- The third case involved the unintentional overdose of meclizine (for chronic vertigo) in the setting of cardiovascular disease (patient was on automatic implantable cardioverter defibrillator or AICD and propafenone). Patient had a history of continued use of quinine for several years.

Tachycardia (n=6):
a) the majority of cases were from the US, and listed events in males,
b) the median age in this group was 51 years, although the range was from 34 to 72 years of age,
c) there was one fatality, in a 34 year old female died of cardiac arrest who had a previous history of quinine-induced adverse events, and
d) indication was listed as leg cramps/muscle spasms in two, and as malaria in a third; however, a fourth patient was treated for multiple myeloma and a fifth patient used quinine along with other drugs in a suicide attempt.

Additional case information:
- In one case, a 34-year old female died of cardiac arrest. In this case the patient had experienced positive rechallenge with quinine twice. This patient was diagnosed with SLE when she was 17 years old and was on dialysis.
- In one case, a 72-year old male with multiple myeloma was on vincristine, Adriamycin (doxorubicin), Decadron (dexamethasone) and prednisone concomitantly.
- In another case, a 55-year old male attempted suicide by taking 41 tablets of quinine 0.3mg, 120 tablets of L-thyroxine 0.1mg, and 30 tablets of cetirizine 10mg.

Chest pain (n=7):
a) the majority of reports were in females from the US,
b) patients were older, with a median age of 73 years,
c) there were confounding factors in the one patient who died after complaining of chest pain.

Additional case information:
- There was one fatality in a 65-year old female patient who experienced chest pain. Pre-existing medical conditions included insulin-dependent diabetes mellitus, angina, and CHF. Apparently she was severely jaundiced and thrombocytopenic and was transfused 6 units of platelets.

Palpitations (n=5)
a) all the cases were in females
b) age ranged from 60 to 86 years, with a median age of 64,
c) serious outcome (hospitalization, life-threatening) was noted in two cases

Overdose/Poisoning reporting a cardiac event (n=11)
a) there were 11 cases of overdosage/poisoning with quinine use,
b) seven cases were from the US and four were foreign,
c) age ranged from two to 86 years with a median age of 26 years,
d) gender was reported in all the cases as eight males and three females,

e) serious outcome was noted in all the cases and included seven deaths

Additional case information:

- In three of the fatalities, suicide appeared to be the motive
  - One patient was depressed and had a history of suicide attempts and drug abuse; this paient was on multiple medications including oxycodone
  - In a second patient, acute intentional overdose was suspected. He took amlodipine, cetirizine and quinine.
  - In the third case of suicide attempt, the patient took two drugs, quinine and hydroclorothiazide
- In two cases of death, quinine seemed to be the only drug that was ingested by the patients
- One death was apparently due to accidental overdose, where the patient took her pain medications (methadone, morphine and tramadol) "more often than usual." The cause of death was listed as narcotic intoxication
- In another death case, the patient was prescribed 10 tablets of quinine (strength unknown) and was on three other medications (two different vitamins and a calcium supplement)
- Cardiac events included arrhythmia, myocardial infarction (heart attack), shock, and cardiac (heart) arrest

Hematological events/Summary of cases:

Thrombocytopenia

The characteristics of the 173 cases are:

- the majority of patients used quinine for leg cramps (123/173)
- there are 15 fatalities in patients experiencing thrombocytopenia; half of the cases identified a specific cause of death, which was described as thrombocytopenia, pulmonary embolus, cardiac arrest, anemia, intra-ventricular hemorrhage and secondary to drug-induced thrombocytopenia
- in approximately one third (33%; 57/173) an intervention took place as follows: blood or platelet transfusion (41), plasma exchange (12), plasmapheresis (3), and administration of fresh frozen plasma (1).
- there were almost 10 times more US cases than foreign (159 US, 16 foreign); US patients were younger (US average age 56, foreign average age 66); almost half of the foreign reports listed a fatality (44%; 7/16), whereas a small fatalities represented a small portion of proportion of the US cases (6%; 9/150)
- from the information provided in the cases, we were able to determine a probable association between thrombocytopenia and the use of quinine in 77 of the reports, including nine of the 15 deaths.

Thrombocytopenia associated fatalities (n=15):

- quinine, alone or in combination with other drugs, was listed as suspect drug for the adverse events mentioned in the cases

- cause of death was listed infrequently; events identified were thrombocytopenia, pulmonary embolus, cardiac arrest, anemia, intra-ventricular hemorrhage and secondary to drug-induced thrombocytopenia
- 8 patients used quinine for leg cramps, and another for symptoms in joints and muscles; indication was not listed for any of the other patients
- more females than males died after experiencing thrombocytopenia (10 females, vs. 6 males)
- where listed (12/15), most of the patients were older than 50 years (9/12), with females being slightly younger than males (average age for females 61, average age for males 67); the overall average age 63, median 66, range 39-84
- more fatalities were reported in US patients (9 from US; 7 foreign) who were slightly younger (average age for US patients was 61 years, average age for foreign patients was 65 years)
- where stated, all the patients used an oral form of quinine (n=7)

#1. 55-year old Australian female, died of thrombocytopenia. Patient was on seven medications, one of which was quinine (dosage form not stated); all seven were listed as suspect drugs. Almost all were started on the same day; however, duration of therapy, time to onset, and indication were not provided. The reporter assessed the causal relationship as probable to all medications. (case # 3045476)

#2. A 66-year old females from Australia experienced thrombocytopenia 4 days after starting 7 medications, one of which was quinine. Despite a recovering platelet count, the patient died approximately 3 weeks after starting the medications. Cause of death was not stated; the reporter's causality assessment for all drugs was possible. (case # 5608858)

#3. A Swedish literature article described death of a male who developed thrombocytopenia following administration of quinine for leg cramps. He took 250 mg of quinine orally for 5 days. It is not clear if the thrombocytopenia developed immediately after quinine use, or at a later time. No additional suspect or concomitant drugs were listed. Cause of death was not stated. (case # 4102965)

#4. An 84-year old Swedish female experienced aplastic anemia, sepsis, and constipation in addition to thrombocytopenia. Oral quinine, glyburide and ibuprofen were listed as suspect drugs. Quinine was used for "symptoms referable to joints". After surgery for hemorrhoids she bled and was transfused. Cause of death was pulmonary emboli. (case # 5029348)

#5. This was the third time similar adverse events occurred in a 34-year old female from New Zealand who experienced pancytopenia, DIC, intravascular hemolysis and probably rhabdomyolisis after ingesting quinine. She was given a platelet infusion. Prior to her death she experienced cardiac arrest, coagulopathy, myopathy, hypoglycemia, and thrombocytopenia. Oral quinine was listed as suspect drug; vitamin B complex and aluminum hydroxide were listed as concomitant drugs. Quinine was used to treat leg cramps. (case # 4780133)

#6. A 70-year old German male experienced thrombocytopenia, five days after starting quinine (indication not listed). Five drugs were listed as suspect: quinine, lasix, tegretol, ibuprofen and amiloride. Despite receiving a platelet transfusion, he died. Cause of death was not listed. (case # 4661504)

#7. A report from France indicated that an 82-year old male with numerous medical conditions was treated over an unspecified course of time with 15 medications. Duration of therapy and indication for these medications was not stated. At some time the patient developed thrombocytopenia, anemia, hematuria and hyperleukocytosis. Patient was transfused. The cause of death was reported as anemia, and also as possibly related to the adverse reactions. Four medications, including quinine, were listed as suspect. (case # 4065931)

#8. An 84-year old Florida male used oral Q-Vel for leg cramps, and was hospitalized for hemorrhagic stroke, leukopenia, thrombocytopenia and vomiting. Q-Vel was listed as suspect drug; patient was on another 4 concomitant products. Specific Cause of death and reporter's assessment were not listed. (case # 4621404)

#9. An 83-year old US female was transferred to the general floor for a decreased platelet count and elevated liver function studies. She had been originally admitted for evaluation of CVA. The patient was jaundiced, her urine was bile colored, and she also had acute renal failure. The patient continued to deteriorate, and expired. The final diagnosis was consumption, coagulopathy and renal failure. Medical history indicated that the patient used quinine 5 grains on a p.r.n. basis. Specific cause of death was not stated. (case # 5360292)

#10. A 65-year old US woman presented with chest pain, jaundiced and thrombocytopenic after 3 days of daily oral quinine for leg cramps. She was on six other medications. She died the day after admission; cause of death was not stated. This patient had a history of congestive heart failure, angina and diabetes. (case #3427642)

#11. A 58-year old male from California used oral quinine for 7 months and died of inter-ventricular hemorrhage. Suspected cause of death was complications secondary to drug-induced thrombocytopenia. Quinine was listed as suspect drug; the patient was on 7 additional concomitant drugs. (case # 3944557)

#12. A 41-year old female from the US used oral Legatrin for leg cramps. She developed pulmonary hemorrhage and severe thrombocytopenia. No other drugs were mentioned. Laboratory test indicated the presence of quinine-dependent platelet reactive antibodies supporting a diagnosis of quinine-induced thrombocytopenia. Cause of death was not listed. (case # 4579497)

#13. A 39-year old male from the US used oral Legatrin for relief of leg cramps. He experienced thrombocytopenia, brain hemorrhage and death. No other drugs were mentioned. Cause of death was not listed. (case # 4602498)

#14. A 79-year old female from the US developed gastrointestinal bleeding and thrombocytopenia. Quinamm was listed as suspect drug. The patient was using Quinamm for night leg cramps. She died due to secondary bleeding from thrombocytopenia. (case # 4335729)

#15. A female from the US used oral Legatrin for nocturnal leg cramps. She developed hypersensitivity, hypotension, skin necrosis and idiopathic thrombocytopenic purpura. Legatrin was listed as suspect drug. Cause of death was not listed. (case # 4621149)

HUS/TTP (n=25):

- None of the patients were under the age of 21; the median age was 58 year, and the range was 21 to 75 years
- There were four times as many females than males with this complaint (20F; 5 M)
- When stated (18/22) reports show that this event can occur regardless of the number of doses ingested; 9 patients develop signs or symptoms after 1-2 days of therapy, 5 after 7-25 days, and 3 after taking quinine for more than 25 days
- Almost all of the patients experienced thrombocytopenia (88%;22/25); 11 indicated patient experienced renal failure, and another 11 showed abnormalities of renal function, such as decreased urine output, hematuria and uremia
- The majority of patients required both plasma exchange and dialysis (68%)
- Approximately half of the patients reported previous use of quinine (48%; 12/25)
- Ten of the 25 cases were listed in published reviews

Agranulocytosis: (n=5):

- All five reports list agranulocytosis in adult US patients; age range 43-85 years, average 57, median 56; 3 of the 5 patients were males
- One report was a fatality, and all others were hospitalizations
- The fatality was in an 85-year old male who used quinine for leg cramps; agranulocytosis was more temporally associated with the use of ceftriaxone that was indicated for septic arthritis; the specific cause of death was not listed
- None of the reports listed an indication for malaria or protozoal infection; Indication was listed as leg cramps in the fatality, and in another two reports as muscle spasm in one and as muscle cramps in the other
- Two reporters stated that the agranulocytosis was due to quinine use; determination of causal association in the remaining three cases is difficult due to concomitant drug use or illness, or lack of information

Renal Events/Summary of cases:

Renal Failure (n=49):

- There were 49 unduplicated cases of renal failure, which is 8% (49/642) of all quinine reports.
- About 18% of the renal failure cases were fatal. In addition, 1 case of renal failure resulted in a renal transplant.
- The average age (56.2 years; range 18-84 years) of the patients experiencing renal failure was similar to the average age (57 years) reported for all quinine reports.

- Renal failure was more commonly reported in female (59%) than male patients (39%).
- The majority of renal failure cases (78%) originated from domestic sources.
- These 49 cases reported 26 events of renal failure, 21 events of acute renal failure, and 1 event of chronic renal failure. Both renal failure and acute renal failure were reported in 5 cases.
- Other commonly reported events included thrombocytopenia (19), vomiting (17), hypotension (8), coagulopathy (6), haemodialysis (5), nausea (5), anuria (4), dyspnoea (4), hemolytic uremic syndrome (4), thrombotic thrombocytopenic purpura (4), abdominal pain (3), asthenia (3), back pain (3), chills (3), coma (3), hepatic function abnormal (3), intentional misuse (3), and pyrexia (3).
- The indication for quinine was specified in 10 cases, including leg cramps in 6 cases, plasmodium infection in 2, leg pain in 1 and intentional overdose in 1 case.
- For the 6 cases with quinine indication of leg cramps, the event of renal failure was possibly related to quinine in 5 cases, based on the reported temporal relationship and positive dechallenge information. The last case was a legal case that did not have enough information for a causal assessment. For the 1 case with a quinine indication of leg pain, a causal relationship could not be clearly established in the aged, polymedicated patient.
- Quinine was administered intravenously in 2 cases and orally in 29 cases; the route of administration was not provided in the remaining cases.
- Intravenous quinine was used in 2 patients with a protozoal infection; both cases had fatal outcomes. One case reported events of acute respiratory distress syndrome, drug ineffective, hepatic failure, hepatitis C, multi-organ failure, acute pancreatitis, and acute renal failure. The second case reported aspergillosis, brain abscess, cerebral infarction, haemolysis, immunosuppression, intracranial pressure increased, pseudomonal lung infection, mucormycosis, muscle spasms, myocardiac abscess, renal abscess, renal failure and systemic mycosis.

In total there were 38 cases from the U.S. and 9 cases from foreign sources, which are summarized below (in two additional reports the source is unknown).

Summary of U.S. renal failure cases (n=38):

- Renal failure was reported more often in females than males (26 vs. 11 cases) at an average of 55 years (range 20-79 years), only 1 patient used intravenous quinine.
- There were few cases specifying an indication for quinine use; quinine was used for leg cramps in 5 cases, babesiosis in 1 case and intentional overdose in 1 case.
- Renal failure was listed most frequently (21 cases), followed by thrombocytopenia (17), vomiting (16), acute renal failure (14), hypotension (6), haemodialysis (5), hemolytic uremic syndrome (4), nausea (4), thrombotic thrombocytopenic purpura (4), abdominal pain (3), anuria (3), back pain (3), chills (3), coagulopathy (3), dyspnoea (3), intentional misuse (3), and pyrexia (3).
- These 38 domestic cases of renal failure resulted in 30 hospitalizations, 6 fatalities and 1 disability.
- The first fatal case occurred in a 40-year-old male patient receiving intravenous quinine (dose unspecified) for a babesiosis infection who developed acute respiratory distress

syndrome, hepatic failure, hepatitis C, multi-organ failure, acute pancreatitis, and acute renal failure. Drug ineffective was also reported. The underlying babesiosis infection was a plausible explanation for the reported events.

- The second fatality involved a completed suicide in a 59-year-old female who developed acidosis, coma, hypotension, mental status changes, multi-organ failure, vomiting, and renal failure requiring hemodialysis. The quinine dose and route of administration were not specified. The patient also ingested acetaminophen, tramadol, lorazepam, naproxen, losartan, levothyroxine, haloperidol, olanzapine, hydroxyzine, and sertraline. Death was due to multi-system organ failure with an elevated acetaminophen concentration and presentation consistent with opiate poisoning. The events were believed to be consistent with acetaminophen/tramadol overdose.
- The third fatality was a 24-year-old male who intentionally ingested 8 g of oral quinine and 5 g of oral hydrochlorothiazide in a suicide attempt and developed cardiac arrest, hypotension and anuria. The patient received hemoperfusion and life support measures, but died of asystolic cardiac arrest 20 hour after ingestion. Postmortem analyses revealed a quinine level of 13 mcg% (the hydrochlorothiazide level was undetectable), which the authors considered to be in excess of the lethal level.
- The fourth fatality was a 64-year-old female who developed arrhythmia, pneumonia, renal failure and vomiting. The quinine dose, indication and route of administration were not specified. This patient with multiple myeloma was also receiving vincristine, adriamycin, verapamil, and ranitidine at the time of the event. Aspiration pneumonia and viral, mycoplasma, and bacterial infections were suspected, but not confirmed. The patient's condition worsened to ARDS requiring mechanical ventilation, which was ultimately fatal.
- The fifth fatality was a 77-year-old female who developed deafness, dyspnea, neurosis, and renal failure. This patient with multiple myeloma was receiving oral quinine (dose and indication unknown) along with adriamycin, vincristine, verapamil and dexamethasone at the time of the event. Quinine had been discontinued 4-6 weeks prior to the event because of deafness. The patient then developed renal failure, but refused dialysis. The patient eventually expired from renal failure secondary to multiple myeloma.
- The last fatality was reported in a 61-year-old female who developed hypotension, leukopenia, oliguria and stomatitis. The patient was receiving oral quinine (dose and indication unspecified) along with verapamil, adriamycin, vincristine and dexamethasone. The case could not be further assessed based on the limited information reported.

Summary of foreign renal failure cases (n=9):

- Renal failure was reported more often in males than females (6 vs. 3 cases) at an average age of 61 years (range 18-84 years).
- The indication for quinine use was only noted in 2 cases, including leg pain and plasmodium falciparum infection. The patient with the plasmodium falciparum infection was the only patient who received intravenous quinine.
- Acute renal failure was listed most frequently (6 cases), followed by renal failure (4), coagulopathy (3), and thrombocytopenia (2).

- These 9 foreign cases of renal failure resulted in 5 hospitalizations, 3 fatalities and 1 disability.
- In the first fatal case, a 26-year-old male receiving quinine 600 mg IV BID for a plasmodium falciparum infection developed aspergillosis, renal failure, hemolysis, cerebral infarction, immunosuppression, increased intracranial pressure, pseudomonal lung infection, mucormycosis, muscle spasms, systemic mycosis, and myocardiac, brain and renal abscesses. The cause of death was a systemic fungal infection with *Aspergillus flavus* and *Absidia corymbifera*, following severe malaria. The reporter stated that the immune suppression may have been caused by malaria or renal failure.
- In the second death, a 70-year-old male with congestive heart failure developed 1° AV block, cardiac failure, coma, cyanosis, abnormal hepatic function, hypotension, hypothermia, lactic acidosis, and acute renal failure. The quinine dose, route of administration and indication were unknown. He also received simvastatin, metformin, isosorbide, glipizide, ranitidine, perindopril, paroxetine, furosemide, warfarin, and gemfibrozil. The case could not be further assessed based on the limited information reported.
- The third death involved an 82-year-old male who developed acute coronary syndrome, anuria, azotemia, chronic bronchitis, positive Coombs test, hematuria, myocardial infarction, normochromic normocytic anemia, oliguria, overdose, prolonged prothrombin time, acute renal failure, superinfection and thrombocytopenia. He had a history of cardiovascular disease, prostate adenoma, chronic bronchitis, arteritis, and thrombosis. The quinine dose, route of administration and indication were unknown. He was also receiving clopidogrel, nicorandil, bisoprolol, linsidomine, simvastatin, tamsulosin, trimetazidine, buflomedil, and tianeptine. The patient was hospitalized for acute coronary syndrome and superinfection of chronic bronchitis and received multiple medications. Over the course of 3 weeks, a progressive anemia developed and the patient died a week later due to anemia. Hemorrhagic and hemolytic anemia were suspected and autoimmune or allergic mechanisms were also suspected. The events were considered possibly related to an adverse reaction.

Nephritis cases (n=2):
Both reports occurred in elderly patients in the U.S. The following summarizes the cases:

- Case 1: a pharmacist reported a case of nephritis in a 65-year-old male with a hypersensitivity reaction, exfoliative dermatitis and leukocytosis. The events began 9 days after the initiation of quinine and abated with discontinuation of quinine. The indication for quinine use and the dose and route of administration were not specified. The patient was receiving furosemide, carbamazepine, cimetidine, and amitriptyline concomitantly. The case was assessed as medically significant.
- Case 2: a literature case of biopsy proven interstitial nephritis with haemolytic anemia, myalgia and thrombocytopenia was reported in a 73-year-old female who had been using quinine 325 mg orally intermittently for 3 years for leg cramps. The results of the renal biopsy revealed prominent focal tubulointerstitial eosinophilic infiltrate consistent with drug-induced acute interstitial nephritis. The maximum serum creatinine noted was 9.2 mg/dL. The authors stated that there was no evidence of hemolytic uremic syndrome.

Skin/hypersensitivity reactions/Summary of cases:
Serious cases/ODS "Serious Skin Reaction" group:

- 13 serious reports were retrieved using the standardized ODS search criteria ODS serious skin reaction group
  - the majority of patients were females (8), from the US (8) and had an average age of 62 years (median 65, range 20-78)
  - all were non-fatal and seven indicated hospitalization; the remaining were serious by regulatory definition or outcome was not mentioned;
  - where stated (n=10), all the patients used oral quinine for leg cramps/limb pain;
  - 4/13 cases were confounded by other drugs or poor temporal association; in the remaining 9 skin reactions could be attributed to quinine use based on temporal association
  - The types of events reported were:

Erythema multiforme (1 case w/thrombocytopenia)	4
Blisters with bleeding/thrombocytopenia	3
Stevens-Johnson syndrome	2
Erythema, blisters, SOB, burning hands/feet	1
Blister lesions on left arm/neck	1
Overdose leading to fall with "contusion and blisters"	1
Bullous pemphigoid	1

Other skin reactions:
The remaining 88 cases were characterized as follows:

- the majority of patients in this group were from the US (70) and used oral quinine for leg/ foot/muscle cramps (58); other indications were restless leg syndrome (1), severe pain (1), arrhythmia (1), malaria (6) and babesiosis (2); 19 did not list an indication
- more males (44) reported this type of events than females (38)
- the average age in this group was 58 years, with a range of 5-84 years
- the majority of reports (88%) listed a serious outcome, that included 6 fatalities and 42 hospitalization
- about one third of the cases (29/88) reported rash/itching, without any serious systemic effects
- another third of the cases (31/88) reported more severe rash/skin reactions where 27 required hospitalization; the type of events reported were:

thrombocytopenia/bleeding/bruising	7
angioedema	6
increased LFTs	5
skin exfoliation	3
skin necrosis	2
shortness of breath	1
hypotension/syncope	1
renal failure	1

- the remaining one third (28/88) reported serious non-skin hypersensitivity reactions, which included three fatalities and 14 hospitalization; the type of events reported were:

SOB/bronschospasm/wheezing	10
thrombocytopenia/bleeding/bruising/DIC	7

angioedema	6
hypotension/syncope	5
anaphylaxis	4
acute pulmonary edema	4
ARDS	4
renal failure	2
serum sickness	1
pulmonaryinfiltrates	1
interstitial fibrosis	1
multi-organ failure	1

- 6/88 were fatalities; 3/6 were associated with quinine use, 2 with illnesses (babesiosis and malaria) and 1 was unrelated to a hypersensitivity reaction; of the 3 related to quinine use one described angioedema, a second angioedema with thrombocytopenia purpura, and a third ARDS subsequent to a quinine overdose case

Additional case information:

- Four of the13 cases captured under the ODS serious skin reaction group showed a poor temporal association between event and quinine use; in the pemphigoid case the patient had been treated with quinine for more than 2 years prior to the event; in another three reporting erythema multiforme-1, blisters with bleeding/thrombocytopenia -1, "contusion and blisters" -1, time to onset was not reported; the remaining 9 cases had good temporal relationships to quinine administration (range several hours to 4 months).
- One case (Stevens-Johnson) was confounded by carbamazepine administration whose treatment started at the same time as quinine therapy.
- Two cases (blisters with bleeding/thrombocytopenia -2) were confounded by celecoxib administration whose treatment started at the same time as quinine therapy

Ophthalmic cases/Summary of cases:

- 28 cases listed an ophthalmologic event; the majority were from the US, and indicated events subsequent to oral use of quinine in approximately equal number of males and females
- the majority listed an indication or use (17/28), described as overdose (12), leg cramps (4), malaria (1), and malignant melanoma (1)
- the majority were clinically severe, as determined by outcome of 4 fatalities and 14 hospitalization;
- there were four fatalities:
  - a 2-year old male from the UK who experienced arrhythmia and a non-specified visual disturbance (no additional information at this time) (case # 4588693)
  - a 26-year old male who died from fungal infection and experienced eyelid-ptosis (case # 4182870)
  - a 59-year old female suicide patient who experienced miosis (case # 5657612)
  - a 51-year old male treated for malignant melanoma whose symptoms were described as pupils reacting sluggishly (case # 5034859)
- there were four permanent/on-going events, 3 associated with OD

  - permanent loss of vision in one, pale and ischemic retina in a second case, and permanent changes to the retinal and optic nerves in OD patients.
  - abnormal vision with papilloedema and retinal hemorrhage in the fourth patient; these events are more closely temporally related to the use of Fentanyl

- The most frequent type of vision related events were:

Blindness	7	(6 associated with OD; 3 permanent damage)
Visual disturbances	6	(2 associated with OD, 2 with retinal disorders, 1 with arrhythmia, and 1 with medication error)
Double vision/blurred vision	4	(1 associated with HUS/TTP, 1 with medication error, and 2 no information available)
Worsening vision	1	(may be associated with co-morbidities, history of glaucoma and cataract; worsening vision preceded the use of quinine)
Abnormal vision	1	(more closely associated with Fentanyl use)
Visual field defect	1	(no information available)
Miosis	1	(associated with suicide)

Summary of the 20 US cases:

- The majority provided gender, age, and dosage form information; thus, we found there were almost equal number of males and females with an average age of 51, who used an oral form of quinine; there were 9 hospitalization and 2 fatalities
- Half stated an indication or use; 4 patients used quinine for leg cramps, and one to treat malignant melanoma; overdose was listed in another three, and two indicated medication errors involving quinine and quinidine
- Blindness was the event mentioned most frequently (5/20); it was associated with overdose in four patients, and was resolved in all; two patients took large doses, inadvertently; one took 8 tablets mixed with cocaine and alcohol, maybe as accidental overdose; and the last one took several grams in a suicide attempt; all were hospitalized due to symptoms associated with the overdose
- Five additional patients were hospitalized with complaints of blurred vision, amblyopia, visual disturbances, eye disorder and eye hemorrhage, one event per patient respectively; however, the hospitalization was most closely associated with HUS/TTP in the first, elevated liver function in the second, generalized physical deterioration in a patient with a history of arrhythmia in the third, renal failure in the fourth, and thrombocytopenia in the last

Summary of the 8 foreign cases,

- There were equal number of male and female patients, where the average age was 37 (median 33, range 2-78 years); and most used an oral form of quinine; there were two deaths, four hospitalizations and one disability
- one patient used quinine for leg cramps and another for malaria; in another four patients quinine was used in an overdose event

- A non-specified visual disturbance was the event mentioned most frequently (4/8); all other events were mentioned once (vision blurred, papilloedema, retinal hemorrhage, eye disorder, eyelid ptosis and blindness)
- Visual disturbances were associated with intentional overdose in three patients who were hospitalized due to symptoms of overdose, and with arrhythmia in a fourth case which was a fatality in a 2-year old child; this fatal case did not indicate indication, dose, concomitant drugs or cause of death
- Blurred vision, retinal hemorrhage and papilloedema occurred in a patient with a history of essential hypertension, and breast, bone and bone marrow cancer, who was also using Fentanyl; she was hospitalized
- Blindness was mentioned together with intentional overdose in a patient with a history of drug overdose

Hearing disorders/Summary of cases (n=28):

- Almost all reports were in US adult patients (average age 54 years); the majority (71%; 20/28) described the event as hearing loss (includes reports of deafness and decreased hearing) with or without tinnitus; about one third (29%; 8/28) mentioned tinnitus alone;
- Leg and muscle aches/cramps was the most popular indication (55%; 12/22); four mentioned suicide/overdose, and two each mentioned malaria, medication error and multiple myeloma; in both medication error reports, quinine was dispensed instead of quinidine;
- Half of the patients developed hearing disorders within two weeks of starting quinine therapy;
- The majority of patients experienced clinically severe events, as determined by outcome of 2 fatalities and 10, and 5 disability;
- Deaths were associated with an underlying disease in one patient and with an apparent overdose of quinine in another;
- 11 reports (excluding deaths) meet our criteria for permanent effect; 2 patients complained of tinnitus, and 9 of hearing loss with or without tinnitus;
- Renal disease was reported in 3 patients; two of the patients had symptoms that meet our criteria for permanent impairment ; and
- The majority of reports (23/28) meet our criteria for positive association between hearing disorder and use of quinine.

Additional case information:

- A 77-year old female died from renal failure secondary to multiple myeloma; she experienced deafness due to quinine (case # 4903762).
- A 17-year old male developed hearing loss after ingesting an undetermined number of quinine "pills", and subsequently experienced cardiac arrest, ARDS, arrhythmia, and multi-organ failure. A specific cause of death was not stated (case # 4042317).
- The events listed in the 11 cases that meet our criteria for permanent hearing disorder are:
    - tinnitus (2): This event was reported in two male patients, both over 60 years of age, who had used quinine for a few days (3-7 days) prior to the event; one of the two patients used quinine for leg cramps (no indication or use was listed in the

second patient); the other patient used several concomitant drugs, one of which (amlodipine) lists tinnitus as an adverse event

- hearing loss (4): this event was reported equally in males and females, who used quinine to treat leg/muscle cramps; in most (3) unilateral hearing loss developed after short term therapy (range 4-8 days in three patients; 3.5 months in the fourth); two may have confounders, because one patient (50-year old male) was also being treated with Norvir that has been associated with tinnitus and hearing loss as adverse events, and another patient (male of unspecified age) possibly took an accidental overdose of 6 capsules in less than 24 hours
- hearing loss + tinnitus (5): this event was reported equally in males and females (1 did not list gender), who used quinine to treat leg/muscle cramps (3) and malaria(1); two may have confounders, because one patient also listed 37-year exposure to industrial noise and concomitant therapy with furosemide, and another was also being treated with diltiazem that has also been associated with tinnitus; two patients used quinine for short time (2 days and 2 months) prior to development of events; one patient experienced bilateral events and another unilateral (no information on the other three); indication was listed in four (cramps 3, malaria 1); three had one or more concomitant medications at the time of the events

Glucose metabolism/Summary of cases (n=7):

- 7 patients reported alterations in glucose metabolism (4 DM and 3 hypoglycemia); 4 patients used quinine for leg or muscle cramps, 1 for restless leg syndrome (2 not stated)
- all the patients were adults with a an average age of 58 years (6/7 were over 50 years of age); almost all were from the US
- None listed an IV formulation (4 oral, 3 not stated)
- Glucose levels were not reported for the DM patients; glucose levels for the hypoglycemic patients were <50 mg/dl, <1 mmole/L, and "1"
- It appears that the DM reported in 4 women was a coincidental finding; two were obese, and two had DM prior to quinine therapy; none of the reporters attributed DM to the use of quinine; the main complaints associated with quinine in these patients were thrombocytopenia, worsening arrhythmia, lack of effect and GI symptoms, one event per patient respectively; none of the reporters attributed DM to the use of quinine
- Hypoglycemic reports were more severe than the DM reports; two reported fatalities; in all the cases reporters attributed the low glucose levels to the use of quinine
  - All three patients had renal disease (2 ESRD and 1 terminal renal failure)
  - Cause of death was not listed in the two fatalities; seizures and hypoglycemia of "3" was reported in one case after 3 days of quinine therapy in an ESRD patient; hypoglycemic coma was reported in a terminal renal failure patient after several months of quinine therapy

Hypotension Events/ Summary of cases (n=19):

a) a minority of the AERS reports listing hypotension (1944) were included in this review, because the majority of the (25/44) listed confounders, such as polypharmacy or closer association with other drugs or procedure,
b) the 19 unique domestic reports listed hypotension mostly in females (19), with an average age of 53,
c) all listed a serious outcome, including 3 fatalities, associated with overdose of quinine and another drug (2) and thrombocytopenia (1) after ingestion of three doses in a 60-hour period,
d) eight patients reported events took place within 24 hours after ingestion of quinine, and another two after 3-4 doses within one week,
e) none of the 19 cases were associated with IV administration,
f) according to our criteria, we found a positive association between drug use and the adverse event in 17 of the 19 reports.

Appendix Two

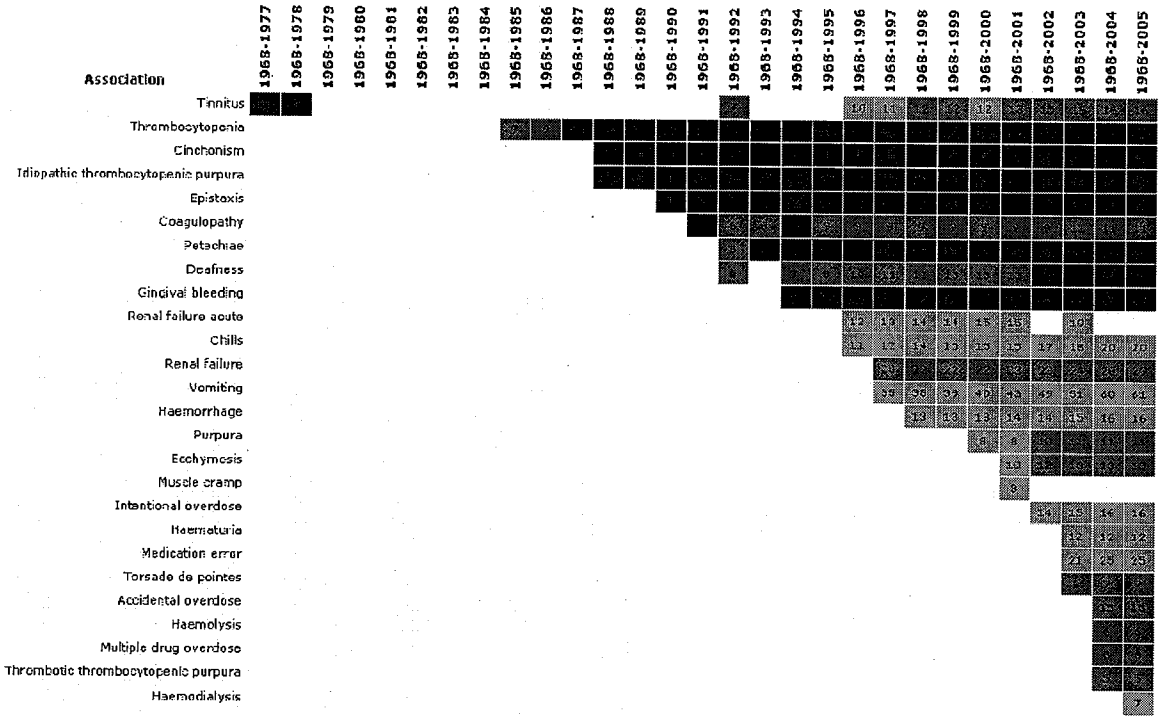
PT terms used to search for HUS/TT cases in AERS:
The 5 PT terms used to capture HUS/TTP cases are: haemolysis, haemolytic uraemic syndrome, renal failure, renal failure acute, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura

PT terms used to search for renal failure cases in AERS:
The 19 PT terms used to capture renal event cases are: acute pre-renal failure, anuria, diabetic end stage renal disease, dialysis, haemodialysis, haemolytic uraemic syndrome, hepatorenal failure, hepatorenal syndrome, neonatal anuria, oliguria, pancreatorenal syndrome, peritoneal dialysis, postoperative renal failure, postrenal failure, renal failure, renal failure acute, renal failure chronic, renal failure neonatal, and renal transplant.

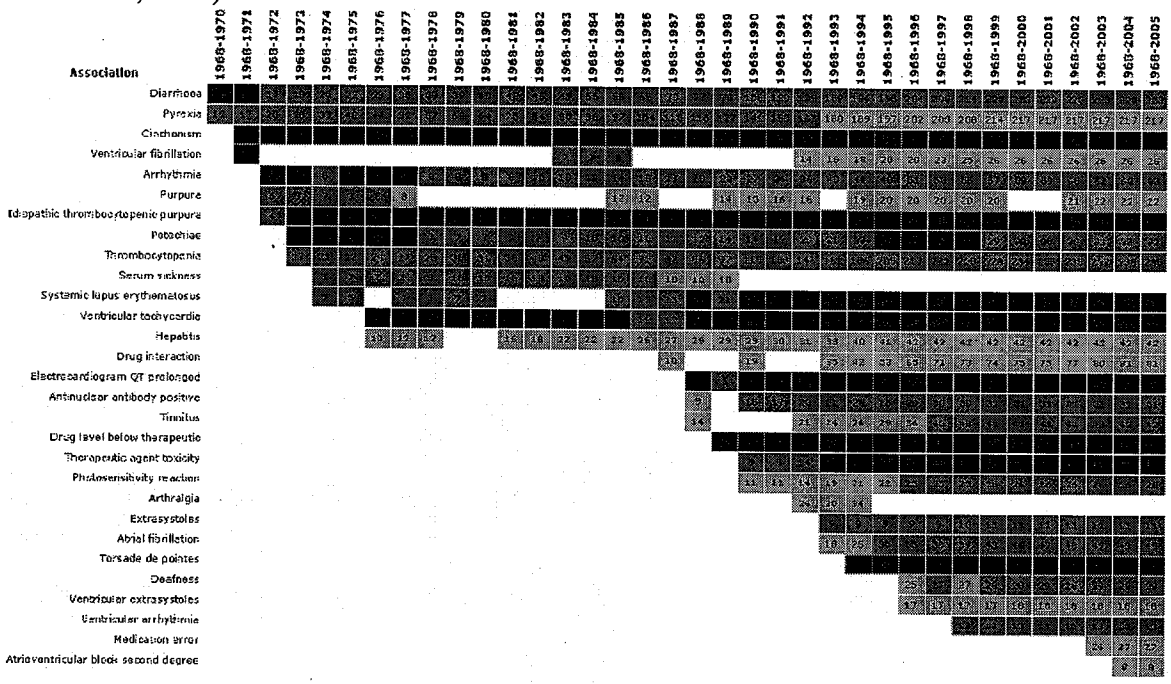
PT terms used to search for hypersensitivity/skin reactions cases in AERS:
The 42 PT terms used to capture hypersensitivity/skin reaction cases are: acute pulmonary oedema, acute respiratory distress syndrome, anaphylactic reaction, anaphylactoid reaction, angioneurotic edema, asthma, blister, blood blister, dermatitis, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, drug eruption, drug hypersensitivity, erythema, erythema multiforme, exanthema, face edema, hypersensitivity, leukocytoclastic vasculitis, oral mucosal blistering, pemphigoid, photosensitivity reaction, pruritus generalized, rash erythematous, rash morbilliform, rash popular, rash pruritic, rash, rash maculo-papular, rash generalized, skin necrosis, Stevens-Johnson Syndrome, stridor, swelling face, tongue blistering, tongue oedema, urticaria, vasculitis, and wheezing.

10.3.2. ODS Data Mining Profiles for Adverse Events Associated with Quinine and Quinidine

Data Mining Profile for Adverse Events Associated with Quinine (data provided by Ana Szarfman, ODS)



Data Mining Profile for Adverse Events Associated with Quinidine (data provided by Ana Szarfman, ODS)



10.3.3 Pregnancy and Lactation Team Consultation Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

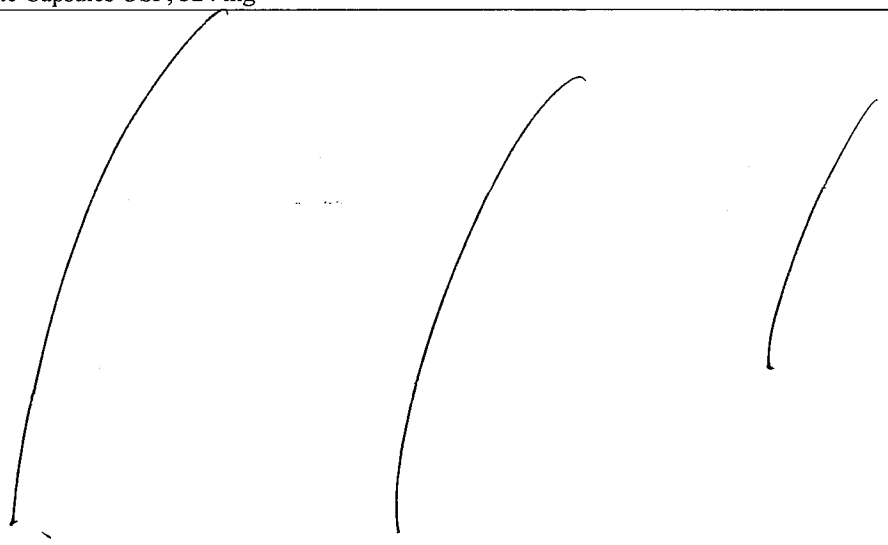
DATE: July 19, 2005

FROM: Gerard G. Nahum, MD
Pregnancy and Lactation Team, OND, HFD-020

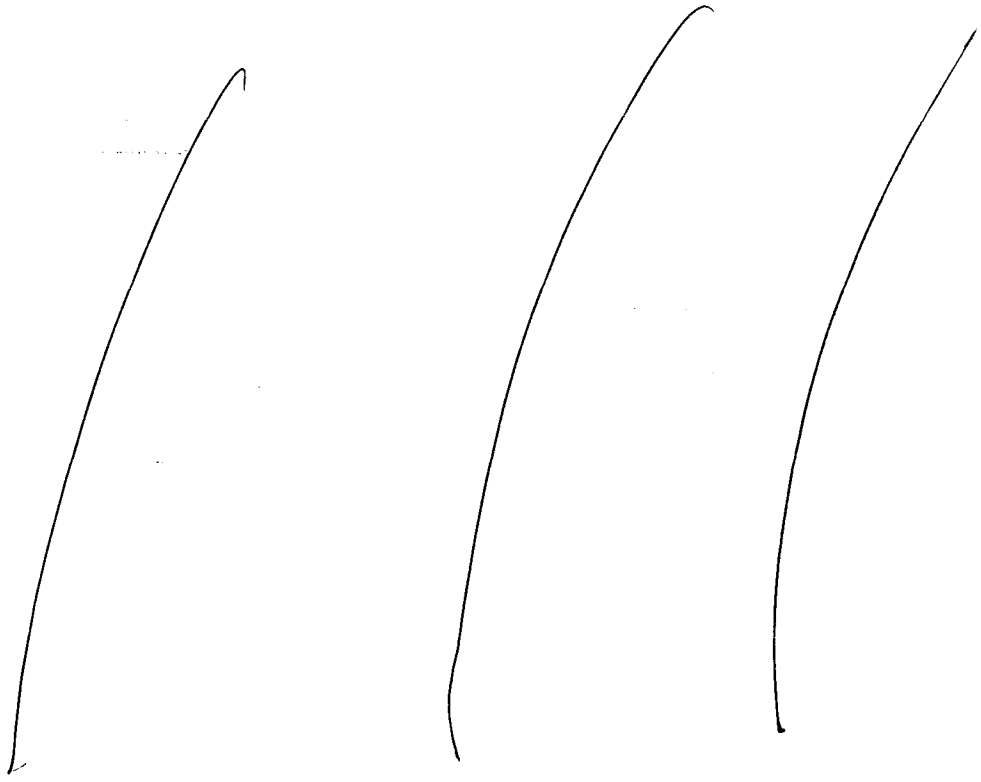
THROUGH: Sandra Kweder, MD
Deputy Director, OND, HFD-020

TO: Renata Albrecht, MD
FDA/ CDER/ OND/ ODE IV/ Division of Special Pathogen and Transplant Products
HFD-590

Pages 410 to 424 of this medical review are appendices that contain reviews and memoranda that appear on their own in other sections of this approval package. These pages have been removed from this review.



10.3.5 DDMAC Labeling Review

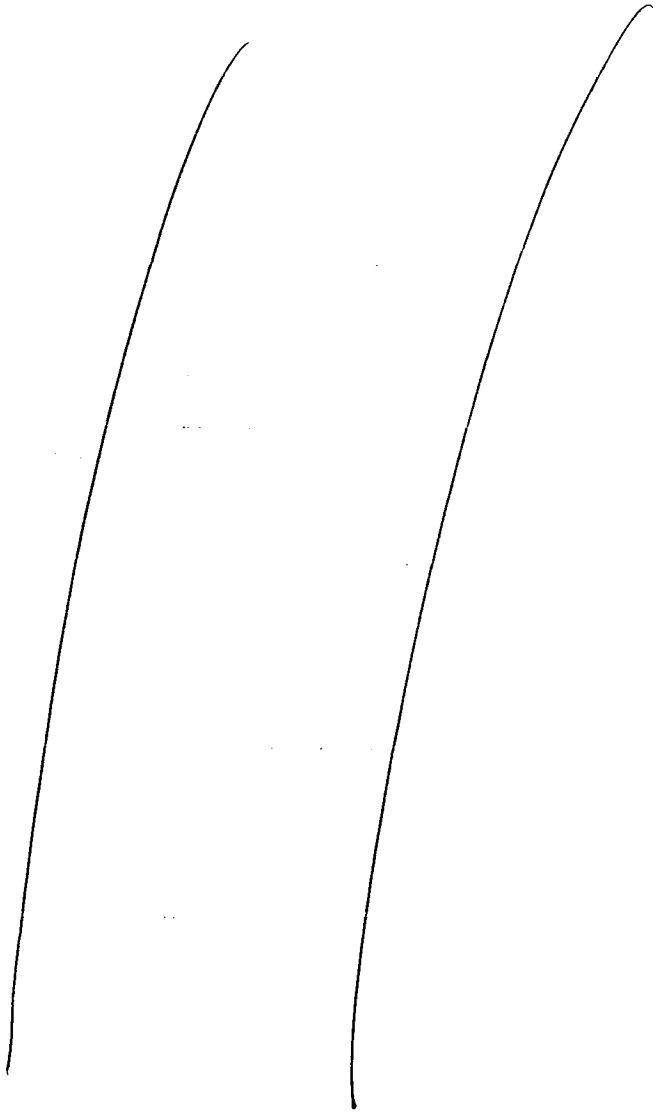


6 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

✓ Deliberative Process



REFERENCES

Abreu-Gerke L, Goerz G, Miller A, Ruzicka T. Acral necrosis after quinine sulfate therapy for nocturnal cramps. Hautarzt 2000;51L332-335.

Aché A, Escorihuela M, Vivas E, *et al.* In vivo drug resistance of falciparum malaria in

mining areas of Venezuela. Trop Med Int Health 2002;7:737-743.

Agarwal N, Cherascu B. Concomitant acral necrosis and haemolytic uraemic syndrome following ingestion of quinine. J Postgrad Med 2002;48:197-198.

Adam I, Idris HM, Mohamed-Ali AA, A/Elbasit IA, Elbashir MI. Comparison of intramuscular artemether and intravenous quinine in the treatment of Sudanese children with severe *falciparum* malaria. East African Med J 2002;79(12):621-625.

Adam I, Elbashir MI. Suicide after treatment of chloroquine-resistant falciparum malaria with quinine. Saudi Med J 2004;25:248-249.

Alvan G, Karlsson KK, Hellgren U, Villen T. Hearing impairment related to plasma quinine concentrations in healthy volunteers. Br J Clin Pharmacol 1991;31:409-412.

Amabeoku GJ, Chikuni O, Akino C, *et al.* Pharmacokinetic interaction of single doses of quinine and carbamazepine, phenobarbitone and phenytoin in healthy volunteers. E African Med J 1993; 70:90-93.

American Academy of Clinical Toxicology 1999; 37: 731-751

Asero R. Fixed drug eruptions caused by tonic water. J Allergy Clin Immunol 2003;111(1):198-199.

Asvadi P, Ahmaki Z, Chong BH. Drug-induced thrombocytopenia: localization of the binding site of GPIX-specific quinine-dependent antibodies. Blood 2003;102(5):1670-1677.

Babalola CP, Bolaji OO, Ogunbona FA, *et al.* Pharmacokinetics of quinine in African patients with acute *falciparum* malaria. Pharm World Sci 1998;20(3):118-122.

Baliga RS, Wingo CS. Quinine induced HUS-TTP: an unusual presentation. Am J Med Sci 2003;326(6):378-380.

Bateman DN, Dyson EH. Quinine toxicity. Adv Drug React Ac Pois Rev 1986;4:215-233.

Bateman DN, Blain PG, Woodhouse KW, *et al.* Pharmacokinetics and clinical toxicity of quinine overdosage: lack of efficacy of techniques intended to enhance elimination. Q J Med. 1985 Feb;54(214):125-31.

Baune B, Furlan V, Taburet AM, Farinotti R. Effect of selected antimalarial drugs and inhibitors of cytochrome P-450 3A4 on halofantrine metabolism by human liver microsomes. Drug Metab. Dispos. 1999; 27:565-8.

Bethell DB, Phoung PT, Phoung CXT, *et al.* Electrocardiographic monitoring in severe *falciparum* malaria. Trans Roy Soc Trop Med Hyg 1996;90:266-269.

Bhalli MA, Samiullah. Falciparum malaria – review of 120 cases. J Coll Physician Surgeon Pakistan 2001;11:300-303.

Bich NN, de Vries PJ, Thien HV, *et al.* Efficacy and tolerance of artemisinin in short combination regimens for the treatment of uncomplicated falciparum malaria. Am J Trop Med Hyg 1996;55:438-443.

Bird MR, O'Neill AI, Buchanan RRC, *et al.* Lupus anticoagulant in the elderly may be associated with both quinine and quinidine usage. Pathology 1995; 27:136-139.

BirkuY, Makonnen, Bjorkman A. Comparison of rectal artemisinin with intravenous quinine in the treatment of severe malaria in Ethiopia. East African Med J 1999; 76: 154-159.

Bodenhamer JE, Smilkstein MJ. Delayed cardiotoxicity following quinine overdose: a case report. J Emergency Med 1993;11:279-285.

Boland ME, Roper SM, Henry JA. Complications of quinine poisoning. Lancet. 1985 Feb 16; 1(8425):384-5.

Bonington A, Davidson RN, Winstanley PA, *et al.* Fatal quinine cardiotoxicity in the treatment of *falciparum* malaria. Trans Roy Soc Trop Med Hyg 1996;90:305-307.

Bregani ER, Tien TV, Cabibbe M, *et al.* Holder monitoring in children with severe Plasmodium *falciparum* malaria during i.v. quinine treatment. J Trop Pediatr 2004;50:61.

Bunnag D, Karbwang J, Na-Bangchang K, Thanavibul A, Chittamas S, Harinasuta T. Quinine-tetracycline for multidrug resistant falciparum malaria. Southeast Asian J Trop Med Public Health 1996;27:15-18.

Bramlet DA, Posalaky Z, Olson R. Granulomatous hepatitis as a manifestation of quinidine hypersensitivity. Arch. Intern. Med. 1980; 140:395-397.

Bruneel F, Gachot B, Wolff M, *et al.* Resurgence of blackwater fever in long-term European expatriates in Africa: report of 21 cases and review. Clin Infect Dis 2001;32(8):1133-1140.

Brumback RA. The neuromuscular junction part II: myasthenia gravis. Am Fam Physician 1981;23(2):126-133.

Buonyasong S. Randomized trial of artesunate and mefloquine in comparison with quinine sulfate to treat P. falciparum malaria in pregnant women. J. Med. Assoc. Thai 2001; 84: 1289-1299.

Burgess JK, Lopez JA, Berndt MC, *et al.* Quinine-dependent antibodies bind a restricted set of epitopes on glycoprotein Ib-IX complex: characterization of the epitopes. Blood 1998;7(1):2366-2373.

Callay JL, Tate WE. Toxic epidermal necrolysis caused by "gin and tonic". Arch. Dermatol. 109:909.

Centers for Disease Control. Guidelines for Treatment of Malaria. April 2004.

Claessen FAP, van Boxtel CJ, Perenboom RM, *et al.* Quinine pharmacokinetics: ototoxic and cardiotoxic effects in healthy Caucasian subjects and in patients with *falciparum* malaria. Trop Med Intern Health 1998;3:482-489.

Clark RB, Sanchez-Chapula J, Salinas-Stefanon E, Duff HJ, Giles WR. Quinidineinduced open channel block of K+ current in rat ventricle. Br. J. Pharmacol. 1995; 115:335-343.

Dannenberg AL, Dorfman SF, Johnson J. Use of quinine for self-induced abortion. Southern Med J 1983;76:846-849.

Davis TME, Supanaranond W, Pukrittayakamee S, *et al.* A safe and effective consecutive-infusion regimen for rapid quinine loading in severe *falciparum* malaria. J Infect Dis 1990;161:1305-1308.

Davis T, Binh T, Thu L, Long T, Johnston W, Robertson K, Barrett H. Glucose and lactate turnover in adults with *falciparum* malaria: effect of complications and Antimalarial therapy. Trans Royal Society Trop Med Hygiene 2002; 96:411-417

Dawson TAJ. Side effect of quinine for nocturnal cramps. Br Med J 1995;310(6981):738.

De Alencar FE, Cerutti C, Durlacher RR, *et al.* Atovaquone and proguanil for the treatment of malaria in Brazil. J Inf Dis 1997;175:1544-1547.

De Souza JM, Sheth UK, De Oliveira MG, *et al.* An open, randomized, phase III clinical trial of mefloquine and of quinine plus sulfadoxine-pyramethamine in the treatment of symptomatic falciparum malaria in Brazil. Bulletin of WHO 1985;63:603-609.

del Pozo BF, Perez-Vizcaino F, Villamor E, Zaragoza F, Tamargo J. Stereoselective effects of the enantiomers, quinidine and quinine, on depolarization- and agonistmediated responses in rat isolated aorta. Br. J. Pharmacol. 1996; 117:105-110.

Di Pierri G, Allegranzi B, Bonora S. Quinine-induced blindness reversed by an increase in a1-acid glycoprotein level. Annals of Internal Medicine 2002;136:339.

De Vries PJ, Bich NN, Thien HV, *et al.* Combinations of artemisinin and quinine for uncomplicated falciparum malaria: efficacy and pharmacodynamics. Antimicrob Agents Chemother 2000;44:1302-1308.

Dias M, Conchon I, Vale T. Allergic contact dermatitis from quinine. Contact Dermatitis 1994;30:121-122.

Duarte EC, Fontes CJF, Gyorkos TW, *et al.* Randomized controlled trial of artesunate plus tetracycline versus standard treatment (quinine plus tetracycline) for uncomplicated Plasmodium falciparum malaria in Brazil. Am J Trop Med Hyg 1996;54:197-202.

Dyson EH, Proudfoot AT, Prescott LF, Heyworth R. Death and blindness due to overdose of quinine. Br. Med. J. 1985; 291:31-33.

Earle DP, Berliner RW, Taggart JV, *et al.* Studies on the chemotherapy of the human malarias. II. Method for the quantitative assay of suppressive antimalarial action in falciparum malaria. J Clin Invest 1948;27(3):75-79.

Everts RJ, Hayhurst MD, Nona BP. Acute pulmonary edema caused by quinine. Pharmacother 2004;24:1221-1224.

Faiz A, Rahman E, Hossain A, *et al.* A randomized controlled trial comparing artemether and quinine in the treatment of cerebral malaria in Bangladesh. Indian J Malariology 2001;38:9-18.

Farver DK, Lavin MN. Quinine-induced hepatotoxicity. Ann Pharmacother 1999;33:32-34

Fernandez-Moreno, *et al.*, Acute dystonic reaction to quinine, An. Int. Med.. 2003, 20:650-651.

Fungladda W, Honrado ER, Thimsam K, *et al.* Compliance with artesunate and quinine plus tetracycline treatment of uncomplicated falciparum malaria in Thailand. Bulletin of WHO 1998; 76: 59-66.

Fulkerson PK. Observations on the cardiovascular effects of quinine. USARV Med Bull 1970;40:35-40.

Gascon Brustenga J, Merlos Pujol A, Bada Ainsa JL. Stevens-Johnson syndrome in a patient treated with quinine and pyimethamine-sulfadoxine. Med. Clin. (Barc). 1986;87:821-822.

Gaudry SE, Sitar DS, Smyth DD, *et al.* Gender and age as factors in the inhibition of

renal clearance of amantadine by quinine and quinidine. Clin Pharmacol Ther 1993; 54:23-27.

George JN, Raskob GE, Shah S, Rizvi M, Hamilton SA, Osborne S, and Vondracek T. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann. Int. Med. 1998; 129:886-890.

Giboda M, Denis MB. Response of Kampuchean strains of Plasmodium falciparum to antimalarials: in-vivo assessment of quinine and quinine plus tetracycline; multipld drug resistance in vitro. J Trop Med 1988;91:205-211.

Glynne P, Salama A, Chaudhry A, *et al.* Quinine-induced immune thrombocytpenic purpura followed by hemolytic uremic syndrome. Am J Kidney Dis 1999;33(1):33-137.

Gottschall JL, Elliot W, Lianos E, McFarland J, Wolfmeyer K, Aster R. Quinine induced immune thrombocytopenia associated with hemolytic uremic syndrome: a new clinical entity. Blood 1991;77:306-310.

Guzzo C, Kaidbey K. Persistent light reactivity from systemic quinine. Photodermatol Photoimmunol Photomed 1990;7:166-168.

Hawthorne M, Sim R, Acton CHC. Quinine induced coagulopathy—a near fatal experience. Aust Dent J. 2000;45(4):282-284.

Heinonen OP, Slone D, and Shapiro S. Antimicrobial and antiparasitic agents. In: Birth Defects and Drugs in Pregnancy. Littleton, Massachusetts: Publishing Sciences Group. 1977; pages 296-313.

Horgan SE, Williams RW. Chronic retinal toxicity due to quinine in Indian tonic water. Eye 1995;9(5):637-8.

Hou M, Horney E, Stockelberg D, *et al.* Multiple quinine-dependent antibodies in a patient with episodic thrombocytopenia, neutropenia, lymphocytopenia, and granulomatous hepatitis. Blood 1997;90(12):4806-4811.

Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clinical Trials 17:1-12.

Jaeger A, Sauder P, Kopferschmitt J, *et al.* Clinical features and management of poisoning due to antimalarial drugs. Med Toxicol Adverse Drug Exp. 1987 Jul-Aug;2(4):242-73.

Jurkiewicz NK, Rodzinski JA, Colatsky TJ. Antiarrhythmic action of quinidine: relative importance of QT-prolongation vs use-dependence. Circulation. 1985;

71(Suppl II):II-225. (Abstract)

Karlsson KK, Berninger E, Gustafsson LL, Alvan G. Pronounced quinine-induced cochlear hearing loss. A mechanistic study in one volunteer at multiple stable plasma concentrations. J Audiolog Med 1995;4:12-24.

Karbwang J, Molunto P, Bunnag D, *et al.* Plasma quinine levels in patients with falciparum malaria when given alone or in combination with tetracycline with or without primaquine. Southeast Asian J Tropical Med Public Health 1991; 22:72-76.

Karbwang J, Sukontason K, Rimchala W, *et al.* Preliminary report: A comparative clinical trial of artemether and quinine in severe *falciparum* malaria. Southeast Asian J Trop Med Public Health 1992;23(4):768-772.

Karbwang J, Davis TME, Looareesuwan S, *et al.* A comparison of the pharmacokinetic and pharmacodynamic properties of quinine and quinidine in healthy Thai males. Br J Clin Pharmacol 1993;35:265-271.

Karbwang J, Na-Bangchang K, Thanavibul A, *et al.* Comparison of oral artesunate and quinine plus tetracycline in acute uncomplicated falciparum malaria. Bull World Health 1994;72:233-238.

Karbwang J, Tin T, Rimchala W, *et al.* Comparison of artemether and quinine in the treatment of severe *falciparum* malaria in south-east Thailand. Trans R Soc Trop Med Hyg 1995;89:668-671.

Karbwang J, Laothavorn P, Sukontason K, *et al.* Effect of artemether on electrocardiogram in severe *falciparum* malaria. Southeast Asian J Trop Med Public Health 1997;28:472-475.

Katz B, Weetch M, Chopra S. Quinine-induced granulomatous hepatitis. Br Med J 1983;286:264-265.

Kawo NG, Msengi AE, Swai AM, Orskov H, Alberti M, McLarty D. The metabolic effects of quinine in childrenwith severe and complicated Plasmodium *falciparum* malaria in Dar es Salaam. Trans Royal Society Trop Med Hygiene. 1991;85:711-713.

Knower MT, Bowton DL, Owen J, Dunagan DP. Quinine-induced disseminated intravascular coagulation: case report and review of the literature. Intensive Care Med 2003;29:1007-1011.

Kochar DK, Kumawat BL, Kochar SK, Sanwal V. Hypoglycemia after oral quinine admininstration. J Assoc Physicians of India 1995;43(9):654, 657.

Kojouri K, Perdue JJ, Medina PJ, George JN. Occult quinine-induced thrombocytopenia.

J Okla State Med Assoc 2000;93(11):519-521.

Kojouri K, Vesely SK, George JN. Quinine-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: frequency, clinical features, and long-term outcomes. Ann Intern Med 2001;135:107-1051.

Kothari UR, Solanki SV, Oza JJ, Doshi KJ, Anadkat NC and Mehta KK. Acute reversible renal failure and Stevens-Johnson syndrome in a patient having glucose-6-phosphate dehydrogenase deficiency. J. Assoc. Phys. Ind. 1977; 25: 299-302.

Krantz MJ, Dart RC, Mehler PS. Transient pulmonary infiltrates possibly induced by quinine sulfate. Pharmacotherapy 2002;22(6);775-778.

Kremsner PG, Zotter GM, Feldmeier H, *et al.* A comparative trial of three regimens for treating uncomplicated falciparum malaria in Acre, Brazil. J Infect Dis 1988;158:1368-1371.

Kremsner PG, Winkler S, Brandts C, Neifer S, Bienzle U, and Graninger W. Clindamycin in combination with chlororquine or quinine is an effective therapy for uncomplicated Plasmodium falciparum malaria in children from Gabon. J. Infect. Dis. 1994; 169:467-470.

Limburg PJ, Katz H, Grant CS, Service FJ. Quinine-induced hypoglycemia. Ann Intern Med 1993;119(3):218-219.

Lockey D and Bateman DN. Effect of oral activated charcoal on quinine elimination. Br. J. Clin. Pharmacol. 1989; 27:92-94.

Ljunggran B, Sjovall P. Systemic quinine photosensitivity. Arch Dermatol 1986;122:909-911.

Lochhead J, Movaffaghy A, Falsini B, Winstanely P, Mberu E, Riva C, Molyneux M, Taylor T, Harding S. The effect of quinine on the electroretinograms of children with pediatric cerebral malaria. J Infect Dis 2003; 187:1342-1345.

Looareesuwan S, White N, Karbwang J, Turner R, Phillips R, Kietinun S, Rackow C, Warrell D. Quinine and severe *falciparum* malaria in late pregnancy. Lancet 1985; 4-8.

Looareesuwan S, Wilairatana P, Vanijanonta S, *et al.* Efficacy of quinine-tetracycline for acute uncomplicated falciparum malaria in Thailand. Lancet 1992;339:369.

Looareesuwan S, Vanijanonta S, Viravan C, *et al.* Randomised trial of mefloquinetetracycline and quinine-tetracycline for acute uncomplicated falciparum malaria. Acta Tropica 1994; 57: 47-53.

Maguire RB, Stroncek DF, Campbell AC. Recurrent pnacytopenia, coagulopathy, and

renal failure associated with multiple quinine-dependent antibodies. Ann Intern Med 1993;199:215-217.

Martin ES, Rogalski K, Black JN. Quinine may trigger Torsades de Pointes during astemizole therapy. PACE 1997;20:2024-2025.

Mathur S, Dooley J, Scheuer PJ. Quinine induced granulomatous hepatitis and vasculitis. Br Med J 1990;300:613.

Matteelli A, Saleri N, Bisoffi Z, Gregis G, Gaiera G, Visona R, Tedoldi S, Scolari C, Marocco S, and Gulletta M. Mefloquine versus quinine plus sulphalene-primethamine (Metakelfin) for treatment of uncomplicated imported falciparum malaria acquired in Africa. Antimicrob. Agents Chemother. 2005; 49:663-667.

McDonald SP, Shanahan EM, Thomas AC, *et al.* Quinine-induced hemolytic uremic syndrome. Clin Nephrol 1997;47(6):397-400.

McGready R. and Nosten F. The Thai-Burmese border: drug studies of Plasmodium falciparum in pregnancy. Ann. Trop Med. Parasitol. 1999; 93: Suppl. 1, S19-S23.

McGready R, Brockman A, Cho T, *et al.* Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans Roy Soc Trop Med Hyg 2000;94:689-693.

McGready R, Cho T, Villegas L, Brockman A, van Vugt M, Looareesuwan S, White NJ, and Nosten F. Randomized comparison of quinine-clindamycin versus artesunate in the treatment of falciparum malaria in pregnancy. Trans. Roy. Soc. Trop. Med. Hyg. 2001; 95:651-656.

Mehta SR, Lazar AI, Kasthuri AS. Experience on loading dose – quinine therapy in cerebral malaria. J Assoc Physicians India 1994;42:376-378.

Metzger W, Mordmüller B, Graninger W, *et al.* High efficacy of short-term quinineantibiotic combinations for treating adult malaria patients in an area which malaria is hyperendemic. Antimicrob Agents Chemother 1995;39:245-246.

Michel D, Wegener JW, Nawrath H. Effects of quinine and quinidine on the transient outward and on the L-type Ca_{2+} current in rat ventricular cardiomyocytes. Pharmacol. 2002; 65:187-192.

Miyashita T, Tokumura Y, Nishiya H, Sugiama H, Yamaguchi M, Ohyatsu I, Aoki M, Ono Y, Kamei K, Shibuya T. A case of mefloquine-resistant *Plasmodium falciparum* malaria with convulsion after antimalarial treatment. Kansenshogaku Zasshi. 1994; 68:152-156.

Mohapatra PK, Namchoom NS, Prakash A, *et al.* Therapeutic efficacy of anti-malarials in Plasmodium falciparum malaria in an Indo-Myanmar border area of Arunachal

Pradesh. Indian J Med Res 2003;118:71-76.

Morrison LD, Velez LI, Shepherd G, *et al.* Death by quinine. Vet Human Toxicol 2003;45(6):303-306.

Moyou-Somo R, Tietche F, Ondoa M, *et al.* Clinical trial of β-arteether versus quinine for the treatment of cerebral malaria in children in Yaounde, Cameroon. Am J Trop Med Hyg 2001;64(5, 6):229-232.

Mueller MS, Runyambo N, Wagner I, *et al.* Randomized controlled trial of a traditional preparation of Artemisia annua L. (Annual Wormwood) in the treatment of malaria. R Soc Trop Med Hyg 2004;98;318-321.

Murphy S, English M, Waruiru C, *et al.* An open randomized trial of artemether versus quinine in the treatment of cerebral malaria in African children. Trans R Soc Trop Med Hyg 1996;90:298-301.

Na-Bangchang K, Tan-airya P, Thanavibul A, Riengchainam S, Shretha S, Karbwang J. Pharmacokinetic and pharmacodynamic interactions of mefloquine and quinine. Int J Clin Pharm Res 1999;19:73-82.

Naraqi S, Okem S, Moyia N, Dutta T, Zzferio B, Lalloo D. Case report: quinine blindness. PNG Med J 1992;35:308-310.

Newton P, Angus B, Chierakul W, *et al.* Randomized comparison of artesunate and quinine in the treatment of severe *falciparum* malaria. Clin Infect Dis 2003;37:7-16.

Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, deVries A, *et al.* The effects of mefloquine treatment in pregnancy. Clin Infect Dis 1999;28:808-15.

Okitolanda W, Pottier A-M, Henquin J-C. Glucose homeostasis in rats treated acutely and chronically with quinine. Eur. J. Pharmacol. 1986; 132:179-185.

Okun MM, Henner M, Paulson C. A quinine-induced drug reaction of photosensitive distribution with histological features mimicking mycosis fungoides. Clin Experimental Dermatol 1994;19:246-248.

Olumese PE, Björkman A, Gbadegesin RA, Adeyemo AA, Walker O. Comparative efficacy of intramuscular artemether and intravenous quinine in Nigerian children with cerebral malaria. Acta Tropica 1999;73:231-236.

Paintaud G, Alvan G, Berninger E, *et al.* The concentration-effect relationship of quinine-induced hearing impairment. Clin Pharmacol ther 1994;55:317-323.

Parola P, Ranque S, Badiaga S, Niang M, Blin O, Charbit J-J, Delmon J, and Brouqui P. Controlled trial of 3-day quinine-clindamycin treatment versus 7-day quinine treatment for adult travelers with uncomplicated falciparum malaria imported from the tropics. Antimicrob. Agents Chemother. 2001; 45:932-935.

Pawar R, Jacobs GH, Smith MC. Quinine-associated acute interstitial nephritis. Am J Kidney Dis 1994;24(2):211-214.

Pearn J, Nixon J, Ansford A, Corcoran A. Accidental poisoning in childhood: five year urban population study with 15 year analysis of fatality. Br. Med. J. 1984; 288:44-46.

Pedersen KE, Madsen JL, Klitgaard NA, *et al.* Effect of quinine on plasma concentrations and renal digoxin clearance. Acta Med Scand 1985;218:229.

Perez JA, Stryker J, Arsura EL, Hewitt JM. Probable quinine-induced hepatotoxicity. West J Med 1994;160:59-60.

Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Safety 1996;14:131-145.

Pineli LL, Schoepfer ACA, Jardim DV, *et al.* Falciparum malaria. Quadrennial analysis during 12 years of the quinine treatment efficacy. Brazilian Soc Trop Med J 1999;32:241-245. Translated into English from original publication.

Price EJ, Bevan JS, Rees A. Quinine-induced cutaneous vasculitis. Br J Clin Pract 1992;46:138-139.

Procop GW, Jessen R, Hyde SR, Scheck DN. Persistence of Plasmodium falciparum in the placenta after apparently effective quinidine/clindamycin therapy. J. Perinatol. 2001; 21:128-130.

Pukrittayakamee S, Chantra A, Vanijanonta S, *et al.* Therapeutic responses to quinine and clindamycin in multidrug-resistant falciparum malaria. Antimicrob Agents Chemother 2000;44:2395-8.

Pukrittayakamee S, Prakongpan S, Wanwimolruk S, *et al.* Adverse effect of rifampin on quinine efficacy in uncomplicated falciparum malaria. Antimicrob Agents Chemother 2003; 47:1509-1513.

Pukrittayakamee S, Chotivanich K, Chantra A, *et al.* Activities of artesunate and primaquine against asexual and sexual stage parasites in falciparum malaria. Antimicrob Agents Chemother 2004;48:1329-1334.

Punukollu RC, Kumar S, Mullen KD. Quinine hepatotoxicity. An underrecognized or rare phenomenon? Arch Intern Med 1990;150:1112-1113.

Rahman MR, Paul DC, Rashid M, et al. A randomized controlled trial on the efficacy of althernative treatment regimens for uncomplicated falciparum malaria in a multidrugresistant falciparum area of Bangladesh—narrowing the options for the National Malaria Control Programme? Trans R Soc Trop Med Hyg 2001;95:661-667.

Reddy JC, Shuman MA, Aster RH. Quinine/quinidine-induced thrombocytopenia: a great imitator. Arch Intern Med 2004;164:218-22.

Ramharter M, Oyakhiroma S, Klouwenberg PK, Adegnika AA, Agnandji ST, Missinou MA, Matsiegui P-B, Mordmuller B, Borrmann S, Jun JF, Lell B, Krishna, S, Graninger W, Issifou S, and Kremsner PG. Clin. Infect. Dis. 2005; 40:1777-1784.

Ringwald P, Louis FJ, Bickii J, *et al.* Efficacy and tolerance in adults of a short (3 days) course of quinine for uncomplicated falciparum malaria. Ann Soc Belge Med Trop 1995;75:141-143.

Roche RJ, Silamut K, Pukrittayakamee S, *et al.* Quinine induces reversible high-tone hearing loss. Br J Pharmacol 1990;29:780-782.

Roden D. Chemotherapy of parasitic infections. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman and Gilman's *The Pharmacological Basis Of Therapeutics.* 9th ed. New York, NY: McGraw-Hill Book Co; 2001. (Available upon request.)

Rogier C, Imbert P, Tall A, *et al.* Epidemiological and clinical aspects of blackwater fever among African children suffering frequent malaria attacks. Trans R Soc Trop Med Hyg 2003;97(2):193-197.

Salcedo JMV, Camargo LMA, Braga, MFV, *et al.* Evaluation of the efficacy of artesunate associated with tetracycline in the therapy of falciparum malaria. Brazil Soc Trop Med J 1997;30:215-222. [English Translation] .

Sanchez-Chapula JA, Ferrer T, Navarro-Polanco RA, Sanguinetti MC. Voltage-Dependent Profile Of Human *ether-a-go-go*-related gene channel block is influenced by a single residue in the S6 transmembrane domain. Mol. Pharmacol. 2003; 63:1051-1058.

Satti G, Elhassan S, Ibrahim S. The efficacy of artemether versus quinine in the treatment of cerebral malaria. Journal of the Egyptian Society of Parasitology 2002;32(2):611-623.

Segal HE, Chinvanthananond P, laixuthai B, *et al.* Preliminary study of WR 33063 in the treatment of falciparum malaria in northeast Thailand. Am J Trop Med Hygiene 1974;23:560-564.

Schlegel A. Factitious granulomatous hepatitis? Am. J. Med. 2004; 116: 500-501.

Sheldon RS, Rahmberg M, Duff HJ. Quinidine/quinine: Stereospecific electrophysiologic and antiarrhythmic effects in a canine model of ventricular tachycardia. J. of Cardiovas. Pharmacol. 1990; 16:818-823.

Sieb JP, Milone M, Engel AG. Efects of the quinoline derivatives quinine, quinidine, and chloroquine on neuromuscular transmission. Brain Research 1996;712:179-189.

Singh N, Devi B, Singh TB, Singh MA, Singh NB. Artemether vs quinine therapy in *Plasmodium falciparum* malaria in Manipur-a preliminary report. J Commun Dis 2000;33(2):83-87.

Sowunmi A. Disposition of oral quinine in African patients suffering from acute uncomplicated *falciparum* malaria. E African Med J 1996;73:519-523.

Spearing RL, Hickton CM, Sizeland P, *et al.* Quinine-induced disseminated intravascular coagulation. Lancet 1990;336:1535-1537.

Srivastava A, Khanduri A, Lakhtakia S, Pandey R, Choudhuri G. Falciparum malaria with acute liver failure. Trop. Gastroenterol. 1996; 17:172-174.

Stroneck DF, Vercellotti GM, Hammerschmidt DE, Christie DJ, Shankar RA, Jacob HS. Characterization of multiple quinine-dependent antibodies in a patient with episodic hemolytic uremic syndrome and immune agranulocyctosis. Blood. 1992; 80:241-248.

Sutherland R, Vincent PC, Raik E, Burgess K. Quinine-induced agranulocytosis: toxic effect of quinine bisulphate on bone marrow cultures in vitro. Br Med J 1977;1:605-607.

Tange R, Dreschler W, Claessen F, Perenboom R. Ototoxic reactions of quinine in healthy persons and patients with *Plasmodium faliparum* infection. Auris Nasus Larynx 1997;24:131-136.

Tapadinhas C, Dias M, Conchon I, Pereira F, and Cardoso J. Contact dermatitis due to quinine-containing hair lotion. Contact Dermatitis. 1994; 31:127.

Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf. 2004;27(1):25-61.

Taylor TE, Wills BA, Courval JM, Molyneux ME. Intramuscular artemether *vs* intravenous quinine: an open, randomized trial in Malawian children with cerebral malaria. Trop Med Int Health 1998;3(1):3-8.

Taylor T, Molyneux M, Wirima J, Fletcher A, Morris K. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe *falciparum* malaria. N Engl J Med 1988;319:1040-1047.

Thomas RHM, Munro DD. Lichen planus in a photosensitive distribution due to quinine. Clin Exp Dermatol 1985;11:97-101.

Thuma P, Bhat G, Mabeza GF, *et al.* A randomized controlled trial of artemotil (β-arteether) in Zambian children with cerebral malaria. Am J Trop Med Hyg 2000;62(4):524-529.

Tigga FV, Satpathy SK, Das BS. Cardiac arrhythmia following intravenous quinine therapy. JAPI 2001;49:946-947.

Tombe M, Bhatt K, Obel A. Quinine loading dose in severe *falciparum* malaria at kenyatta national hospital, Kenya. East African Med J 1992; 670-674.

Touze JE, Heno P, Fourcade L, *et al.* The effects of antimalarial drugs on ventricular repolarization. Am J Trop Med Hyg 2002;67:54-60.

Tracy JW, Webster LT. Drugs used in the chemotherapy of protozoal infections: Malaria. In: Goodman & Gilman's the pharmacological basis of therapeutics. Eds, Hardman JG, Limbird LE. New York: McGraw-Hill Medical Pub. Division, 2001:1087-1088.

Tran Hien, Day N, Phu N, *et al.* A controlled trial of artemether or quinine in Vietnamese adults with severe *falciparum* malaria. New Eng J Med 1996;335(2):76-83.

Tran Thi Hong , Day NPJ, Chuong LV, *et al.* Blackwater fever in southern Vietnam: a prospective descriptive study of 50 cases. Clin Infect Dis 1996; 23:1274-1281.

van Hensbroek MB, Onyiorah E, Jaffar S, *et al.* A trial of artemether or quinine in children with cerebral malaria. New Eng J of Med 1996;335(2):69-75.

Vanijanonta S, Chantra A, Phophak N, *et al.* Therapeutic effects of chloroquine in combination with quinine in uncomplicated falciparum malaria. Ann Trop Med Parasitol 1996;90:269-275.

Wahlberg JE and Boman A. Contact sensitivity to quinidine sulfate from occupational exposure. Contact Dermatitis 1981; 7:27-31.

Wanwimolruk S, Sunbhanich M, Pongmarutai M, *et al.* Effects of cimetidine and raniditine on the pharmacokinetics of quinine. Br J Clin Pharmacol 1986; 22:346-350.

Watt G, Long GW, Padre LP, *et al.* Chloroquine and quinine: a randomized, double-blind comparison of efficacy and side effects in the treatment of Plasmodium falciparum malaria in the Philippines. Trans R Soc Trop Med Hyg 1988; 82: 205-208.

Weinke T, Held T, Trautmann M, *et al.* Malaria therapy in 452 patients, with special reference to the use of quinine. J Infect 1992;25:173-180.

Wenstone R, Bell M, Mostafa SM. Fatal adult respiratory distress syndrome after quinine overdose. Lancet 1989; 1(8647):1143-1144.

White NJ. The treatment of malaria. N Engl J Med 1996;335:800-806.

White NJ, Looareesuwan S, Warrell DA. Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. J Cardiovasc Pharmacol 1983a;5:173-175.

White NJ, Chanthavanich P, Krishna S, *et al.* Quinine disposition kinetics. Br J Clin Pharmacol 1983b;16:399-403.

White NJ, Warrell DA, Chanthavanich P, *et al.* Severe hypoglycemia and hyperinsulinemia in *falciparum* malaria. New Eng J Med 1983c; 309:61-66.

World Health Organization. Antimalarial drug combination therapy. Report of a WHO Technical Meeting 2001. WHO/CDS/RBM/2001.35.

World Health Organization. The use of antimalarial drugs: report of an informal consultation, Geneva, 13 – 17 November 2000 (WHO/CDS/RBM/2001.33).

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Mary Singer
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MEDICAL OFFICER

Eileen Navarro
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:	July 20, 2005
FROM:	Gerard G. Nahum, MD Pregnancy and Lactation Team, OND, HFD-020
THROUGH:	Sandra Kweder, MD Deputy Director, OND, HFD-020
TO:	Renata Albrecht, MD FDA/ CDER/ OND/ ODE IV/ Division of Special Pathogen and Transplant Products HFD-590
SUBJECT:	Quinine sulfate for the treatment of Plasmodium falciparum malaria – NDA 21-799 (Mutual Pharmaceutical)
Consult received:	June 16, 2005
Due date:	July 20, 2005

I. EXECUTIVE SUMMARY

Quinine has been marketed as a drug in the United States since before 1938. It is the oldest known treatment for *Plasmodium falciparum* malaria.

The sponsor (Mutual Pharmaceutical) submitted an NDA to the Division of Special Pathogens and Transplant Products on October 12, 2004 for quinine sulfate capsules as a treatment for uncomplicated *P. falciparum* malaria. The Division has requested that the Pregnancy and Lactation Team (PLT) provide feedback on the pregnancy section of the proposed label. Based on two submitted studies in pregnant patients, the sponsor has proposed a pregnancy category of —

The PLT has proposed modified labeling language that includes (A) a change in the pregnancy letter category to "C", (B) [redacted]

and (F) the quantity of quinine that is excreted in breast milk.

II. BACKGROUND

Quinine is an alkaloid found in the bark of the cinchona tree. It is the oldest known drug for the treatment of *P. falciparum* malaria and has been marketed in the United States since before 1938. Quinine can either be used alone or in combination with other antiparasitic drugs to treat malaria.

P. falciparum malaria results in increased risk of adverse pregnancy outcomes and carries a higher risk of morbidity and mortality in pregnant women than for the general population. Although the mechanism is not understood, pregnant women have a reduced immune response and they less effectively clear malaria infections. Even with effective treatment, malaria parasites sequester and replicate within the placenta.[1] Pregnancy increases the severity of *P. falciparum* infection and malaria episodes increase during the 2nd and 3rd trimesters. Pregnancies complicated by malaria have been reported to result in an increased incidence of spontaneous abortion, preterm labor and delivery, intrauterine growth retardation, low birth weight, fetal wastage (spontaneous abortions and stillbirths), and maternal death.

Mutual Pharmaceutical has submitted an NDA to the Division of Special Pathogens and Transplant Products for quinine sulfate capsules as a treatment for uncomplicated *P. falciparum* malaria. The anticipated adult oral dosage recommendation two capsules (648 mg) three times a day for 7 days, c

Many experts and organizations, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), suggest that quinine is both safe and effective to treat uncomplicated *P. falciparum* malaria during pregnancy.[2] This conclusion is based on information derived primarily from limited case-control data and case series. Although chloroquine is recommended as a first-line of treatment by the CDC for pregnant women infected with chloroquine-sensitive strains of *P. falciparum*, many such infections are chloroquine resistant.[2]

Other drugs that are available to treat uncomplicated chloroquine-resistant *P. falciparum* malaria include mefloquine (pregnancy category C), atovaquone/ proguanil [Malarone] (pregnancy category C), tetracycline (pregnancy category D), doxycycline (pregnancy category D), and clindamycin (pregnancy category B).[2] Despite their pregnancy category C ratings, mefloquine and atovaquone/ proguanil are generally not recommended by WHO and CDC for use in pregnant women, because there are no adequate and well-controlled studies to support their use during pregnancy.[2] All three of the other drugs that are recommended for treating uncomplicated chloroquine-resistant *P. falciparum* malaria (tetracycline, doxycycline, and clindamycin) are recommended for use in conjunction with quinine sulfate as the primary treatment. Only clindamycin is recommended by the CDC in conjunction with quinine sulfate during pregnancy.[2]

III. LITERATURE REVIEWED

The information reviewed by the PLT includes the materials submitted by the sponsor in their NDA. As part of the review, the sponsor's proposed product label and the supporting peer-reviewed literature concerning the use of quinine by pregnant and lactating women were considered. An additional literature search using the PubMed search engine was also conducted and relevant studies that were not contained within the sponsor's submission were also reviewed. Besides the sponsor's proposed label, the primary sources of information that have been relied on by the PLT for making recommendations concerning the pregnancy and lactation labeling are the nine that are listed below:

1. Procop GW, Jessen R, Hyde SR, Scheck DN. Persistence of Plasmodium falciparum in the placenta after apparently effective quinidine/ clindamycin therapy. J Perinatol 2001;21:128-30.
2. Centers for Disease Control and Prevention. Treatment of Malaria (Guidelines for Clinicians); June 28, 2004. www.cdc.gov/malaria/pdf/clinicalguidance.pdf
3. Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, deVries A, *et al.* The effects of mefloquine treatment in pregnancy. Clin Infect Dis 1999;28:808-15.
4. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Antimicrobial and antiparasitic agents. Littleton, Massachusetts: Publishing Sciences Group 1977:299,302.
5. McGready R, Brockman A, Cho T, Cho D, van Vugt M, Luxemburger C, *et al.* Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans Royal Soc Trop Med Hyg 2000;94:689-93.
6. McGready R, Cho T, Samuel, Villegas L, Brockman A, van Vugt M, *et al.* Randomized comparison of quinine-clindamycin versus artesunate in the treatment of falciparum malaria in pregnancy. Trans Royal Soc Trop Med Hyg 2001;95:651-6.
7. Bounyasong S. Randomized trial of artesunate and mefloquine in comparison with quinine sulfate to treat P. falciparum malaria pregnant women. J Med Assoc Thai 2001;84:1289-99.
8. Phillips RE, Looareesuwan S, White NJ, Silamut K, Kietinun S, Warrell DA. Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. Br J Clin Pharmacol 1986;21:677-83.
9. Dannenberg AL, Dorfman SF, Johnson J. Use of quinine for self-induced abortion. South Med Assoc 1983;76:846-9.

IV. REVIEW OF HUMAN DATA AND ANALYSIS

There are few controlled studies that have investigated the pregnancy outcomes of women exposed to quinine during pregnancy for the treatment of malaria. The quantity and quality of available data are limited. Still, there appears to be sufficient human pregnancy exposure information to suggest that quinine is not a major human teratogen [see (A)-(E)]. The findings of relevant studies are summarized below:

(A) Nosten *et al* (1999)[3]

A total of 656 Karen women (from Thailand) were diagnosed with *Plasmodium falciparum* malaria during pregnancy and were treated at some time during gestation with quinine sulfate alone during the period July 1991 through June 1994. The dose was 10 mg/kg of salt administered orally TID for 7 days. Concurrently, 2,470 pregnant women in the same communities received obstetrical care who had no documented malaria or antiparasitic treatment. Of the 656 women who were treated with quinine sulfate alone, 633 (96.5%) had sufficient information available for analysis. Pregnancy outcomes for the two groups are abstracted and compared in the table below:

Pregnancy Outcome	**Malaria** Group Treated with **Quinine Sulfate** alone	**Control** Group without Malaria or Any Antiparasitic Treatment	**Odds Ratio** (95% confidence interval or chi-square p-value)
Spontaneous Abortion	3.5%	10.9%	0.32 (95% CI 0.21-0.48)*
Stillbirth	1.6% (n=633)	1.8% (n=2201)	0.87 (p = 0.73)†
Low Birth Weight	17.8%	12.7%	1.4 (95% CI 1.1-1.9)
Congenital Malformations	1.4% (n=633)	1.7% (n=2201)	0.82 (p = 0.72)†

* Inverse Odds Ratio with 95% inverse confidence interval (calculated by G. Nahum)
† Odds Ratio with associated p-value calculated using chi-square analysis (calculated by G. Nahum)

There was no clinically relevant or statistically significant difference in either the rate of stillbirths (OR = 0.87) or in the rate of congenital malformations (OR = 0.82) between the malaria/ quinine treatment and normal/ no antiparasitic treatment control group. Although there appeared to be a statistically significant difference in the rate of low birth weight between the two groups, (a) malaria alone has been associated with an increased risk of low birth weight, (b) the difference in the mean birth weights was small and not clinically significant (a decrease of 134 gm in the treated group as compared with controls, 95% CI -31 to -209 gm), and (c) the gestational dating of the pregnancies was poor (based on historical last menstrual period dating) and there was no comparison of the mean gestational age at delivery between the two groups.

(B) Heinonen et al (1977)[4]

As part of the Collaborative Perinatal Project (USA), 3,248 children with drug exposures during pregnancy had congenital malformations in a cohort of 50,282 mother-child pairs (overall malformation rate 6.5%). Among 104 mother-child pairs who were exposed to quinine during the first 4 lunar months of pregnancy, 2 children were classified as malformed, yielding a malformation rate of 1.9%. The reported crude relative risk for congenital malformations in the quinine-exposed group was 0.30, while the standardized relative risk was 0.28. No dose, duration, or exposure information was available.

(C) McGready *et al* (2000)[5]

A total of 42 Karen women (from Thailand) who were diagnosed with *Plasmodium falciparum* malaria during pregnancy were treated with quinine sulfate from October 1995 through July 1997. Patients had a mean age of 23 years (range 16-36 years) and a mean weight of 50 kg (range 41-67 kg). The mean gestational age at treatment was 24 weeks (range 15-38 weeks) and 29% of the patients were primiparous.

The dose of quinine sulfate administered was 10 mg/kg of salt every 8 hours for 7 days. Overall, 12% of patients were lost to follow-up. Of those who remained for evaluation, no mid-trimester abortions or stillbirths occurred, and no congenital abnormalities were documented. There were 2 neonatal deaths: one occurred at 23 days of life due to symptomatic *P. falciparum* infection and another at 6 weeks of life due to beri-beri. One infant was blind from retinopathy of prematurity (delivered at 31.0 weeks of gestation).

(D) McGready *et al* (2001)[6]

A total of 65 Karen women (from Thailand) who were diagnosed with *Plasmodium falciparum* malaria during the 2nd and 3rd trimesters of pregnancy were treated with a combination of quinine sulfate and clindamycin from October 1997 through January 2000. The dose of quinine sulfate administered was 10 mg/kg of salt every 8 hours for 7 days, together with clindamycin, 5 mg/kg every 8 hours for 7 days. Overall, 8.5% of patients were lost to follow-up. Of those who remained, there was one stillbirth due to placental abruption, which was unlikely to be treatment related. There were 2 congenital abnormalities: one in a singleton (a midline epidermoid cyst just superior to the bridge of the nose), and one in a twin (one twin was normal and the other had a gastroschesis). There were 2 neonatal deaths, both of which occurred during the first week of life from causes unrelated to malaria.

(E) Bounyasong (2001)[7]

Twenty-eight patients from Thailand who had *P. falciparum* malaria diagnosed at >27 weeks of pregnancy were treated with quinine sulfate 10 mg/kg orally every 8 hours for at least 7 days. Maternal characteristics were (mean values): age = 27.2 years; parity = 1.6; height = 157 cm; pre-pregnancy weight = 58.7 kg; gestational age at start of treatment = 27.7 weeks. The mean gestational age at delivery was 38.65 weeks and the mean birth weight was 2785 gm. The mean Apgar score at 1 minute was 8.8 and at 5 minutes was 9.9; the mean arterial cord blood pH at delivery was 7.34. No congenital anomalies were noted. The incidence of placental calcification (3 of 26 cases) and the occurrence of intrauterine growth restriction (2 of 27 cases) were not different in the quinine sulfate treated group than in a second group of 28 women with *P. falciparum* malaria treated with artesunate and mefloquine.

(F) Phillips et al (1986)[8]

In addition to these studies that have examined pregnancy outcomes after maternal exposure to quinine during pregnancy, a study by Phillips *et al* contains information concerning quinine concentrations in the umbilical cord blood and breast milk of pregnant and lactating women treated for *P. falciparum* malaria.[8] Patients were from eastern Thailand and, if life-threatening infection was diagnosed and parenteral treatment

was required, they were treated with an initial IV loading dose of either 10 mg/kg or 20 mg/kg every 8 hours of quinine dihydrochloride (equivalent to 8.3 and 16.7 mg of base, respectively), followed by consolidation therapy during convalescence with a maintenance dose of quinine sulfate tablets until a 7 day course of treatment was completed. Patients fell into three groups: (1) those >29 weeks pregnant and with malaria of sufficient severity to require intravenous quinine treatment; (2) those receiving quinine shortly before or while in labor; and, (3) those receiving quinine while breastfeeding. The findings were:

(i) Eight women aged 16-32 years who delivered live infants 1 to 6 days after starting quinine therapy had placental cord plasma quinine concentrations between 1.0 and 4.6 mg/l (mean 2.4 mg/l). The mean (±SD) ratio of cord plasma to maternal plasma quinine concentration was 0.32 ±0.14. There was a significant correlation between cord blood and maternal plasma quinine concentrations ($r = 0.78$, $p < 0.05$).

(ii) Breast milk was collected from 30 women aged 16-39 years. All received 2 to 7 doses of quinine when milk samples were collected and all began lactating from 1 and 10 days previously. In 25 women who were breastfeeding and who had taken oral quinine sulfate for 1 to 10 days (mean 4.0 days), breast milk concentrations were 0.5-3.6 mg/l (mean 2.6 mg/l) and milk:plasma ratios were 0.11-0.53 (mean 0.31). In 5 women who required parenteral therapy with intravenous quinine dihydrochloride, breast milk quinine concentrations ranged between 0.5-8.0 mg/l (mean 3.4 mg/l) and the milk:plasma ratios were 0.11-0.32 (mean 0.21). Three patients who had just begun to lactate produced colostrums containing 0.4, 0.9, and 1.9 mg/l of quinine, with colostrum:maternal plasma ratios of 0.11, 0.26, and 0.25, respectively. The authors concluded that the total dose of quinine excreted in breast milk is usually less than 2 to 3 mg per day.

(G) Dannenberg *et al* (1983)[9]

A series of four cases of women who attempted self-termination of an intrauterine pregnancy using quinine as an abortifacient was reported by Dannenberg *et al* in 1983.[9] Based on these cases and a complete review of the available literature, the authors found that no documented case of pregnancy loss occurred following an ingested quinine dose of less than 5.2 gm of salt (approximately 5-times the recommended daily dose for treatment of malaria). This dose was sufficient to result in patient complaints of tinnitus, diminished hearing, blurred vision, nausea, vomiting, chest pain, dyspnea, tachycardia, abdominal pain, back pain, and leg weakness. The authors concluded that "the efficacy of quinine as an abortifacient is not clear".

V. LABELING RECOMMENDATIONS

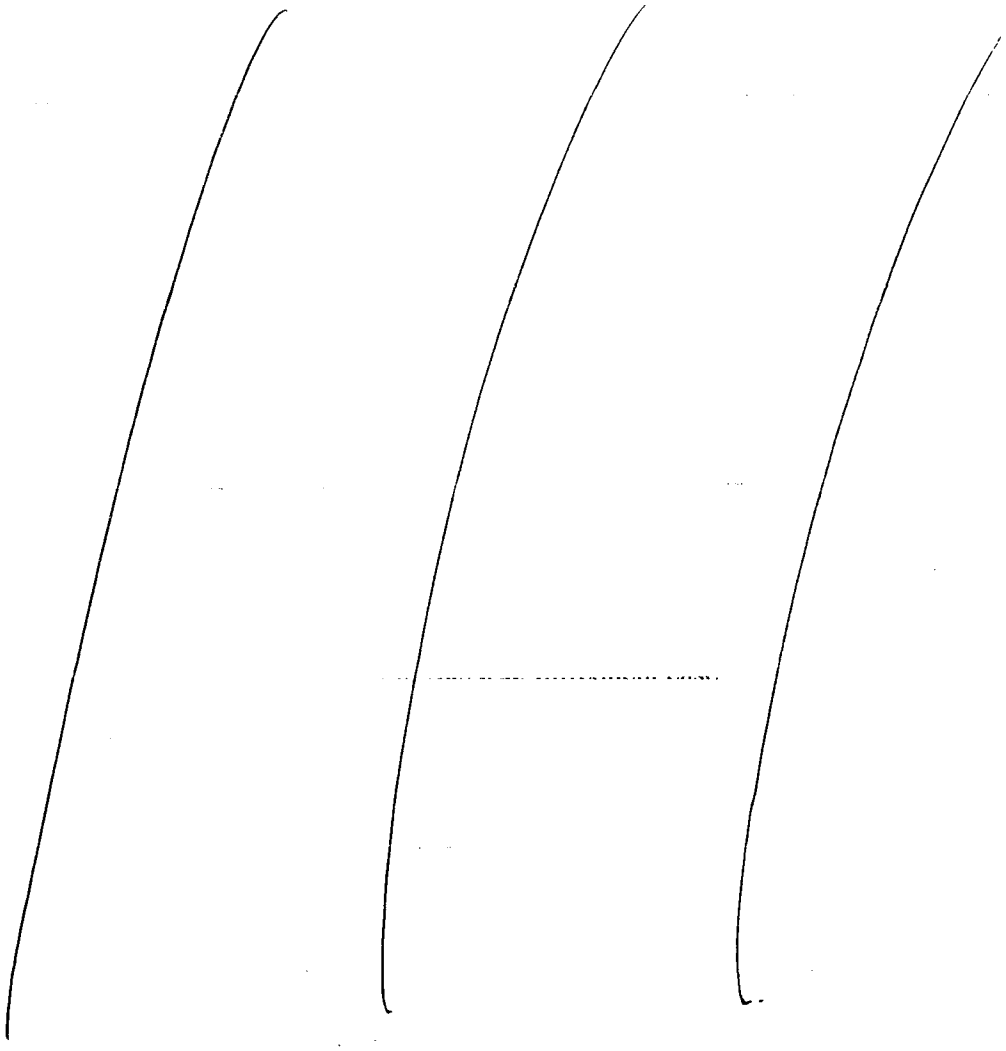
Based on the information reviewed by the PLT, the following suggestions are made to the sponsor's proposed label for quinine sulfate:

1 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process



VI. CONCLUSIONS

Plasmodium falciparum malaria is a potentially life-threatening illness that is associated with significantly increased adverse pregnancy outcomes. Although other potential treatments for malarial infection in pregnancy exist, quinine sulfate remains a CDC-recommended first-line treatment for chloroquine-resistant *P. falciparum* infection in pregnant patients. Other drugs that can be used to treat *P. falciparum* malaria presently carry a pregnancy category C rating, yet they are not recommended for treatment of malaria during pregnancy.

Accordingly, the PLT recommends that a pregnancy category C rating be assigned to quinine sulfate, in addition to the other proposed changes to the product label as shown above.

If not already done, the PLT also recommends that the Division contact the Office of Drug Safety (ODS) to review the Adverse Events Reporting System (AERS) for any other spontaneous case reports of adverse events relating to quinine use during pregnancy.

_____
Gerard G. Nahum, MD
Medical Officer

Concurrence by:

_____
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