 5 or 7 days + tetracycline 250 mg 4 x daily for 7 days	AEs not reported
De Alencar, et al., 1997	Randomized, open-label	175 (154 evaluable) 77 QT 77 AP	Males 16-65 years	Brazil	NA	QT: quinine 600 mg 3 x daily + tetracycline 250 mg 4 x daily for 7 days; AP: atovaquone 1 g + proguanil 400 mg daily for 3 days	AEs reported
Villalobos, et al., 1997	Randomized, open-label	42 AS-T (PO) AS (IV)-T (PO) Q (IV)-T (PO) QT (PO) M (PO)	Males and females 8-64 years old	Brazil	NA	See individual study report (appendix)	Some adverse events reported
Duarte, et al., 1996	Randomized, blinded	176 88 AS-T 88 QT	Patients ≥ 14 years old	Brazil	NA	AS-T: initial dose 100mg AS (oral), then 50 mg q 12 h + tetracycline 500 mg q 8 h for total of 7 days; QT: quinine 1 g q 12 h for 3 days + tetracycline 500 mg q 8 h for 7 days	AEs reported
Fungladda, et al., 1998	Randomized, open-label	137 60 QT 77 AS	Patients 15-60 years old	Thailand	NA	QT: quinine 600 mg 3 x daily + tetracycline 500 mg 2 x daily for 7 days; AS: artesunate 300 mg initial dose on day 1, then 100 mg daily for 4	AEs reported, but specific AEs not quantified

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						more days	
Looareesuwana, et al., 1994	Randomized, open-label	102 52 MT 50 QT	Patients 16-60 years old	Thailand	NA	QT: quinine 600 mg 3 x daily + tetracycline 250 mg 4x daily for 7 days; MT: mefloquine 750 mg initial dose, then 500 mg 6 hours after initial dose+ tetracycline (same as above for 7 days)	Adverse events reported
Vanijanonta, et al., 1996	Randomized, open-label	50 25 QT 25 QCQ	Males 14-51 years old	Thailand	NA	QT: quinine 10 mg/kg 3 x daily + tetracycline 4 mg/kg 4 x daily for 7 days; QCQ: same dose and duration of quinine +chloroquine 25 mg/kg total dose over 54 hours	Some adverse events reported
Karbwang, et al., 1994	Randomized, open-label	64 33 QT 31 AS	Males 15-35 years old	Thailand	NA	QT:quinine 600 mg q8h + tetracycline 250 mg 250 mg q 6h for 7 days; AS: 200 mg initial dose, then 100 mg 12 hr later, then 100 mg daily for 4 days (5 days total)	Adverse events reported

Q5T7= quinine 5 days+tetracycline 7 days; Q7T7= quinine 7 days+tetracycline 7 days; QT= quinine=tetracycline; AP= atovaquone-proguanil; AS-T= artesunate+tetracycline; M= mefloquine; AS= artesunate; MT= mefloquine=tetracycline; QCQ= quinine+ chloroquine; AS=artesunate
 PO= per os (by mouth)

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Table 86: Published Randomized, Controlled Studies with Parenteral Quinine for Treatment of Severe Malaria

Study	Study Design	N	Study population	Study location	Quinine dose and duration	Comparator(s) dose and duration	Comments
Singh, et al., 2000	Randomized, open label	52 26 Q 26 AR	Patients >15 years old	India	10 mg/kg daily* IV for 7 days	AR: initial dose 4 mg/kg IM, then 2 mg/kg for 4 days (5 days total duration)	Adverse events reported
Newton, et al., 2003	Randomized, open-label	113 54 Q 59 AS	Patients ≥ 15 years old	Thailand	20 mg/kg IV loading dose, then 10 mg/kg IV q8 h, then same dose PO for 7 days total	AS: initial dose 2.4 mg/kg IV, then 1.2 mg/kg in 12 hours and daily, followed by oral AS 12 mg/kg for total of 7 days**	Some adverse events reported
Satti, et al., 2002	Randomized, open-label	77 39 Q 38 AR	Children 3 months to 15 years old	Sudan	10 mg/kg q 8 h IV, then PO for 7 days	AR: 1.6 mg/kg q 12 h IM on day 1, then 1.6 mg/kg IM daily for 4 days (5 days total)	Some adverse events reported
Adam, et al., 2002	Randomized, open-label	41 21 Q 20 AR	Children	Sudan	20 mg/kg IV loading dose, then 10 mg/kg q 8h IV, then PO for total of 7 days	AR: 3.2 mg IM loading dose, then 1.6 mg daily for 4 days (5 days total)	Some adverse events reported
Faiz, et al., 2001	Randomized, open-label	105 54 Q 51 AR	Patients 14-50 years old	Bangladesh	20 mg/kg IV loading dose, then 10 mg/kg q 8h IV then PO for total of 7 days	AR: for weight > 45 kg: 160 mg IM initial dose, the 80 mg/kg† IM daily for 4 days (5 days total); for weight < 45 kg: 3.2 mg/kg IM initial dose, then 1.6 mg/kg daily for 4 days	Some adverse events reported
Thuma, et al., 2000	Randomized, open-label	95 47 Q 48 AML	Children 0-10 years old	Zambia	20 mg/kg IV loading dose, then 10 mg/kg q 8 h IV then PO for total of 7 days	AML: 3.2 mg/kg IM loading dose, then 1.6 mg/kg IM daily for 5 days total	Adverse events reported
Moyou-Somo, et	Randomized, open-label	102 51 Q	Children 0-10 years	Cameroon	20 mg/kg IV loading dose,	AE: 3.2 mg/kg IM loading dose,	Adverse events not