

The following table shows studies considered primary (pivotal) for review of the efficacy of quinine combination therapy.

**Table 13: Randomized Controlled Trials of Quinine Combination Therapy**

| <b>Studies Submitted by Applicant:</b>                                | <b>Study Included in Comparison of Efficacy across Studies</b> | <b>Reason for not including Study in Comparison of Efficacy</b> |
|---|--|---|
| Duarte, et al., 1996  | Yes- primary study   | NA  |
| Fungladda, et al., 1998   | No   | Timing of endpoint  |
| Salcedo, et al., 1997   | No   | Combined IV and oral therapy data                               |
| De Alencar, et al., 1997  | Yes  | NA  |
| Bunnag, et al., 1996  | Yes  | NA  |
| Vanijanonta, et al., 1996   | Yes  | NA  |
| Looareesuwan et al., 1994   | Yes  | NA  |
| Karbwang, et al., 1994  | Yes-primary  | NA  |
| Kremsner, et al., 1988  | Yes  | NA  |
| De Souza, et al., 1985  | Yes  | NA  |
| <b>Additional studies provided by applicant upon request:</b>         |  |   |
| Kremsner, et al., 1994 (pediatric)                                    | Yes  | NA  |
|   |  |   |
| <b>Additional Studies (from Medical Officer's literature search):</b> |  |   |
| Ramharter, et al., 2005 (pediatric)                                   | Yes-primary  | NA  |
| McGready, et al., 2001 (pregnancy)                                    | No   | Timing of endpoint  |
| Buonyasong , 2001 (pregnancy)   | No   | Different endpoint  |

The applicant also submitted a number of non-randomized or uncontrolled studies of oral quinine mono- or combination therapy. These studies were not included with the randomized, controlled trials for evaluation of efficacy in this review, and are considered supportive studies for the NDA. Additionally, the applicant provided a number of randomized, controlled studies of parenteral quinine for treatment of severe malaria. These studies are considered supportive, and are summarized briefly in this review.

Two additional studies were identified (one by review of the literature, and the other by the applicant upon request) which address the question of malaria treatment in returned travelers Parota, et al. (2001; Mateelli, et al. (2005). These studies, are summarized briefly for this review, and are not included with the studies above to evaluate efficacy.

**Medical Officer Comments:** *Most cases of malaria in the U.S. are in travelers returned from malaria endemic areas, and in this country, treatment of these patients is relevant to this NDA. These studies are discussed briefly in section 6.1.4 below.*

### 6.1.2 General Discussion of Endpoints

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

#### Early Treatment Failure:

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

#### Late Treatment Failure:

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

#### Adequate Clinical and Parasitological Response:

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

Most of the randomized, controlled studies listed in section 4.2 above did not describe a primary endpoint. Most of these studies, which were performed in areas of intense malaria transmission, however, evaluated cure at 28 days (parasitological response), and this was the endpoint used to compare efficacy for this review. The WHO definitions for parasitological response and level of resistance used in this review were as follows (WHO 2000):

- **S:** (sensitive) = initial clearance of parasitemia, without recrudescence during follow-up period (*modified for this review to clearance of parasitemia by day 7, and no recrudescence within 28 days. This is referred to as "cure" or "28-day cure", the primary endpoint for this review.*)

- **RI:** (resistant) = initial clearance of parasitemia, but recrudescence by day 8 or more (*modified for this review to clearance of parasite within 7 days but recrudescence by day 28*)
- **RII:** (resistant) = initial clearance or reduction of parasitemia to < 25% initial value, and recrudescence on day 7 (*modified for this review to marked reduction of parasitemia but no clearance by day 7*)
- **RIII:** (resistant) = no initial reduction of parasitemia, or increase in parasitemia (*modified for this review to no marked reduction in parasitemia within 48 hours*)

**Medical Officer Comments:** *Most studies also included clinical endpoints such as parasite clearance time and fever clearance time. Most did not include the endpoint of Early or Late Treatment Failure, or Adequate Clinical and Parasitological Response, as defined above. However, in most of the studies a parasitological response of "S" was considered equivalent to "Adequate Clinical and Parasitological Response" for areas of intense malaria transmission, evaluated at 28 days. Parasitological Response is a surrogate marker for malaria cure rather than a clinical endpoint. Patients who are semi-immune may have parasitemia without symptoms of malaria; while parasitemia in a non-immune individual would almost always result in clear symptomatology. Thus the validity of this surrogate endpoint alone in semi-immune patients is debatable. However, although most did not use the WHO endpoint of adequate clinical and parasitological response, in the majority of studies reviewed for this NDA, patients with a parasitological response of "S" were also noted to have clinically responded to treatment.*

*One additional problem with the 28 day parasitological response as an endpoint is that unless molecular genotyping is done to discriminate recurrence vs. re-infection of patients remaining in a malarious area, the response rates may be lower than expected. Most of the studies reviewed for this NDA did not distinguish between recrudescence and reinfection.*

### 6.1.3 Study Design

Only randomized, controlled studies were reviewed for determination of efficacy. See Appendix, section 10.1, for description of study design and review of individual studies. There were only 2 randomized, controlled, double-blinded studies which evaluated efficacy of oral quinine sulfate, (Duarte, et al., 1996; Watt, et al., 1988) submitted by the applicant for this NDA. The studies designated as primary (or pivotal) for this review were randomized, active-controlled studies which described the randomization method, and indicated the numbers of patients excluded or withdrawn from the study after randomization, and discussed sample size determination. Study quality was evaluated by the method of Jadad, et al. (1996). Using this method, a quality score of 1-6 is assigned, based on the following questions:

1. Was the study randomized?
2. Was the study described as double-blind?
3. Was there a description of study withdrawals and dropouts?

If the answer to each item (1-3) was “yes”, one point was assigned; and zero points for “no”. Additionally, extra points were assigned as follows:

- For question 1: 1 additional point was given if the method to generate the sequence of randomization was described, and it was appropriate;
- and/or:
- For question 2: the method of blinding was described and it was appropriate

One point was deducted if:

- For question 1, the method to generate the randomization sequence was described, but was inappropriate;

and/or:

- For question 2: the study was described as double-blind, but the method of blinding was inappropriate

The following table shows the quality score determined using this method for each study of quinine monotherapy.

**Table 14: Quality Scores\* for Randomized, Controlled Studies of oral Quinine Monotherapy**

| Study                         | Quality Score |
|-------------------------------|---------------|
| Watt, et al., 1988            | 2             |
| Pukrittayakamee, et al., 2004 | 1             |
| Mueller, et al., 2004         | 2             |
| Ache, et al, 2002             | 1             |
| Rahman, et al., 2001          | 1             |
| Pukrittayakamee, et al., 2000 | 1             |
| McGready, et al., 2000        | 1             |
| De Vries, et al., 2000        | 2             |
| Bich, et al., 1996            | 3             |
| Metzger, et al., 195          | 2             |
| Segal, et al., 1974           | 1             |

\*Scoring method described by Jadad, et al. (1996). Score was assigned by Medical Officer.

*Medical Officer Comments: Most of these studies were not blinded, and did not describe the methods for randomization, or reasons for study withdrawal or dropout, thus explaining the low quality scores.*

The following table shows the quality score determined using this method for each study of quinine combination therapy.

**Table 15: Quality Scores\* for Randomized, Controlled Studies of oral Quinine Combination Therapy**

| Study                     | Quality Score |
|---------------------------|---------------|
| Duarte, et al., 1996      | 4             |
| Fungladda, et al., 1998   | 1             |
| Salcedo, et al., 1997     | 2             |
| De Alencar, et al., 1997  | 0             |
| Bunnag, et al., 1996      | 1             |
| Vanijanonta, et al., 1996 | 1             |
| Looareesuwan et al., 1994 | 2             |
| Karbwang, et al., 1994    | 1             |
| Kremsner, et al., 1988    | 2             |
| De Souza, et al., 1985    | 2             |
| Kremsner, et al., 1994    | 1             |
| Ramharter, et al., 2005   | 3             |
| McGready, et al., 2001    | NE            |
| Buonyasong, 2001          | NE            |

\*Scoring method described by Jadad, et al. (1996). Score was assigned by Medical Officer by review of each individual study.  
 NE= not evaluated

*Medical Officer Comments: Most of the studies available for review were not blinded, and did not describe the methods for randomization, or reasons for study withdrawal or dropout, thus explaining the low quality scores.*

#### 6.1.4 Efficacy Findings

The following sections summarize the efficacy of quinine monotherapy and combination therapy for treatment of uncomplicated *P. falciparum* malaria in the randomized, controlled studies reviewed for this NDA. Additionally, the efficacy of parenteral quinine for treatment of severe malaria is summarized for comparison.

##### **Quinine Monotherapy**

WHO treatment guidelines published in 2000 recommend quinine as first line treatment in areas with multidrug-resistant malaria where *P. falciparum* does not respond to chloroquine, sulfa - pyrimethamine combinations and mefloquine. In areas with marked decrease in susceptibility of *P. falciparum* to quinine, combination of quinine with doxycycline, tetracycline, or clindamycin is recommended. Additionally, quinine is considered by the WHO a reasonable option for travelers who develop malaria who are returning to non-endemic areas and the drug-resistance profile of the parasite is unknown (WHO 2000). Quinine in combination with an antimicrobial agents such as tetracycline, doxycycline, or clindamycin, is recommended in the 2004 CDC guidelines for treatment of uncomplicated *P. falciparum* malaria acquired from areas of

chloroquine resistance or if the identification of the acquired parasite is unknown (CDC 2004 Guidelines for Treatment of Malaria in the U.S.).

### Dosing and Duration of Exposure

Most of the studies used a quinine dose of 10 mg/kg 3 times daily (or every 8 hours) for a duration of 7 days. A summary of quinine dosing and duration, as well as study completion was summarized by the applicant in the following table. Overall, 407/504 (81%) patients randomized to quinine monotherapy completed follow-up.

Table. Quinine Dosing and Duration of Therapy in Randomized, Controlled Trials of Quinine Monotherapy (applicant's Table 4, ISE)

| Author (year)<br>Country                        | Quinine Dosage Regimen                             | Duration<br>(Days) | No. Patients Completed<br>/ Randomized (%<br>Completed) |
|---|--|--------------------|---|
| <b>RANDOMIZED, DOUBLE-BLIND STUDIES (N=1)</b>   |  |                    |   |
| Watt <i>et al.</i> , 1988<br>(Philippines)      | 648 mg (sulfate salt) every 8 hours                | 5                  | 10/10 (100%)  |
| <b>RANDOMIZED, OPEN-LABEL STUDIES (N=10)</b>    |  |                    |   |
| Pukrittayakamee <i>et al.</i> , 2004 (Thailand) | 10 mg/kg (sulfate salt) 3 times daily              | 7                  | 25/30 (83%)   |
| Mueller <i>et al.</i> , 2004 (Congo)            | 500 mg (sulfate salt) 3 times daily                | 7                  | 36/48 (75%)   |
| Aché <i>et al.</i> , 2002 (Venezuela)           | 10 mg/kg (sulfate salt) every 8 hours              | 7                  | 48/48 (100%)  |
| Rahman <i>et al.</i> , 2001 (Bangladesh)        | 10 mg/kg (sulfate salt) every 8 hours              | 7                  | 49/49 (100%)  |
| McGready <i>et al.</i> , 2000 (Thailand)        | 10 mg/kg (sulfate salt) every 8 hours              | 7                  | 27/42 <sup>1</sup> (67%)                                |
| Pukrittayakamee <i>et al.</i> , 2000 (Thailand) | 10 mg/kg (sulfate salt) 3 times daily              | 7                  | 53/68 (78%)   |
| De Vries <i>et al.</i> , 2000 (Vietnam)         | 10 mg/kg (sulfate salt) 3 times daily              | 7                  | 69/84 (82%)   |
| Bich <i>et al.</i> , 1996 (Vietnam)             | 10 mg/kg (sulfate salt) 3 times daily              | 7                  | 44/59 (75%)   |
| Metzger <i>et al.</i> , 1995 (Gabon)            | 12 mg/kg every 12 hours <sup>2</sup>               | 1.5 <sup>3</sup>   | 37/40 (92%)   |
| Segal <i>et al.</i> , 1974 (Thailand)           | 2 tablets sulfate salt (540 mg base) every 8 hours | 6                  | 22/26 (85%)   |
| <b>TOTAL</b>                                    |  |                    | <b>407/504 (81%)</b>                                    |

<sup>1</sup>36 patients completed Day 28 follow-up and 34 patients completed Day 35 follow-up. No efficacy summary was provided for Day 28 therefore Day 35 data are used in this document <sup>2</sup>Not specified to be dosed as the salt or base <sup>3</sup>This three-dose regimen was commonly given in Central Africa at the time <sup>4</sup>Duration of follow-up was 63 days

**Medical Officer Comments:** In comparison with most of these studies, one study, Metzger, *et al.* (1995) used non-standard quinine dosing (12 mg/kg q12h) for 3 doses over a 1.5 day treatment period. The doses of 500 or 648 mg

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*quinine sulfate salt or 540 mg quinine base used in several of these studies would be equivalent to 8-10 mg/kg quinine sulfate (salt) in a 60-70 kg adult. Current treatment guidelines recommend quinine sulfate 542 mg base (650 mg salt) 3 times daily in adults (CDC guidelines, 2004), or 8 mg base/kg 3 times daily (WHO 2000).*

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**Summary of Efficacy for Randomized, Controlled Studies of Quinine Monotherapy**

The applicant summarized efficacy in the following table to compare efficacy across the individual studies of differing designs and different endpoints. As noted above, the primary endpoint used by the applicant, and for this review is the 28-day cure rate, determined by parasitological response, i.e. a response of "S" or cure at the 28 day endpoint, defined as initial parasite clearance with no recrudescence of parasitemia up to the 28 day follow-up (longer than 28 days in several studies). For the intent-to-treat (ITT) populations, cure rates ranged from 61-100% across all studies, counting patients lost-to follow-up as treatment failures. For evaluable patients, cure rates ranged from 38-100% for all studies with quinine monotherapy, including the Metzger (1995) study which used a 3-dose course of quinine. If only studies which evaluated a 7-day course of quinine are included for comparison, cure rates ranged from 67-100% in evaluable patients. For a 7 day course of quinine monotherapy, the lowest rate of cure, 67%, was reported in the study by McGready, et al. (2000) which evaluated quinine in pregnant women who lived on the western border of Thailand. Cure rate in this study was determined at 63 days post-treatment initiation, rather than 28 days, although PCR analysis of parasites in patients with the return of parasitemia prior to day 63 indicated only 2 new infections.

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**Table 16: Clinical and Parasitological Response to Quinine Monotherapy in Patients with Uncomplicated *P. falciparum* Malaria (applicant's Table 5, ISE)**

| Study  | Treatment/<br>Duration<br>Codes(No.<br>Enrolled) | Clinical Response                 |    |                                    | Parasitological Response:N/D (%) |                 |                 |                 |                 |        |        |        |        |        |        |        |
|--|--|-----------------------------------|----|------------------------------------|----------------------------------|-----------------|-----------------|-----------------|-----------------|--------|--------|--------|--------|--------|--------|--------|
|  |  | Fever Clearance<br>Time (Hours)   |    | Parasite Clearance<br>Time (Hours) | S or Cure                        |                 |                 | RI              |                 |        | RII    |        |        | RIII   |        |        |
|  |  | Mean or<br>Median ±<br>SD [Range] | N  | Mean ± SD<br>[Range]               | N                                | ITT             | EVAL            | ITT             | EVAL            | ITT    | EVAL   | ITT    | EVAL   | ITT    | EVAL   |        |
| <b>RANDOMIZED, DOUBLE-BLIND STUDIES (N=1)</b>          |  |                                   |    |                                    |                                  |                 |                 |                 |                 |        |        |        |        |        |        |        |
| Watt <i>et al.</i> ,<br>1988<br>(Philippines)          | Q5 (10)  | 43.2 ± 20.0                       | 10 | 60.3 ± 12.5                        | 10                               | 10/10<br>(100%) | 10/10<br>(100%) | NR              | NR              | NR     | NR     | NR     | NR     | NR     | NR     | NR     |
|  | CQ3 (10)   | 46.3 ± 24.7                       | 10 | 76.1 ± 29.3                        | 10                               | 10/10<br>(100%) | 10/10<br>(100%) | NR              | NR              | NR     | NR     | NR     | NR     | NR     | NR     | NR     |
| <b>RANDOMIZED, OPEN-LABEL STUDIES (N=10)</b>           |  |                                   |    |                                    |                                  |                 |                 |                 |                 |        |        |        |        |        |        |        |
| Pukrittayakam<br><i>ee et al.</i> , 2004<br>(Thailand) | Q7 (30)  | 63 ± NR [7 -<br>152]              | 30 | 80 ± 26<br>[NR]                    | 30                               | 21/30<br>(70%)  | 21/25<br>(84%)  | 4/30<br>(13%)   | 4/25<br>(16%)   | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
|  | Q7T7 (30)  | 33 ± NR [8 -<br>117]              | 30 | 81 ± 19<br>[NR]                    | 30                               | 22/30<br>(73%)  | 22/22<br>(100%) | 0 (0%)          | 0 (0%)          | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
|  | A7 (23)  | 34 ± NR [7 -<br>180]              | 23 | 69 ± 19<br>[NR]                    | 23                               | 19/23<br>(83%)  | 19/21<br>(90%)  | 2/23<br>(8.7%)  | 2/21<br>(9.5%)  | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Mueller <i>et al.</i> ,<br>2004(Congo)                 | Q7 (48)  | NR                                | -- | NR                                 | --                               | 27/48<br>(56%)  | 27/343<br>(79%) | NR              | NR              | NR     | NR     | NR     | NR     | NR     | NR     | NR     |
|  | A(5 g)7 (45)                                     | NR                                | -- | NR                                 | --                               | 11/45<br>(24%)  | 11/323<br>(34%) | NR              | NR              | NR     | NR     | NR     | NR     | NR     | NR     | NR     |
|  | A(9 g)7 (39)                                     | NR                                | -- | NR                                 | --                               | 9/39<br>(23%)   | 9/303<br>(30%)  | NR              | NR              | NR     | NR     | NR     | NR     | NR     | NR     | NR     |
| Aché <i>et al.</i> ,<br>2002<br>(Venezuela)            | Q7 (48)  | NR                                | -- | NR                                 | --                               | 48/48<br>(100%) | 48/48<br>(100%) | 0 (0%)          | 0 (0%)          | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
|  | CQ3 (12)   | NR                                | -- | NR                                 | --                               | 0 (0%)          | 0 (0%)          | 12/12<br>(100%) | 12/12<br>(100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
|  | CQ4 (52)   | NR                                | -- | NR                                 | --                               | 40/52<br>(77%)  | 40/52<br>(77%)  | 12/52<br>(23%)  | 12/52<br>(23%)  | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| S/P1 (53)  | NR   | --                                | NR | --                                 | 41/53<br>(77%)                   | 41/53<br>(77%)  | 12/53<br>(23%)  | 12/53<br>(23%)  | 0 (0%)          | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

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| Study   | Treatment/<br>Duration<br>Codez(No.<br>Enrolled) | Clinical Response                 |                              |                  | Parasitological Response:N/D (%) |                |                              |                |                  |              |                 |              |                 |
|---|--|-----------------------------------|------------------------------|------------------|----------------------------------|----------------|------------------------------|----------------|------------------|--------------|-----------------|--------------|-----------------|
|   |  | Fever Clearance<br>Time (Hours)   |                              | N                | S or Cure                        |                | RI                           |                | RII              |              | RIII            |              |                 |
|   |  | Mean or<br>Median ± SD<br>[Range] | Mean ± SD<br>[Range]         |                  | ITT                              | IVAL           | ITT                          | IVAL           | ITT              | IVAL         | ITT             | IVAL         |                 |
| Rahman <i>et al.</i> ,<br>2001<br>(Bangladesh)      | Q7 (NR <sub>4</sub> )                            | 33.9 ± 27.6<br>[NR]               | 54.5 ± 21.8<br>[NR]          | 49               | 49                               | --             | 40/49<br>(82%)               | --             | 5/49<br>(10%)    | --           | 1/49<br>(2%)    | --           | 3/49<br>(6%)    |
| McGready <i>et al.</i> , 2000<br>(Thailand)         | Q3S/P1<br>(NR <sub>4</sub> )                     | 35.1 ± 24.7<br>[NR]               | 56.4 ± 27.1<br>[NR]          | 145              | 145                              | --             | 96/145<br>(66%)              | --             | 32/145<br>(22%)  | --           | 5/145<br>(3%)   | --           | 12/145<br>(8%)  |
|   | CQ3 (NR <sub>4</sub> )                           | 33.5 ±<br>29.0[NR]                | 68.9 ± 35.5<br>[NR]          | 149              | 149                              | --             | 34/149<br>(23%)              | --             | 32/149<br>(21%)  | --           | 24/149<br>(16%) | --           | 59/149<br>(40%) |
|   | M1 (NR <sub>4</sub> )                            | 25.5 ± 26.5<br>[NR]               | 57.1 ± 29.1<br>[NR]          | 70               | 70                               | --             | 51/70<br>(73%)               | --             | 9/70<br>(13%)    | --           | 3/70<br>(4%)    | --           | 7/70<br>(10%)   |
|   | Q7 (42)  | NR <sub>12</sub>                  | NR <sub>12</sub>             | NR <sub>12</sub> | 42                               | --             | 27/41<br>(67%) <sup>12</sup> | --             | NR <sub>12</sub> | --           | NR              | --           | NR              |
| Pukrittayakam<br><i>et al.</i> , 2000<br>(Thailand) | M2A3 (66)  | NR <sub>12</sub>                  | NR <sub>12</sub>             | NR <sub>12</sub> | 66                               | --             | 64/65<br>(98%) <sup>12</sup> | --             | NR <sub>12</sub> | --           | NR              | --           | NR              |
|   | Q7 (68)  | 56 ± NR [4 -<br>152]              | 77 ± 25<br>[NR]              | 68               | 68                               | 46/68<br>(68%) | 46/53<br>(87%)               | 7/68<br>(10%)  | 7/53<br>(13%)    | 0 (0%)       | 0 (0%)          | 0 (0%)       | 0 (0%)          |
|   | Q7C7 (68)  | 47 ± NR [8 -<br>120]              | 79 ± 20<br>[NR]              | 68               | 68                               | 60/68<br>(88%) | 60/60<br>(100%)              | 0 (0%)         | 0 (0%)           | 0 (0%)       | 0 (0%)          | 0 (0%)       | 0 (0%)          |
|   | Q7T7 (68)  | 36 ± NR [8 -<br>117]              | 77 ± 23<br>[NR]              | 68               | 68                               | 47/68<br>(69%) | 47/48<br>(98%)               | 1/68<br>(1%)   | 1/48<br>(2%)     | 0 (0%)       | 0 (0%)          | 0 (0%)       | 0 (0%)          |
| De Vries <i>et al.</i> , 2000<br>(Vietnam)          | Q7 (84)  | 47 ± NR<br>[NR] <sub>5</sub>      | 62 ± NR<br>[NR] <sub>5</sub> | 79               | 79                               | 56/84<br>(67%) | 56/69<br>(81%)               | 11/84<br>(13%) | 11/69<br>(16%)   | 1/84<br>(1%) | 1/69<br>(1%)    | 1/84<br>(1%) | 1/69<br>(1%)    |
|   | A1Q3 (96)  | 41 ± NR<br>[NR] <sub>6</sub>      | 41 ± NR<br>[NR] <sub>6</sub> | 92               | 92                               | 46/96<br>(48%) | 46/74<br>(62%)               | 28/96<br>(29%) | 28/74<br>(38%)   | 0 (0%)       | 0 (0%)          | 0 (0%)       | 0 (0%)          |
|   | A1Q5 (88)  | 43 ± NR<br>[NR] <sub>7</sub>      | 42 ± NR<br>[NR] <sub>7</sub> | 87               | 87                               | 66/88<br>(75%) | 66/78<br>(85%)               | 12/88<br>(14%) | 12/78<br>(15%)   | 0 (0%)       | 0 (0%)          | 0 (0%)       | 0 (0%)          |
| Bich <i>et al.</i> ,<br>1996<br>(Vietnam)           | Q7 (59)  | 41 ± 23 [0 -<br>112] <sub>8</sub> | 66 ± 24 [24<br>-128]         | 55               | 55                               | 36/59<br>(61%) | 36/44<br>(82%)               | 7/59<br>(12%)  | 7/44<br>(16%)    | 1/59<br>(2%) | 1/44<br>(2%)    | 0 (0%)       | 0 (0%)          |
|   | A1Q3 (45)  | 34 ± 19 [0 -<br>80] <sub>8</sub>  | 43 ± 14 [16<br>-72]          | 44               | 44                               | 23/45<br>(51%) | 23/32<br>(72%)               | 9/45<br>(20%)  | 9/32<br>(28%)    | 0 (0%)       | 0 (0%)          | 0 (0%)       | 0 (0%)          |

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|                                     | A ID3 (53)             | 31 ± 23 [0 - 120] <sup>8</sup> | 49 | 41 ± 19 [16 - 136] | 49 | 13/53 (24%) | 13/42 (31%) | 26/53 (49%) | 26/42 (62%) | 0 (0%) | 3/53 (6%) | 3/42 (7%) |
|-------------------------------------|------------------------|--------------------------------|----|--------------------|----|-------------|-------------|-------------|-------------|--------|-----------|-----------|
| Metzger <i>et al.</i> , 1995(Gabon) | Q1.5 <sup>9</sup> (40) | NR                             | -  | NR <sub>10</sub>   | 37 | 14/40 (35%) | 14/37 (38%) | 23/40 (57%) | 23/37 (62%) | 0 (0%) | 0 (0%)    | 0 (0%)    |

- NR=not evaluated or reported; ENR=enrolled; DC=discontinued; LOST=lost to follow-up; EVAL=evaluable; ITT=intention to treat population; Q=quinine; CQ=chloroquine; A=artemisinin or artesunate; T=tetracycline; C=clindamycin; M=mefloquine; W=WR 33063; SP=sulfadoxine/pyrimethamine
- <sup>1</sup>Parasitological response generally defined as: S=parasite clearance by Day 7 without recrudescence up to Day 28; RI=initial disappearance with recrudescence before Day 14 (early RI) or from Day 14 to Day 28 (late RI); RII=initial decrease in parasitemia to < 25% of initial value, followed by resurgence; RIII=no response or a small decrease to not less than 25% of the initial value, assessed at 48 hours after initiation of therapy
- <sup>2</sup>Treatment/Duration codes = drug abbreviation followed by duration of treatment in days. Combination therapy is represented as first drug abbreviation, duration, second drug abbreviation, duration
- <sup>3</sup>Reported cure at 28 days follow-up but not by cures/failures so data from Day 35 follow-up is used in the table (Mueller *et al.*, 2004)
- <sup>4</sup>The number of patients enrolled per treatment is not reported. Demographic and efficacy data are based on the number of patients completing the 28-day study (Rahman *et al.*, 2001)
- <sup>5</sup>The 95% confidence intervals for fever and parasite clearance times = 41 to 53 hours and 57 to 67 hours, respectively (De Vries *et al.*, 2000)
- <sup>6</sup>The 95% confidence intervals for fever and parasite clearance times = 37 to 46 hours and 38 to 44 hours, respectively (De Vries *et al.*, 2000)
- <sup>7</sup>The 95% confidence intervals for fever and parasite clearance times = 38 to 47 hours and 39 to 46 hours, respectively (De Vries *et al.*, 2000)
- <sup>8</sup>A fever clearance time of 0 means that there was no fever on admission (Bich *et al.*, 1996)
- <sup>9</sup>This 3-dose regimen was commonly given in Central Africa (Metzger *et al.*, 1995)
- <sup>10</sup>The publication reports that the mean duration of parasitemia for quinine, quinine + clindamycin, and quinine + doxycycline were 2.2, 2.4, and 2.2 days, respectively (Metzger *et al.*, 1995)
- <sup>11</sup>These are reported as treatment failures; for the purpose of this table, they are categorized as RI (Segal *et al.*, 1974)
- <sup>12</sup>Only 19 women were febrile on admission and all were afebrile by 48 hours (treatment group not specified). Proportions of patients negative for parasites by 48 hours were 18/42 (43%) in the quinine group and 54/66 (82%) in the mefloquine-artesunate group. Also, cure rates were not reported by treatment group; however, 13 of 108 women had reappearance of parasite. Using PCR-confirmation of recrudescence, Day 63 cure rates by survival analysis were calculated as 98% in 65 mefloquine-artesunate patients and 67% of 41 quinine patients (McGready *et al.*, 2000).

**Medical Officer Comments:** *Most of these studies did not show an ITT analysis, but where the number of randomized patients in each treatment group was shown, efficacy in the ITT population was calculated by the applicant. In the ITT analysis, patients lost to follow-up were considered failures. In the studies which were performed in outpatient settings in malaria-endemic areas, where patients may live long distances from study sites, those who did not return for follow-up were more likely to be treatment successes than failures. Thus, data from the evaluable population rather than the ITT population may more accurately reflect quinine efficacy in most of these studies. Most of these studies were done in an inpatient setting except for Mueller, et al (2004); Ache, et al (2002), and McGready, et al. (2000). In general, however, efficacy in the ITT is considered to more accurately reflect efficacy than the evaluable population.*

### **Quinine Monotherapy: Other Clinical Endpoints**

#### **Fever Clearance Time**

Fever clearance time was reported in 7 of these studies. Mean or median fever clearance times are shown in the table above. Generally within studies, mean fever clearance time was longer in the quinine monotherapy arms than with quinine combination therapy or comparators. Fever clearance time in at least 2 of the studies, Pukritayakamee, et al. (2000 and 2004), however, may have been affected by routine use of acetaminophen for fever.

*Medical Officer Comments: Because fever clearance time was generally reported as either mean or median, comparison of this parameter across studies is difficult. However, it is notable that fever clearance time was generally longer than the parasite clearance time for both quinine and comparators, and may affect the perception of efficacy.*

#### **Parasite Clearance Time**

Parasite clearance time (PCT) was measured in 8 of these studies. Mean fever clearance times are shown in table \_above. Parasite clearance times ranged from 60 to 80 hours for monotherapy. Within studies, parasite clearance time was generally similar for quinine monotherapy and quinine combination therapy (Pukritayakamee, et al., 2004, Pukritayakamee, et al., 2000, Rahman, et al., 2001); while PCT was longer with quinine monotherapy than with artemisinin regimens (Pukritayakamee, et al., 2004, De Vries, et al., 2000, Bich, et al., 1996)

*Medical Officer Comments: Artemisin derivatives are known to be more rapidly-acting than quinine.*

#### **Efficacy of Quinine Monotherapy by Gender, Age, and Race**

None of the studies which evaluated quinine monotherapy enrolled only pediatric patients. However, pediatric patients (< 16 years old) were enrolled in most of these studies. Similarly, patients over 65 years old were enrolled in most of these studies, however, outcomes were not reported by age in these studies. The applicant stated in the Integrated Summary of Efficacy “there is no evidence that quinine is less effective in children or older adults.” However, further information or data supporting that statement was not provided.

*Medical Officer Comments: Worldwide experience with quinine for centuries can lend support to the Applicant’s statement above; however, no randomized, controlled trials which evaluated quinine monotherapy in children were*

*submitted with the original NDA. Two randomized, controlled trials of quinine combination therapy in pediatric patients are discussed below.*

Although some of these studies enrolled only male patients, none enrolled only female patients except for the study by McGready, et al., (2000) which enrolled female patients in their second and third trimester of pregnancy. Female patients were a distinct minority in these studies, (13% of all patients enrolled). In studies which did enroll female patients, outcomes were not analyzed by gender.

#### **Efficacy of Quinine for Uncomplicated Malaria in Pregnant Women**

The applicant submitted one randomized, controlled study in pregnant women (McGready, et al., 2000). This study is reviewed in detail in Appendix, section 10.1 In brief, quinine monotherapy in 42 pregnant women in the second or third trimester of pregnancy was compared to mefloquine plus artesunate in 66 women in the same stages of pregnancy. The cure rate, determined at 63 days post-treatment initiation was 67% for the quinine treatment arm, and 98% for the mefloquine-artesunate treatment group.

*Medical Officer Comments: This study was performed at the Thailand-Myanmar border, where mefloquine and quinine resistance have been documented, which may explain the comparatively low cure rates in the quinine group. The level of resistance (RI, RII, and RIII) in patients with recrudescence was not reported in this study. Other studies in Thailand suggest greater efficacy with quinine combination therapy than quinine alone, and this most likely would apply to pregnant women as well. Tetracycline or doxycycline, however, should not be used in pregnancy, and clindamycin may be a reasonable alternative in conjunction with quinine. One published study was found in the literature which evaluated a combination of quinine plus clindamycin in pregnant women in Thailand (McGready, et al., 2001). This study is discussed below.*

One additional randomized, controlled study was identified in the literature which evaluated quinine monotherapy (7 days) compared to artesunate (5days) plus mefloquine (1 day) (Bounyasong, 2001). Thai women in their second or third trimester of pregnancy with P. falciparum malaria received quinine monotherapy (29 patients) or artesunate plus mefloquine (28 patients). Fever and parasite clearance time were significantly shorter in the artesunate-mefloquine group (mean 4.5 and 3.5 days, respectively) compared to the quinine treatment group (mean 7.0 and 8.0 days for PCT and FCT, respectively). Parasitological response was not reported as an endpoint in this study, but the author noted that none of the patients in either treatment group had parasite recrudescence at 28 days.

*Medical Officer Comments: It is not clear why parasite and fever clearance time are much longer in this study than in those cited in table 16 above. In the study by McGready, et al (2000) in pregnant women,, fever and parasite clearance times were not reported.*

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A third randomized, controlled study performed in Thailand was found in the published literature, comparing a 7 day course of oral quinine sulfate plus clindamycin (N=65) to a 7 day course of oral artesunate (N=64) in pregnant women with uncomplicated *P. falciparum* malaria (McGready, et al., 2001). In this study, cure rates were 100% at follow-up (day 42 after treatment initiation) for both treatment regimens.

**Efficacy of Quinine Monotherapy for Uncomplicated Malaria by Geographical Region**

When the efficacy of quinine monotherapy is compared to quinine combination regimens or non-quinine antimalarial agents, differences were noted by geographical area. In Southeast Asia (Thailand and Vietnam) efficacy of the 7 day quinine regimen was 0-31% less than the comparator, except in the study by Bich, et al., 1996, in which the comparators were short- course artesunate plus quinine or doxycycline, and the 7-day quinine monotherapy regimen showed improved outcomes. In the single South American study, cure rates were higher for the 7-day quinine treatment regimen than with chloroquine or sulfadoxine-pyrimethamine. In the African study by Mueller, et al., 2004, efficacy of 7 days of quinine monotherapy was significantly better than that with either artemisinin tea preparation. In the two studies which evaluated short courses of quinines (1.5 or 3 days) to quinine combination therapy, cure rates were significantly higher with the combination therapy (Metzger, et al., 1995; Kremsner, et al., 1994).

**Table 17: Efficacy of Quinine Monotherapy by Geographical Location**

| Study/Geographical Region                          | Treatment /Duration | Cure Rate (28 days) in Evaluable Population n/N (%) | Comparator Treatment/Duration | Cure Rate (28 days) in Evaluable Population n/N (%) | Treatment Difference (Quinine Monotherapy % cure minus Comparator % Cure) |
|--|---------------------|---|-------------------------------|---|---|
| <b>Southeast Asia</b>                              |                     |   |                               |   |   |
| Pukrittayakamee, et al., 2004 (Thailand)           | Q7                  | 21/25 (84)  | Q7T7                          | 21/22 (100)   | -16   |
| McGready, et al., 2000 (Thailand) (pregnant women) | Q7                  | 27/41 (67)  | A7                            | 19/21 (90)  | -6  |
|  |                     |   | M2A3                          | 64/64 (98)  | -31   |
| Pukrittayakamee, et al., 2000 (Thailand)           | Q7                  | 46/53 (87)  | Q7T7                          | 47/48 (98)  | -11   |
| Bich, et al., 1996 (Vietnam)                       | Q7                  | --  | Q7C7                          | 60/60 (100)   | -13   |
|  |                     |   | A1Q3                          | 23/32 (72)  | +10   |
|  |                     |   | A1D3                          | 13/42 (31)  | +51   |
| <b>South America</b>                               |                     |   |                               |   |   |
| Ache, et al., 2002 (Venezuela)                     | Q7                  | 48/48 (100)   | CQ3                           | 0/12 (0)  | +100  |
|  |                     |   | CQ4                           | 40/52 (77)  | +23   |
|  |                     |   | SP1                           | 41/53 (77)  | +23   |
| <b>Africa</b>                                      |                     |   |                               |   |   |
| Mueller, et al., 2004 (Dem. Rep. Congo)            | Q7                  | 31/36 (86)  | A(5g)7                        | 11/32 (34)  | +52   |
| Metzger, et al., 1995 (Gabon)                      | Q 1.5               | 14/37 (38)  | A(9g)7                        | 9/30 (30)   | +56   |
|  |                     |   | Q1.5C3                        | 33/36 (92)  | -54   |
|  |                     |   | Q1.5D3                        | 32/35 (91)  | -53   |
| Kremsner, et al., 1994 (Gabon) (pediatric)         | Q3                  | 10/31 (32)  | Q3C3                          | 30/34 (88)  | -56   |

**Medical Officer Comments:** The quinine monotherapy studies not included in this table were Watt et al., 1995; Segal, 1974; Devries, et al., ; Rahman, et al., 2001. These were not included in this summary for the reason discussed previously (problems with randomization, endpoints, etc.). Additionally, because of the timing of the end-point (63 days), the McGready study

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*cannot be directly compared to the others. In the Clinical Studies section of the label, we have proposed the following statement regarding treatment of uncomplicated P. falciparum malaria with quinine:*

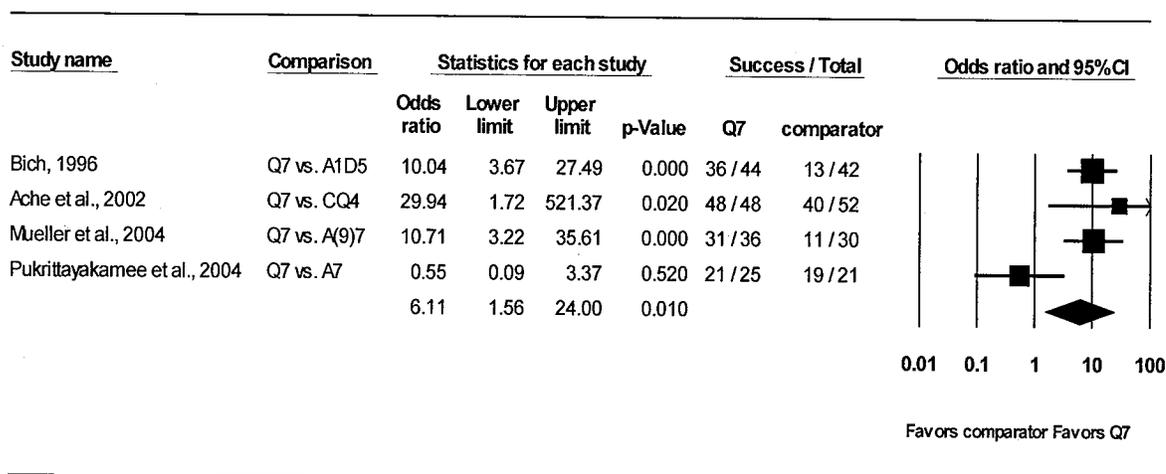
*"In areas where multi-drug resistance of P. falciparum is increasing, such as Southeast Asia, cure rates with 7 days of oral quinine monotherapy were at least 80%; while cure rates for 7 days of oral quinine combined with an antimicrobial agent (tetracycline or clindamycin) were greater than 90%. In areas where multi-drug resistance of the parasite was not as widespread, cure rates with 7 days of quinine monotherapy ranged from 86 to 100%. Cure was defined as initial clearing of parasitemia within 7 days without recrudescence by day 28 after treatment initiation. P falciparum malaria that is clinically resistant to quinine has been reported in some areas of South America Southeast Asia, and Bangladesh, and quinine may not be as effective in those areas.*

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### Efficacy of Quinine Monotherapy: Statistical Analysis

For full details, see the review by Ms. LaRee Tracy, Statistical Reviewer. In brief, a meta-analysis was performed by the Statistical Reviewer and is summarized in this section. Four studies (Bich, et al., 1996; Pukrittayakamee, et al., 2004; Mueller, et al., 2004; and Ache, et al., 2002) which each evaluated quinine monotherapy in comparison to a treatment regimen which used 7 day duration of therapy were sufficiently similar in study design for efficacy analysis. These studies included 630 randomized patients, of whom 187 received 7 days of quinine monotherapy, and 153 (82.7%) were evaluable. Cure rates in the ITT and evaluable populations ranged from 82 to 100% and 61 to 100%, respectively. These studies represent different geographical areas, including Southeast Asia (Bich et al., 1996; Pukrittayakamee, et al., 2004), South America (Ache, et al., 2002), and Africa (Mueller, et al., 2004), and differences in efficacy of quinine monotherapy may be due to geographical differences in parasite resistance. The random effects model resulted in an estimated odds ratio of 6.11, 95% CI [1.56, 24.00], p-value = 0.01, suggesting that the probability of cure with 7 days quinine monotherapy was 6.11 times greater than with the non-quinine comparators used in this setting. The forest plot of this analysis with 95% confidence intervals is shown below.

**Figure 5. Meta-Analysis of Quinine Monotherapy (7-day duration) for Evaluable Populations (Statistical Review’s Analysis)**



*Medical Officer Comments: For the endpoint of parasitological cure in this analysis, the odds ratio favored Q7(7 days of quinine monotherapy) over the comparators used in these studies (A1D5= 1 day artemisin plus 5 days*

*doxycycline; CQ4= chloroquinine; A(9)7= 7 days of artemisin tea containing 9 g herb/day; A7=7 days artesunate.*

### Quinine Combination Therapy

The applicant provided 16 randomized, controlled studies (one blinded, 15 open-label), 6 of which were included in the summary of quinine monotherapy because they had a quinine treatment arm. These studies are included in this section for comparison with the monotherapy treatment arm. A total of 2405 patients were randomized in the 16 studies, 1299 of whom were randomized to a quinine-containing regimen.

### Dosing and Duration of Therapy

The following table shows study drug dosing and duration for the quinine-containing combinations and comparator regimens.

**Table 18: Quinine Dosing and Duration of Therapy in Studies of Quinine Combination Therapy for Uncomplicated *P. falciparum* Malaria (applicant's Table 12, ISE)**

| Author (year)<br>Country                           | Drugs and Oral Dosage Regimens   | No. Patients<br>Randomized | Duration<br>(Days) |
|--|--|----------------------------|--------------------|
| <b>RANDOMIZED, BLINDED STUDY (N=1)</b>             |  |                            |                    |
| Duarte <i>et al.</i> ,<br>1996<br>(Brazil)         | Q 1000 mg every 12 hours + T 500 mg every<br>8 hours   | 88                         | Q3T7               |
| <b>RANDOMIZED, OPEN-LABEL STUDIES (N=15)</b>       |  |                            |                    |
| Pukrittayakamee <i>et al.</i> , 2004<br>(Thailand) | Q 10 mg/kg (sulfate salt) 3 times daily + T 4<br>mg/kg 4 times daily   | 30                         | Q7T7               |
|  | A 3.3 mg/kg (adult dose 200 mg) on Day 1 and<br>then 1.65 mg/kg  | 23                         | A7                 |
| Rahman <i>et al.</i> ,<br>2001<br>(Bangladesh)     | Q 10 mg/kg (sulphate salt) every 8 hours followed<br>by a single dose of SP (calculated as 25 mg/kg<br>sulfadoxine) after the last dose of Q | 145                        | Q3SP1              |
| Pukrittayakamee <i>et al.</i> , 2000<br>(Thailand) | Q 10 mg/kg (sulfate salt) 3 times daily + T 4<br>mg/kg 4 times daily   | 68                         | Q7T7               |
|  | Q 10 mg/kg (sulphate salt) 3 times daily + C.5<br>mg/kg base 4 times daily   | 68                         | Q7C7               |
| De Vries <i>et al.</i> ,<br>2000 (Vietnam)         | A 20 mg/kg single dose followed by Q 10 mg/kg<br>3 times daily   | 96                         | A1Q3               |
|  | A 20 mg/kg single dose followed by Q 10 mg/kg<br>3 times daily   | 88                         | A1Q5               |
| Funladda <i>et al.</i> ,<br>1998 (Thailand)        | Q 600 mg (base) 3 times daily + T 500 mg twice<br>daily  | 60                         | Q7T7               |
| Salcedo <i>et al.</i> ,<br>1997 (Brazil)           | Q 10 mg/kg (salt not specified) every 8 hours + T<br>500 mg every 8 hours  | 14 <sub>3</sub>            | Q3T7               |
|  | A 100 mg followed by 50 mg every 12 hours + T<br>500 mg every 8 hours  | 16 <sub>3</sub>            | A5T7               |
| De Alencar <i>et al.</i> ,<br>1997 (Brazil)        | Q 600 mg (base) 3 times daily + T 250 mg 4 times<br>daily  | 77                         | Q7T7               |

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|  |  |                                    |                            |
|--|--|------------------------------------|----------------------------|
| Bunnag <i>et al.</i> ,<br>1996 (Thailand)            | Q 600 mg (base) 3 times daily + T 250 mg 4 times daily   | 48                                 | Q5T7                       |
|  | Q 600 mg (base) 3 times daily + T 250 mg 4 times daily   | 42                                 | Q7T7                       |
| Vanijanonta <i>et al.</i> ,<br>1996 (Thailand)       | Q 10 mg/kg (sulphate salt)4 mg/kg every 8 hours + T  | 25                                 | Q7T7                       |
|  | Q 10 mg/kg (sulphate salt)mg base/kg (total dose ove every 8 hours + CQ 25 r 3 days)   | 25                                 | Q7CQ3                      |
| Bich <i>et al.</i> , 1996)<br>(Vietnam)              | A 20 mg/kg (single dose) followed by Q 10 mg/kg 3 times daily  | 45                                 | A1Q3                       |
| Metzger <i>et al.</i> ,<br>1995 (Gabon) <sup>1</sup> | Q 12 mg/kg every 12 hours for 3 doses + C 5 mg/kg every 12 hours for 6 doses   | 40                                 | Q1.5C3                     |
|  | Q 12 mg/kg every 12 hours for 3 doses + D 2 mg/kg every 12 hours for 6 doses   | 40                                 | Q1.5D3                     |
| Looareesuwan <i>et al.</i> , 1994<br>(Thailand)      | Q 600 mg (salt) every 8 hours + T 250 mg 4 times daily   | 52                                 | Q7T7                       |
| <b>Author (year)<br/>Country</b>                     | <b>Drugs and Oral Dosage Regimens</b>  | <b>No. Patients<br/>Randomized</b> | <b>Duration<br/>(Days)</b> |
| Karbawang <i>et al.</i> ,<br>1994(Thailand)          | Q 600 mg (as sulfate salt)mg every 6 hours every 8 hours + T 250   | 33                                 | Q7T7                       |
|  | A 200 mg initially and then 100 mg every 12 hours (total dose 700 mg)  | 31                                 | A5                         |
| Kremsner <i>et al.</i> ,<br>1988(Brazil)             | Q 15 mg sulfate salt/kg every 12 hours + C 10 mg/kg every 12 hours   | 40                                 | Q3C3                       |
|  | Q 15 mg sulfate salt/kg every 12 hours + SP 100/50 mg every 24 hours for 2 doses   | 30                                 | Q3SP2                      |
|  | AM 10 mg/kg initially and 7.5 mg/kg 24 and 48 hours later  | 25                                 | AM2                        |
| De Souza <i>et al.</i> ,<br>1985(Brazil)             | Q 600 mg (base) + three tablets of 25 mg sulfadoxine / 500 mg pyrimethamine as a single dose on Day 0, followed by Q 600 mg (base) every 8 hours for the next 2 days | 50                                 | Q3SP1                      |
| <b>TOTAL</b>   |  | <b>Quinine: 975<br/>Other: 324</b> |                            |

Q=quinine; T=tetracycline; C=clindamycin; D=doxycycline; A=artemisinin or artesunate; SP=sulfadoxine/pyrimethamine; AM=amodiaquine; CQ=chloroquine <sup>1</sup>Study from Western Africa includes an ineffective 3-day quinine monotherapy regimen commonly used in that area at that time.

<sup>2</sup>Primaquine treatment, aimed at stopping transmission of the sexual stage of *P. falciparum*, is not discussed in this ISE

<sup>3</sup>This study included both intravenous and oral artesunate and quinine dosing regimens using the same dose/duration. Efficacy parameters were grouped by medication, regardless of the route of administration.

**Medical Officer Comments:** *The quinine dosing in these studies was generally 10 mg (quinine sulfate salt) 3 times daily (or every 8 hours), or 600 mg (quinine base) 3 times daily, with the exception of Duarte, et al., 1996 (1 g quinine every 12 hours), Metzger, et al., 1995 (12 mg/kg quinine twice daily), and Kremsner, et al., 1988 (15 mg/kg quinine*

*twice daily). Two additional studies which evaluated quinine combinations were identified, Kremsner, et al., 1994, and Ramharter, et al. 2005, both randomized, active-controlled, open-label pediatric studies in Gabon, both of which provided useful information. In Kremsner, et al., 1994 quinine was dosed at 12 mg (base)/kg every 12 hours for 6 doses; while in Ramharter, et al., 2005, quinine was dosed at 15 mg/kg twice daily in combination with clindamycin, each for 3 days.*

**Summary of Randomized, Controlled Studies for Quinine Combination Therapy**

Parasitological cure rates (S), indicating initial parasite clearance and no recrudescence of parasitemia at 28-day follow-up, was the designated primary endpoint for this review. Cure rates are summarized in the following table, in addition to the endpoints of parasitologic and fever clearance times. Those studies comparing quinine monotherapy to quinine combination therapy were discussed above. Quinine combination regimens were compared to a wide variety of other antimalarial drug combinations, and cure rates were quite variable. In general, treatment failure in the evaluable population was due to RI resistance (i.e. low-level resistance) for quinine-containing regimens, with the exception of the study done in Bangladesh (Rahman, et al., 2001) in which 5/145 (3%) patients who received 3 days of quinine plus one day of sulfadoxine-pyrimethamine had RII, and 12/145 (8%) had RIII failure. Similarly in Kremsner, et al., (1988), 2/30 (7%) patients treated with 3 days of quinine plus 2 days of sulfadoxine-pyrimethamine had RII failure.

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**Table 19: Clinical and Parasitological Response in Studies of Quinine Combination Therapy for Uncomplicated *P. falciparum* Malaria (applicant's Table 13)**

| Study  | Treatment/<br>Duration<br>Code(s) (No.<br>Enrolled) | Clinical Response               |     |                                    |     | Parasitological Response: N/D (%) |                              |               |                 |        |                 |        |                 |
|--|---|---------------------------------|-----|------------------------------------|-----|-----------------------------------|------------------------------|---------------|-----------------|--------|-----------------|--------|-----------------|
|  |   | Fever Clearance<br>Time (Hours) |     | Parasite Clearance<br>Time (Hours) |     | S OR CURE                         |                              | RI            |                 | RII    |                 | RIII   |                 |
|  |   | Mean ± SD<br>[Range]            | N   | Mean ± SD<br>[Range]               | N   | ITT                               | EVAL                         | ITT           | EVAL            | ITT    | EVAL            | ITT    | EVAL            |
| <b>RANDOMIZED, DOUBLE-BLIND STUDIES (N=1)</b>              |   |                                 |     |                                    |     |                                   |                              |               |                 |        |                 |        |                 |
| Duarte <i>et al.</i> ,<br>1996(Brazil)                     |   | NR                              | --  | NR <sub>2</sub>                    | --  | 68/88<br>(77%)                    | --                           | 1/88<br>(1%)  | --              | 0 (0%) | --              | 0 (0%) | --              |
|  | A7T7 (88)   | NR                              | --  | NR <sub>2</sub>                    | --  | 70/88<br>(79%)                    | --                           | 2/88<br>(2%)  | --              | 0 (0%) | --              | 0 (0%) | --              |
| <b>RANDOMIZED, OPEN-LABEL STUDIES (N=11)</b>               |   |                                 |     |                                    |     |                                   |                              |               |                 |        |                 |        |                 |
| Pukrittayakam<br>ee <i>et al.</i> , 2004<br>(Thailand)*    |   | 63 ± NR [7 -<br>152]            | 30  | 80 ± 26<br>[NR]                    | 30  | 21/30<br>(70%)                    | 21/25<br>(84%)               | 4/30<br>(13%) | 4/25<br>(16%)   | 0 (0%) | 0 (0%)          | 0 (0%) | 0 (0%)          |
|  | Q7 (30)   | 33 ± NR [8 -<br>117]            | 30  | 81 ± 19<br>[NR]                    | 30  | 22/30<br>(73%)                    | 22/22<br>(100%)              | 0 (0%)        | 0 (0%)          | 0 (0%) | 0 (0%)          | 0 (0%) | 0 (0%)          |
|  | Q7T7 (30)   | 34 ± NR [7 -<br>180]            | 23  | 69 ± 19 [19]                       | 23  | 19/23<br>(83%)                    | 19/21<br>(90%)               | 2/23<br>(9%)  | 2/21<br>(9.5%)  | 0 (0%) | 0 (0%)          | 0 (0%) | 0 (0%)          |
| Rahman <i>et al.</i> ,<br>2001<br>(Bangladesh)*            |   | 33.9 ± 27.6<br>[NR]             | 49  | 54.5 ± 21.8<br>[NR]                | 49  | --                                | 40/49 <sub>3</sub><br>(82%)  | --            | 5/49<br>(10%)   | --     | 1/49<br>(2%)    | --     | 3/49<br>(6%)    |
|  | Q7 (NR <sub>8</sub> )                               | 35.1 ± 24.7<br>[NR]             | 145 | 56.4 ± 27.1<br>[NR]                | 145 | --                                | 96/145 <sub>3</sub><br>(66%) | --            | 32/145<br>(22%) | --     | 5/145<br>(3%)   | --     | 12/145<br>(8%)  |
|  | Q3SP1<br>(NR <sub>8</sub> )                         | 33.5 ± 29.0<br>[NR]             | 149 | 68.9 ± 35.5<br>[NR]                | 149 | --                                | 34/149 <sub>3</sub><br>(23%) | --            | 32/149<br>(21%) | --     | 24/149<br>(16%) | --     | 59/149<br>(40%) |
|  | CQ3 (NR <sub>8</sub> )                              | 25.5 ± 26.5<br>[NR]             | 70  | 57.1 ± 29.1<br>[NR]                | 70  | --                                | 51/70 <sub>3</sub><br>(73%)  | --            | 9/70<br>(13%)   | --     | 3/70<br>(4%)    | --     | 7/70<br>(10%)   |
|  | M1 (NR <sub>4</sub> )                               | 56 ± NR [4 -<br>152]            | 68  | 77 ± 25<br>[NR]                    | 68  | 46/68<br>(68%)                    | 46/53<br>(87%)               | 7/68<br>(10%) | 7/53<br>(13%)   | 0 (0%) | 0 (0%)          | 0 (0%) | 0 (0%)          |
| Pukrittayakam<br>ee <i>et al.</i> ,<br>2000*<br>(Thailand) |   | 47 ± NR [8 -<br>120]            | 68  | 79 ± 20<br>[NR]                    | 68  | 60/68<br>(88%)                    | 60/60<br>(100%)              | 0 (0%)        | 0 (0%)          | 0 (0%) | 0 (0%)          | 0 (0%) | 0 (0%)          |
|  | Q7 (68)   |                                 |     |                                    |     |                                   |                              |               |                 |        |                 |        |                 |
|  | Q7C7 (68)   |                                 |     |                                    |     |                                   |                              |               |                 |        |                 |        |                 |

| Study (Vietnam)*                          | Treatment/<br>Duration<br>Code <sub>6</sub> (No.<br>Enrolled) | Clinical Response               |    |                                    |    | Parasitological Response <sub>1</sub> /ND (%) |                           |              |             |           |           |           |           |           |           |           |           |           |           |  |  |
|---|---|---------------------------------|----|------------------------------------|----|---|---------------------------|--------------|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|--|--|
|   |   | Fever Clearance<br>Time (Hours) |    | Parasite Clearance<br>Time (Hours) |    | S O R C U R E                                 |                           |              |             | R I       |           |           |           | R I I     |           |           |           | R I I I   |           |  |  |
|   |   | Mean ± SD<br>[Range]            | N  | Mean ± SD<br>[Range]               | N  | ITT   | EVAL                      | ITT          | EVAL        | ITT       | EVAL      | ITT       | EVAL      | ITT       | EVAL      | ITT       | EVAL      | ITT       | EVAL      |  |  |
| De Vries <i>et al.</i> , 2000             | Q7T7 (68)   | 36 ± NR [8 - 117]               | 68 | 77 ± 23 [NR]                       | 68 | 47/68 (69%)                                   | 47/48 (98%)               | 1/68 (1%)    | 1/48 (2%)   | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
|   | Q7 (84)   | 47 ± NR [NR] <sub>7</sub>       | 79 | 62 ± NR [NR] <sub>7</sub>          | 79 | 56/84 (67%)                                   | 56/69 (81%)               | 11/84 (13%)  | 11/69 (16%) | 1/84 (1%) | 1/69 (1%) | 1/84 (1%) | 1/69 (1%) | 1/84 (1%) | 1/69 (1%) | 1/84 (1%) | 1/69 (1%) | 1/84 (1%) | 1/69 (1%) |  |  |
| Fungladda <i>et al.</i> , 1998 (Thailand) | A1Q3 (96)   | 41 ± NR [NR] <sub>10</sub>      | 92 | 41 ± NR [NR] <sub>10</sub>         | 92 | 46/96 (48%)                                   | 46/74 (62%)               | 28/96 (29%)  | 28/74 (38%) | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
|   | A1Q5 (88)   | 43 ± NR [NR] <sub>11</sub>      | 87 | 42 ± NR [NR] <sub>11</sub>         | 87 | 66/88 (75%)                                   | 66/78 (85%)               | 12/88 (14%)  | 12/74 (15%) | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
| Salcedo <i>et al.</i> , 1997 (Brazil)     | Q7T7 (60)   | NR                              | -- | NR                                 | -- | 41/60 (68%)                                   | 41/53 (77%) <sub>14</sub> | NR           | NR          | NR        | NR        | NR        | NR        | NR        | NR        | NR        | NR        | NR        | NR        |  |  |
|   | A5 (77)   | NR                              | -- | NR                                 | -- | 61/77 (79%)                                   | 61/61 (100%) <sub>4</sub> | NR           | NR          | NR        | NR        | NR        | NR        | NR        | NR        | NR        | NR        | NR        | NR        |  |  |
| De Alencar <i>et al.</i> , 1997 (Brazil)  | Q3T7 (14)   | 34.7 ± 17.3 [NR]                | NR | 65.2 ± 17.4 [NR]                   | NR | 12/14 (86%)                                   | NR <sub>15</sub> (81.8%)  | 1/14 (7%)    | --          | 0 (0%)    | --        | 0 (0%)    | 1/14 (7%) | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
|   | A5T7 (16)   | 20.2 ± 5.2 [NR]                 | NR | 37.3 ± 11.5 [NR]                   | NR | 15/16 (94%)                                   | NR <sub>15</sub> (88.8%)  | 1/16 (6%)    | --          | 0 (0%)    | --        | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
| Bich <i>et al.</i> , 1996 (Vietnam)*      | M1 (12)   | 32.4 ± 17.7 [NR]                | NR | 58.9 ± 16.7 [NR]                   | NR | 11/12 (92%)                                   | NR <sub>15</sub> (85.7%)  | 1/12 (8%)    | --          | 0 (0%)    | --        | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
|   | Q7T7 (NR)   | 28.5 ± 19.8 [NR]                | 56 | 64.5 ± 23.1 [NR]                   | 77 | NR  | 77/77 (100%)              | 0 (0%)       | 0 (0%)      | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
| Bunnag <i>et al.</i> , 1996               | A7P3 (NR)   | 18.8 ± 17.7 [NR]                | 63 | 56.1 ± 14.1 [NR]                   | 77 | NR  | 76/77 (99%)               | NR           | 1/77 (1%)   | NR        |  |  |
|   | Q7 (59)   | 41 ± 23 [0 - 112] <sub>9</sub>  | 55 | 66 ± 24 [24 - 128]                 | 55 | 36/59 (61%)                                   | 36/44 (82%)               | 7/59 (12%)   | 7/44 (16%)  | 1/59 (2%) | 1/44 (2%) | 1/59 (2%) | 1/44 (2%) | 1/59 (2%) | 1/44 (2%) | 1/59 (2%) | 1/44 (2%) | 1/59 (2%) | 1/44 (2%) |  |  |
| Bunnag <i>et al.</i> , 1996               | A1Q3 (45)   | 34 ± 19 [0 - 80] <sub>9</sub>   | 44 | 43 ± 14 [16 - 72]                  | 44 | 23/45 (51%)                                   | 23/32 (72%)               | 9/45 (20%)   | 9/32 (28%)  | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
|   | A1D3 (53)   | 31 ± 23 [0 - 120] <sub>9</sub>  | 49 | 41 ± 19 [16 - 136]                 | 49 | 13/53 (24%)                                   | 13/42 (31%)               | 26/53 (49%)  | 26/42 (62%) | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |
| Bunnag <i>et al.</i> , 1996               | Q5T7 (48)   | 75 ± NR [4 - 136]               | 48 | 88 ± NR [45 - 159]                 | 48 | 40/48 (83%)                                   | 40/46 (87%)               | 6/48 (12.5%) | 6/46 (13%)  | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    | 0 (0%)    |  |  |



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

|                                      | AM2 (29)   | NR               | -- | 82.7 ± NR<br>[NR] | 7  | 1/29 (3%)      | 1/25<br>(4%)    | 6/29<br>(21%) | 6/25<br>(24%) | 7/29<br>(24%) | 7/25<br>(28%) | 11/29<br>(38%) | 11/25<br>(44%) |
|--------------------------------------|------------|------------------|----|-------------------|----|----------------|-----------------|---------------|---------------|---------------|---------------|----------------|----------------|
| De Souza et<br>al., 1985<br>(Brazil) | Q3SP1 (50) | NR <sup>13</sup> | -- | NR <sup>13</sup>  | -- | 46/50<br>(92%) | 46/50<br>(92%)  | 4/50<br>(8%)  | 4/50<br>(8%)  | 0 (0%)        | 0 (0%)        | 0 (0%)         | 0 (0%)         |
|                                      | M1 (50)    | NR <sup>12</sup> | -- | NR <sup>12</sup>  | -- | 49/50<br>(98%) | 49/49<br>(100%) | 0 (0%)        | 0 (0%)        | 0 (0%)        | 0 (0%)        | 0 (0%)         | 0 (0%)         |

**Medical Officer Comments:** Moderate or high-level resistance to the short course of quinine plus sulfadoxine-pyrimethamine regimen is not unexpected, given the high prevalence of sulfa-pyrimethamine resistance worldwide, and short course of quinine, which may not be long enough to eradicate parasites. The high recrudescence rates in the study performed in Bangladesh (Rahman, et al., 2001) with all treatment regimens may reflect multi-drug parasite resistance, including quinine resistance in that region, although this hypothesis was not proven.

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These data are further summarized by geographical area in the table below. The study by Salcedo, et al. (1997) study is not included here because data from intravenous (IV) and oral treatment regimens were combined. In Brazil, the efficacy of quinine-containing regimens was similar to those with artesunate, and atovaquone-proguanil. In the Kremsner, et al., 1988 study, cure rates with quinine-clindamycin were higher than 3 days of quinine plus 2 days sulfadoxine-pyrimethamine or amodiaquine. Failures in the evaluable population in this study were mainly due to RI resistance, although for amodiaquine, a large proportion of the failures were RII or RIII. In the De Souza, et al., (1985) study, 3 days of quinine plus single dose sulfadoxine-pyrimethamine cure rates were similar to single dose mefloquine.

**Table 20: Cure Rates (28 days) for Quinine Combination Therapy and Antimalarial Drug Comparators (South American studies)**

| Study                    | Geographical Location | Antimalarial Treatment Regimen | Cure Rate in Evaluable Population n/N (%) |
|--------------------------|-----------------------|--------------------------------|---|
| Duarte, et al., 1996     | Brazil                | Q3T7*                          | 68/88 (77) (ITT)                          |
|                          |                       | A7T7                           | 70/88 (79) (ITT)                          |
| De Alencar, et al., 1997 | Brazil                | Q7T7                           | 77/77 (100)                               |
|                          |                       | AT3P3                          | 76/77 (99)                                |
| Kremsner, et al., 1988   | Brazil                | Q3C3                           | 36/40 (90)                                |
|                          |                       | Q3SP2                          | 9/30 (30%)                                |
|                          |                       | AM2                            | 1/25 (4%)                                 |
| De Souza, et al., 1985   | Brazil                | Q3SP1                          | 46/50 (92)                                |
|                          |                       | M1                             | 49/49 (100)                               |

Q= quinine; T= tetracycline; A= artesunate or artemisinin; SP= sulfadoxine-pyrimethamine; M=mefloquine; AM= amodiaquine; AT= atovaquone; P= proguanil

\*e.g. Q3T7= 3 days of quinine plus 7 days tetracycline

***Medical Officer Comments:** Overall, the highest cure rates in Brazil were with a 7 day quinine plus tetracycline regimen, atovaquone-proguanil, or mefloquine. However, cross-study comparisons are not always valid given differences in study design and populations. Additionally, this review is not intended to determine optimal antimalarial therapy for a given geographical region.*

In the studies from Southeast Asia, the Fungladda, et al. (1998) study was not included in the following table because cure rates were not determined at 28 days. Additionally, De Vries, et al., (2000) was not included because it was a continuation of the Bich, et al., 1996 study. Comparison cure rates with a number of different combination antimalarial therapies are shown in the table below for Southeast Asian studies.

**Table 21: Cure Rates (28 days) for Quinine Combination Therapy and Antimalarial Drug Comparators (Southeast Asian studies)**

| Study                          | Geographical Location | Antimalarial Treatment Regimen | Cure Rate in Evaluable Population n/N (%) |
|--------------------------------|-----------------------|--------------------------------|---|
| Pukrittayakamee, et al., 2004  | Thailand              | Q7                             | 21/25 (84)                                |
|                                |                       | Q7T7                           | 22/22 (100)                               |
|                                |                       | A7                             | 19/21 (90)                                |
| Pukritatayakamee, et al., 2000 | Thailand              | Q7                             | 46/53 (87)                                |
|                                |                       | Q7C7                           | 60/60 (100)                               |
|                                |                       | Q7T7                           | 47/48 (98)                                |
| Bich, et al., 1996             | Vietnam               | Q7                             | 36/44 (82)                                |
|                                |                       | A1Q3                           | 23/32 (72)                                |
|                                |                       | A1D3                           | 13/42 (31)                                |
| Bunnag, et al., 1996           | Thailand              | Q5T7                           | 40/46 (87)                                |
|                                |                       | Q7T7                           | 40/40 (100)                               |
| Vaninjanonta, et al., 1996     | Thailand              | Q7T7                           | 17/18 (94)                                |
|                                |                       | Q7CQ3                          | 11/18 (61)                                |
| Looareesuwan, et al., 1994     | Thailand              | Q7T7                           | 45/46 (98)                                |
|                                |                       | M1T7                           | 44/47 (94)                                |
| Karbwan, et al., 1994          | Thailand              | Q7T7                           | 30/30 (100)                               |
|                                |                       | A5                             | 29/30 (97)                                |

Q= quinine; T= tetracycline; A= artesunate or artemisinin; SP= sulfadoxine-pyrimethamine; M=mefloquine; AM= amodiaquine; AT= atovaquone; P= proguanil; CQ= chloroquine

*Medical Officer Comments: As discussed previously, the quinine plus tetracycline 7 day combination consistently had higher cure rates than 7 day quinine monotherapy in Southeast Asia. Regimens with the lowest efficacy in this region were A1Q3 and A1D3 (Bich, et al., 1996), and Q7CQ3 (Vaninjanonta, et al., 1996). Regarding the latter regimen, it is not clear why treatment with the quinine-chloroquine had lower cure rates than what would be expected with quinine alone (82-87% in other studies). One in vitro data however, suggested that there may be either antagonism or additive activity with chloroquine and quinine against strains of P. falciparum (Rahman, 1997). The prevalence of chloroquine resistance is so high in this region, that it would be unlikely that chloroquine would have significant antimalarial activity in this region.*

Most of the studies with quinine combination therapy in Africa were with short course regimens. As previously discussed, the short courses of quinine combination therapy resulted in higher cure rates than for short course of quinine alone. In only one of these studies (Ramharther, et al., 2005) was another antimalarial combination compared to a quinine combination. The combination of artesunate plus clindamycin was similar with regards to efficacy to quinine plus clindamycin.

**Table 22: Cure Rates (28 days) for Quinine Combination Therapy and Antimalarial Drug Comparators (African studies)**

| Study                                     | Geographical Location | Antimalarial Treatment Regimen | Cure Rate in Evaluable Population n/N (%) |
|---|-----------------------|--------------------------------|---|
| Metzger, et al., 1995                     | Gabon                 | Q1.5                           | 14/37 (38)                                |
|   |                       | Q1.5C3                         | 33/36 (92)                                |
|   |                       | Q1.5 D3                        | 32/35 (91)                                |
| Kremsner, et al., 1994 (pediatric study)  | Gabon                 | Q3                             | 10/31 (32)                                |
|   |                       | Q3C3                           | 30/34 (88)                                |
| Ramharter, et al., 2005 (pediatric study) | Gabon                 | QC3                            | 45/48 (94)                                |
|   |                       | AC3                            | 40/46 (87)                                |

*Medical Officer Comments: Cure rates for short course quinine combinations were comparable to that observed in Mueller, et al., 2004 with quinine alone for 7 days (86% cure in evaluable population). Short courses of quinine alone (1.5 and 3 days) resulted in high failure rates. The combination of artesunate-clindamycin was similar to quinine-clindamycin in the study by Ramharter, et al., 2005.*

**Fever clearance Time**

Mean fever clearance times ranged from 30 to 64 hours in the treatment arms which received quinine combination therapy and in which means, rather than median hours were determined. Fever clearance time was similar in treatment arms which received quinine monotherapy, in which mean fever clearance times ranged from 34-60 hours in those studies where means were determined.

*Medical Officer Comments: The wide range in mean fever clearance times between studies may have been related to acetaminophen use in some of the studies. There was no apparent difference in mean fever clearance time in groups who received quinine mono- or combination therapy.*

**Parasite Clearance Time**

For quinine combination therapy (excluding artemisinin-based combinations), mean parasite clearance times ranged from 56-90 hours; while for quinine monotherapy, the mean parasite clearance time ranged from 54 to 80 hours. For artemisinin-based combination regimens, mean parasite clearance times ranged from 37 to 43 hours.

*Medical Officer Comments: Artemisinin and derivatives are generally considered faster acting antimalarial agents than quinine and others with regards to parasite killing. None of these agents are currently licensed for use in the U.S.*

### **Efficacy of Quinine Combination Therapy by Age, Gender, and Race**

None of these studies described patient race or ethnic origin. Pediatric patients and patients over 65 were enrolled in a number of these studies. However, outcomes were not evaluated separately by age. Two studies of quinine combination therapy in pediatric patients were reviewed separately and included in the table below showing cure rates for quinine mono- vs. combination therapy (Kremsner, et al., 1994; Ramharter, et al., 2005). See individual study reviews in Appendix, section 10.1 for full details. In brief, Kremsner, et al. (1994) showed cure rates of 32% (10/31 evaluable patients) with a 3 day regimen of quinine monotherapy, and 88% (30/34 evaluable patients) for a 3 day course of quinine plus clindamycin. Ramharter, et al., (2005) demonstrated similar efficacy with 3 days of quinine plus clindamycin, 45/48 (94%) cure, and 40/46 (87%) cure with a 3-day course of artesunate-clindamycin. Both of these studies were performed in Gabonese children.

*Medical Officer Comments: Cure rates in these pediatric patients with short-course quinine combination regimens (88-94%) in Gabon were somewhat lower than cure rates observed with 7-day courses of quinine combination therapy in Thai adults (94-100%). One would expect higher cure rates in children who receive longer courses of quinine monotherapy or combination therapy, but no study results are currently available. The very low cure rate (32%) with a short course (3 days) of quinine monotherapy observed in Kremsner, et al. (1994), is similar to that observed with a 3 dose regimen of oral quinine (12 mg/kg twice daily) in adults in the Democratic Republic of Congo (38%, 14/37) in the study by Metzger, et al (1995).*

### **Efficacy of Quinine Combination Therapy in Pregnant Women**

A randomized, controlled study performed in Thailand was found in the published literature, which compared a 7 day course of oral quinine sulfate plus clindamycin (N=65) to a 7 day course of oral artesunate (N=64) in pregnant women (second or third trimester) with uncomplicated *P. falciparum* malaria (McGready, et al., 2001). In this study, cure rates by survival analysis (not further defined) were 100% in the evaluable population at follow-up (day 42 after treatment initiation) for both treatment regimens. The authors noted however, that PCR-confirmed recrudescence was seen in 1 patient treated with artesunate; and no recrudescence was reported in patients treated with quinine.

*Medical Officer Comments: Although the results of this study are promising regarding the use of the quinine-clindamycin regimen in pregnancy, further randomized, controlled studies to determine efficacy of quinine mono- or combination therapy in pregnant women are needed.*

### **Summary of Efficacy of Quinine Monotherapy and Combination Therapy by Geographic Location**

For studies which evaluated the 7 day regimen of quinine alone, cure rates at 28 days ranged from 82-87% in Asia, Southeast Asia and Africa, 100% in Brazil (one study), and 84-87% in Thailand, as shown in the following table. The Thai study showing cure rates of 95% was performed in 1972, and because of increasing quinine resistance in Thailand, those results may not reflect what would occur with quinine monotherapy today. Therefore, that study was not

included in the range of cure rates noted above. The cure rates in evaluable population were higher than in the ITT populations (data not shown) because patients lost to follow-up were considered failures). Shorter courses of quinine monotherapy resulted in unacceptable cure rates (Metzger, et al, 1995; and Kremsner, et al, 1994 in a pediatric study in Gabon). In Thailand, cure rates with 7-day regimens of quinine plus tetracycline resulted in 28-day cure rates of 94-100%, and in one study (Pukrittayakamee, et al., 2000) the combination of quinine plus clindamycin for 7 days resulted in 100% cure. With one exception, only shorter course quinine combination regimens were studied in South America and Africa. De Alencar, et al., 1997 evaluated a 7 day regimen of quinine plus tetracycline in Brazil, with resulting cure rates of 100% in the evaluable population. Duarte, et al., 1996 evaluated a 3 day course of quinine plus tetracycline in Brazil, with cure rates of 77% (68/88 patients) in the intent-to treat population (data from evaluable population was not provided). However, only 1/88 patients failed due to recrudescence (RI resistance), suggesting that the cure rate might have been higher if all patients had returned for follow-up. Three studies evaluated regimens with 3 days quinine plus clindamycin. Cure rates in evaluable populations were 90% (Kremsner, et al., 1988) in Brazil, 94% (Ramharter, et al., 2005) in Gabonese children, and 88% (Kremsner, et al., 1994) in Gabonese children. In the latter study, short-course quinine monotherapy (3 days) was compared to the 3-day quinine plus clindamycin combination, and cure rates were significantly higher in the latter (88% for combination vs. 32% for monotherapy). In the study by Metzger, et al., (1995), in which only 3 doses of quinine (12 mg/kg twice daily) were used, combination of quinine with 3 days of clindamycin or doxycycline significantly improved cure rates (38% for quinine monotherapy; 92% for quinine plus clindamycin; 91 for quinine plus doxycycline). These studies are summarized in the following table.

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**Table 23: Summary of Efficacy for Quinine Mono or Combination Therapy In Randomized, Controlled Studies #**

| Study                               | Location   | Dates     | Quinine Monotherapy (duration) | Efficacy* quinine monotherapy n/N (% cure) | Quinine Combination (duration) | Efficacy* of quinine combination n/N (% cure ) |
|-------------------------------------|------------|-----------|--------------------------------|--|--------------------------------|--|
| Pukrittayakamee, et al 2004         | Thailand   | --        | Q7                             | 21/25 (84)                                 | QT7                            | 21/22 (100)                                    |
| McGready, et al, 200                | Thailand   | 1995-1997 | Q7                             | 27/41 (67)**                               | --                             | --   |
| Pukrittayakamee, et al., 2000       | Thailand   | 1995-1997 | Q7                             | 46/53 (87)                                 | QT7                            | 47/48 (98)                                     |
|                                     |            |           |                                |  | QC7                            | 60/60 (100)                                    |
| Segal, et al 1974                   | Thailand   | 1972      | Q6                             | 21/22 (95)                                 | --                             | --   |
| Bunnag, et al., 1996                | Thailand   | 1990-1992 | --                             | --   | Q5T7                           | 40/46 (87)                                     |
|                                     |            |           | --                             | --   | Q7T7                           | 40/40 (100)                                    |
| Vaninjanonta, et al., 1996          | Thailand   | 1993-1994 | --                             | --   | Q7T7                           | 17/18 (94)                                     |
| Looaresuwan, et al., 1994           | Thailand   | 1991      | --                             | --   | QT7                            | 45/46 (98)                                     |
| Karbwang, et al., 1988              | Thailand   | --        | --                             | --   | QT7                            | 30/30 (100)                                    |
| De Vries, et al., 2000              | Vietnam    | --        | Q7                             | 56/69 (81)                                 | --                             | --   |
| Bich, et al., 1996                  | Vietnam    | 1993-     | Q7                             | 36/44 (82)                                 | --                             | --   |
|                                     |            |           |                                |  |                                |  |
| Ache, et al., 2002                  | Venezuela  | 1999-2000 | Q7                             | 48/48 (100)                                | --                             | --   |
| Duarte, et al., 1996                | Brazil     | 1992-1993 | --                             | --   | Q3T3                           | 68/88(77) (ITT)                                |
| De Alencar, et al., 1997            | Brazil     | 1995-1996 | --                             | --   | QT7                            | 77/77 (100)                                    |
| Kremsner, et al., 1988              | Brazil     | 1987      | --                             | --   | Q3SP2                          | 9/30 (30)                                      |
|                                     |            |           | --                             | --   | Q3C3                           | 36/40 (90)                                     |
| De Souza, et al., 1985              | Brazil     | --        | --                             | --   | Q3SP1                          | 46/50 (92)                                     |
|                                     |            |           |                                |  |                                |  |
| Mueller, et al., 2004               | Congo      | 2001      | Q7                             | 31/36 (86)                                 | --                             | --   |
| Metzger, et al., 1995               | Gabon      | 1993-1994 | Q1.5                           | 14/37 (38)                                 | Q1.5C3                         | 33/36 (92)                                     |
|                                     |            |           |                                |  | Q1.5 D3                        | 32/35 (91)                                     |
| Ramharter, et al., 2005 (pediatric) | Gabon      | 2003-2004 | --                             | --   | QC3                            | 45/48 (94)                                     |
| Kremsner, et al., 1994 (pediatric)  | Gabon      | 1992      | Q3                             | 10/31 (32)                                 | Q3C3                           | 30/34 (88)                                     |
|                                     |            |           |                                |  |                                |  |
| Rahman, et al., 2001                | Bangladesh | 1996-1997 | Q7                             | 40/49 (82) (ITT)                           | Q3SP1                          | 96/145 (66) (ITT)                              |

\*efficacy = 28 day cure rate in evaluable population

\*\* 63-day cure rate

# Note that comparator antimalarial agents, except for quinine in combination with an antimicrobial agent, were not included in this table for simplification.

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

**Medical Officer Comments:** *Except for one study in Brazil which reported 100% cure rates with 7-days quinine monotherapy (Ache, et al., 2002), combination of quinine with an antimicrobial agent (tetracycline or clindamycin) for 7 days resulted in higher cure rates than for monotherapy. Additionally, 7 days of quinine monotherapy resulted in higher cure rates than 3 days of quinine monotherapy; however, many patients, particularly in the outpatient setting, might not be expected to complete 7 days because of quinine intolerance due to cinchonism. Some studies suggest that a shorter course (3 days) of quinine given in combination with clindamycin is preferable to 3 days quinine monotherapy. However, these data are limited. The CDC recommends 3-day quinine combination regimens (with doxycycline, tetracycline, or clindamycin) for treatment of uncomplicated, chloroquine-resistant *P. falciparum* malaria in geographical regions other than Southeast Asia (CDC 2004 Guidelines for the Treatment of Malaria in the U.S.);*

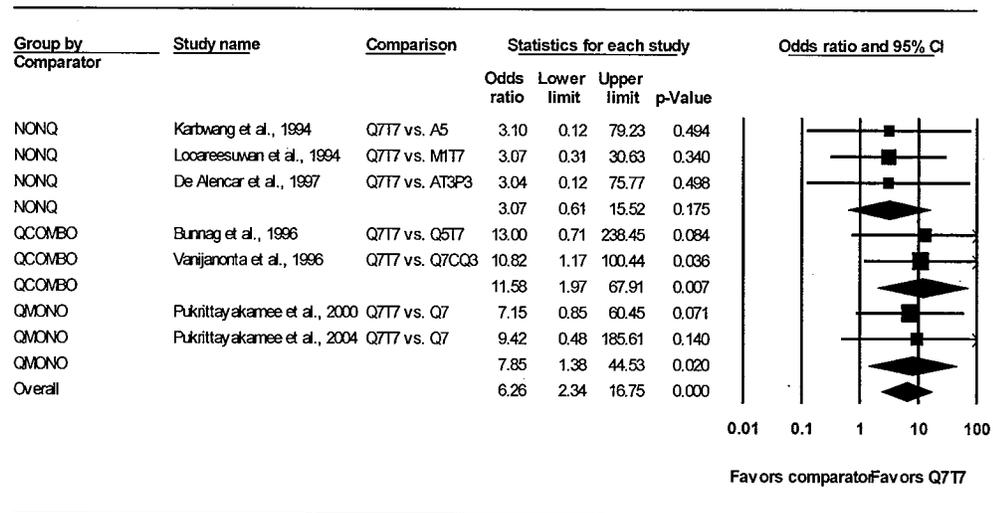
*Additionally, only one randomized controlled study evaluated the combination of quinine plus doxycycline, and although cure rates were improved with the combination over quinine alone, the quinine dosing regimen was not standard (12 mg/kg twice daily for 3 doses), and cannot be used in direct support of efficacy for this NDA. Theoretically, doxycycline, a tetracycline derivative which can be dosed twice daily, rather than 4 times daily, could be substituted for tetracycline, as recommended by the CDC and other treatment guidelines. However, that remains to be proven in a randomized, controlled trial.*

#### **Statistical Analysis: Quinine Combination Therapy**

See Ms. LaRee Tracy's review for full details of meta-analysis which was performed to analyze overall treatment effect. In brief, 7 studies which evaluated quinine combination therapy were used in this analysis, including Bunnag et al., 1996; de Alencar, et al., 1997; Karbwang et al., 1994; Looareesuwan et al., 1994; Pukrittayakamee, et al., 2004; Pukrittayakamee et al., 2000 and Vanijanonta et al., 1996). Studies were chosen based on similar study design, and dose and duration of quinine combination therapy. These studies all evaluated a 7 day regimen of quinine in combination with tetracycline (Q7T7) and measured outcome at 28 days. Across studies, a total of 861 patients were randomized, and 325 received a Q7T7 regimen. Cure rates ranged from 94 to 100% in the evaluable population and between 68 and 100% in the ITT population. Using a fixed-effects model, the overall estimated effect size was 6.26 (odds ratio) favoring the Q7T7 regimen versus all comparators. The 95% CI [2.34, 16.75] and p-value= 0.0003 showed statistical significance. The fixed-effect model for studies having a non-quinine comparator showed an odds ratio of 3.07, 95% CI [0.61, 15.5], p-value=0.18, i.e. no significant difference between treatment groups. Between studies having a quinine combination comparator, the fixed effect was 11.6 (odds ratio), 95% CI [1.97, 67.9], p-value= 0.007, favoring quinine combination therapy. Between the two studies which compared quinine combination and quinine

monotherapy (7 days), the estimated fixed effect was 7.85 (odds ratio), 95% CI [1.38, 44.52], p-value=0.020, favoring the quinine combination therapy. This analysis is shown in the figure below.

**Figure 6. Meta-Analysis of Quinine plus Tetracycline (7 day therapy) Studies in Evaluable Populations Sub-Grouped by Comparator Type (Analysis by Statistical Reviewer)**



**Medical Officer Comments:** The overall odds ratio of 6.26 in favor of the quinine plus tetracycline (7 day) combination therapy, favor the Q7T7 regimen in comparison to a number of different comparators. When sub-group analysis was performed the Q7T7 regimen was favored over quinine monotherapy, and over other 2 other quinine combination regimens (Q5T7 and Q7CA3), but not over the non-quinine comparators (A5, MIT7 and AT3P3). This meta-analysis, although useful in comparing treatment regimens, only represents an estimate of treatment effect and should be interpreted with caution, particularly for the sub-group analyses, as further discussed by the Statistical Reviewer. It is also notable that all 7 of these studies were conducted in Thailand, except for the study by De Alencar, et al., 1997, which was performed in Brazil. Thus, we cannot draw definitive conclusions regarding the superiority of quinine combination therapy to other antimalarial agents or to quinine monotherapy.

**Efficacy of Quinine Combination Therapy in Treatment of Returned Travelers**

Two randomized, controlled studies were identified which address the issue of malaria treatment in returned travelers. In an open-label study by Mateelli. et al. (2005), a regimen of quinine (3

days) plus a single dose of sulfadoxine-pyrimethamine was compared to mefloquine (25 mg/kg in 3 doses) for treatment of uncomplicated *P. falciparum* malaria in returned travelers in Italy from 1999 to 2003. Most patients acquired malaria in western Africa (Senegal, Ghana, and Nigeria), and the majority of patients were foreign-born, but had resided in non-endemic areas for at least 5 years prior to the study. The primary endpoint was early cure rate, defined as clinical and parasitological cure prior to hospital discharge. Rate of recrudescence at 28 days was a secondary endpoint. Outcomes are shown in the following table.

**Table 24: Outcome Measures in Study of Malaria in Returned Travelers (Mateelli, et al., 2005)**

| Outcome Measures                                      | Quinine (3 days) + SP (single dose)<br>N=94 | Mefloquine<br>N=93 |
|---|---|--------------------|
| Cure at end of treatment (evaluable population)       | 91/91* (100%)                               | 92/92* (100%)      |
| Cure at end of treatment (intent-to-treat population) | 91/94 (96.8%)                               | 92/93 (96.8%)      |
| Cured at day 28 (evaluable population)                | 67/67** (100%)                              | 68/68** (100%)     |
| Cured at day 28 (ITT population)                      | 67/94 (71.3%)                               | 68/93 (73.1%)      |

SP= sulfadoxine-pyrimethamine

\*Denominator is the number of patients who completed treatment. One patient in the mefloquine group developed persistent severe vomiting; while 3 patients in the quinine+ SP group treatment was discontinued prematurely due to persistent vomiting (1 patient), disease progression (1 patient), and pancreatitis, acute respiratory distress syndrome, and ECG changes in 1 patient.

\*\*Denominator is the number of patients who completed follow-up at 28 days.

*Medical Officer Comments: Early cure rates (defined above) and 28-day cure rates were similar in both treatment groups in this study. Because most of these patients were actually foreign-born individuals who had returned home to visit relatives or friends, they may have had some residual immunity, and these results may not apply to non-immune individuals. Sulfadoxine-pyrimethamine resistance is now widespread in Africa, and combination with quinine would not be expected to provide additional antimalarial activity.*

The second study of malaria treatment in returned travelers (Parola, et al., 2001), was a randomized, double-blinded, active-controlled study in which 115 patients were randomized to either quinine for 7 days, or quinine plus clindamycin for 3 days, conducted from 1996 to 1998 in France. In both treatment arms, patients received intravenous quinine for 3 days. Most patients had returned to France from travel in sub-Saharan Africa, or the Comoro islands. In the quinine monotherapy arm, patients received an additional 4 days of oral quinine; and in the combination therapy arm, patients received 3 days of intravenous clindamycin in addition to 3 days of intravenous quinine. An adequate clinical response (negative parasitemia and fever at day 28)

was observed in 96% of 54 evaluable patients who received 7-days quinine monotherapy, and 100 % of 51 evaluable patients who received 3 days intravenous quinine and clindamycin.

*Medical Officer Comments: Although adequate clinical response was similar for the two treatment groups in this study, these data cannot be compared directly to oral quinine regimens because of the use of intravenous quinine in all or part of the dosing period.*

### **Efficacy of Parenteral Quinine for Severe Malaria**

In support of this NDA for oral quinine for treatment of uncomplicated *P. falciparum* malaria, the applicant submitted a number of studies which evaluated parenteral (intravenous or intramuscular) quinine for treatment of severe *P. falciparum* malaria, including cerebral malaria. Although these studies are not directly applicable to this application because of the differences in dosing regimens, including use of a loading dose of quinine, as well as difference in route of administration, efficacy in the most severe cases of malaria would be supportive, and the safety information in these studies may be useful for comparison. The primary endpoint in most of the studies of severe malaria was survival. Unlike uncomplicated *P. falciparum*, where mortality is low, mortality rates in severe falciparum malaria may be 20-30% with appropriate treatment. These studies were all conducted in Southeast Asia or Africa; and many were pediatric studies. Intravenous quinine is not available or approved for use in this country. When parenteral therapy is required for severe malaria in the U.S., generally intravenous quinidine has been used, often in combination with an antimicrobial agent such as doxycycline.

### **Dosing and Duration**

In the majority of these studies parenteral quinine (IV or IM) a loading dose of 20 mg/kg quinine was given, followed by 10 mg/kg every 8 hours. In most of the studies, IV quinine was switched to oral quinine, when oral medication was tolerated.

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**Table 25: Dosing and Duration of Exposure to Quinine in Published, Randomized, Controlled Trials of Quinine for Treatment of Severe *P. falciparum* Malaria (Applicant's Table 8, ISE)**

| Author, year (Country)                        | Quinine Dosage Regimen   | Route (Duration [Days])                     | No. Patients Randomized |
|---|--|---|-------------------------|
| <b>RANDOMIZED, DOUBLE-BLIND STUDIES</b>       |  |   |                         |
| <b>INTRAVENOUS QUININE</b>                    |  |   |                         |
| <u>Singh et al., 2002</u><br>(India)          | IV loading dose: None<br>IV dose: 10 mg/kg every 8 hours <sup>b</sup><br>Oral maintenance dose: None                                     | IV<br>(7)                                   | 26                      |
| <b>INTRAMUSCULAR QUININE</b>                  |  |   |                         |
| <u>Tran et al., 1996</u><br>(Vietnam)         | IM loading dose: 20 mg salt/kg<br>IM maintenance dose: 10 mg salt/kg every 8 hours<br>Oral maintenance dose: 10 mg salt/kg every 8 hours | IM <sup>b</sup> /ORAL <sup>a,c</sup><br>(7) | 276                     |
| <b>RANDOMIZED, OPEN-LABEL STUDIES</b>         |  |   |                         |
| <b>INTRAVENOUS QUININE</b>                    |  |   |                         |
| <u>Karbwang et al., 2003</u><br>(Thailand)    | IV loading dose: 20 mg salt/kg<br>IV maintenance dose: 10 mg salt/kg every 8 hours<br>Oral maintenance dose: 10 mg/kg every 8 hours      | IV <sup>b</sup> /ORAL <sup>a</sup><br>(7)   | 54                      |
| <u>Satti et al., 2002</u><br>(Sudan)          | IV loading dose: None<br>IV dose: 10 mg/kg every 8 hours<br>Oral maintenance dose: 10 mg/kg every 8 hours                                | IV/ORAL<br>(7)                              | 39                      |
| <u>Adam et al., 2002</u><br>(Sudan)           | IV loading dose: 20 mg salt/kg<br>IV maintenance dose: 10 mg salt/kg<br>Oral maintenance dose: 10 mg/kg                                  | IV <sup>b</sup> /ORAL<br>(7)                | 21                      |
| <u>Eriz et al., 2001</u><br>(Bangladesh)      | IV loading dose: 20 mg salt/kg<br>IV maintenance dose: 10 mg salt/kg every 8 hours<br>Oral maintenance dose: 10 mg salt/kg every 8 hours | IV/ORAL<br>(7)                              | 54                      |
| <u>Tombo et al., 2000</u><br>(Zambia)         | IV loading dose: 20 mg salt/kg<br>IV maintenance dose: 10 mg salt/kg every 8 hours<br>Oral maintenance dose: 10 mg salt/kg every 8 hours | IV/ORAL<br>(7)                              | 44                      |
| <u>Moyou-Semse et al., 2001</u><br>(Cameroon) | IV loading dose: 20 mg salt/kg<br>IV maintenance dose: 10 mg salt/kg every 8 hours<br>Oral maintenance dose: 10 mg salt/kg every 8 hours | IV <sup>b</sup> /ORAL<br>(7)                | 51                      |
| <u>Taylor et al., 1998</u><br>(Malawi)        | IV loading dose: 20 mg salt/kg<br>IV maintenance dose: 10 mg salt/kg every 8 hours<br>Oral maintenance dose: 10 mg salt/kg every 8 hours | IV <sup>b</sup> /ORAL <sup>a</sup><br>(7)   | 88                      |

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**Summary of Efficacy of Parenteral Quinine in Randomized, Controlled Trials**

Overall, survival rates across all studies with parenteral quinine ranged from 58-95%, with the lowest survival rates reported in Thailand (Karbwang, et al., 1992 and 1995), and the highest in children in Sudan (Adam et al., 2002, and Satti, et al., 2002). Artemisinin derivatives were the comparators in each of these studies. Survival rates reported in the artemisinin treatment arms ranged from 82 to 100%. A summary of efficacy provided by the applicant is shown in the following table. In general coma recovery times were similar for quinine and non-quinine treatment arms within studies; and parasite clearance time was generally shorter in artemisinin than quinine treatment groups.

**Table 26: Clinical Response to Parenteral Quinine Therapy for Treatment of Severe Malaria (applicant's Table 9, ISE)**

| Study  | Treatment/<br>Duration Code (No.<br>Randomized) | Survival Rate<br>n/N (%) | Coma Recovery Time<br>(hours)<br>Mean or Median<br>± SD [Range] | Fever Clearance<br>Time (hours)   |     | Parasite Clearance<br>Time (hours) |     | N   |
|--|---|--------------------------|---|-----------------------------------|-----|------------------------------------|-----|-----|
|  |   |                          |   | Mean or<br>Median ± SD<br>[Range] | N   | Mean or<br>Median ±<br>SD [Range]  | N   |     |
| <b>RANDOMIZED, DOUBLE-BLIND STUDIES</b>      |   |                          |   |                                   |     |                                    |     |     |
| <b>INTRAVENOUS QUININE (N=1)</b>             |   |                          |   |                                   |     |                                    |     |     |
| Singh <i>et al.</i> , 2000<br>(India)        | Q7 (26)   | 22/26 (84%)              | 72 ± NR [NR]  | 78 ± NR<br>[NR]                   | 22  | 96 ± NR<br>[NR]                    | 22  | 22  |
|  | A5 (26)   | 24/26 (92%)              | 60 ± NR [NR]  | 84 ± NR<br>[NR]                   | 24  | 72 ± NR<br>[NR]                    | 24  | 24  |
| <b>INTRAMUSCULAR QUININE (N=1)</b>           |   |                          |   |                                   |     |                                    |     |     |
| Tran <i>et al.</i> , 1996<br>(Vietnam)       | Q7SP (276)                                      | 229/276 (83%)            | 48 ± NR [0 – 768]   | 90 ± NR [0 –<br>144]              | 276 | 90 ± NR [16<br>– 414]              | 276 | 276 |
|  | A3 (284)*                                       | 248/284 (87%)            | 66 ± NR [0 – 828]   | 127 ± NR [0<br>– 756]             | 284 | 72 ± NR [4<br>– 330]               | 284 | 284 |
| <b>RANDOMIZED, OPEN-LABEL STUDIES (N=11)</b> |   |                          |   |                                   |     |                                    |     |     |
| <b>INTRAVENOUS QUININE</b>                   |   |                          |   |                                   |     |                                    |     |     |
| Newton <i>et al.</i> , 2003<br>(Thailand)    | Q7 (54)   | 34/461 (74%)             | 18 ± NR [1 – 188]   | 65 ± NR [12.<br>– 383]            | 54  | 76 ± NR<br>[70.2 –<br>81.8]        | NR  | NR  |
|  | A7 (59)   | 48/541 (89%)**           | 17 ± NR [1 – 125]   | 41 ± NR [3 –<br>138]              | 59  | 62.5 ± NR<br>[53.4 –<br>71.8]      | NR  | NR  |
| Satti <i>et al.</i> , 2002<br>(Sudan)        | Q7 (39)   | 37/39 (95%)              | 26 ± 15 [NR]  | 36 ± 18 [NR]                      | 26  | 41 ± 12<br>[NR]                    | 26  | 26  |
|  | A4 (38)   | 35/38 (92%)              | 21 ± 11 [NR]  | 31 ± 13 [NR]                      | 29  | 36 ± 18<br>[NR]                    | 29  | 29  |
| Adam <i>et al.</i> , 2002<br>(Sudan)         | Q7 (21)   | 20/21 (95%)              | 20 ± 16.9 [NR]  | 18 ± 8.1<br>[NR]                  | 20  | 22.4 ± 11.5<br>[NR]                | 20  | 20  |
|  | A5 (20)   | 20/20 (100%)             | 12.5 ± 5.2 [NR]   | 30 ± 21 [NR]                      | 20  | 16 ± 9.2<br>[NR]                   | 20  | 20  |

| Study   | Treatment/<br>Duration Code (No.<br>Randomized) | Survival Rate<br>n/N (%) | Coma Recovery Time<br>(hours)  |    | Fever Clearance<br>Time (hours)   |    | Parasite Clearance Time<br>(hours) |    |
|---|---|--------------------------|--------------------------------|----|-----------------------------------|----|------------------------------------|----|
|   |   |                          | Mean or Median<br>± SD [Range] | N  | Mean or<br>Median ± SD<br>[Range] | N  | Mean or<br>Median ±<br>SD [Range]  | N  |
| Faiz <i>et al.</i> , 2001<br>(Bangladesh)     | Q7 (54)   | 44/54 (81%)              | 53.4 ± 36 [NR]                 | 54 | 47 ± 31.5<br>[NR]                 | 54 | 60.7 ± 39<br>[NR]                  | 54 |
|   | A5 (51)   | 42/51 (82%)              | 74.2 ± 51.8 [NR]               | 51 | 58 ± 15.6<br>[NR]                 | 51 | 52.1 ± 33.3<br>[NR]                | 51 |
| Thuma <i>et al.</i> , 2000<br>(Zambia)        | Q7 (44)   | 35/44 (79%)              | 44 ± 44.9 [NR]                 | 35 | 33 ± 19.9<br>[NR]                 | 35 | 57 ± 24.1<br>[NR]                  | 34 |
|   | A5 (48)   | 38/48 (79%)†             | 61 ± 57.6 [NR]                 | 38 | 50 ± 48.6<br>[NR]                 | 36 | 53 ± 26.4<br>[NR]                  | 38 |
| Moyou-Somo <i>et al.</i> ,<br>2001 (Cameroon) | Q7(51)  | 37/51 (72%)              | 30.3 ± 28.9 [NR]               | 37 | 45.0 ± 26.7<br>[NR]               | 36 | 40.7 ± 18.9<br>[NR]                | 37 |
|   | A (51)  | 43/51 (84%)              | 34.8 ± 18.8 [NR]               | 43 | 42.2 ± 34.9<br>[NR]               | 39 | 46.3 ± 28.5<br>[NR]                | 43 |
| Taylor <i>et al.</i> , 1998<br>(Malawi)       | Q7 (88)   | 69/81 (85.2%)            | 20 ± NR [10 –<br>54]‡          | 69 | 45 ± NR [33<br>–60]‡              | 69 | 40 ± NR [32<br>–48]‡               | 69 |
|   | A3 (95)   | 72/83 (87%)              | 18 ± NR [8 – 30]‡              | 72 | 31 ± NR [24<br>–52]‡              | 72 | 32 ± NR [25<br>–36]‡               | 72 |
| Olumese <i>et al.</i> , 1999<br>(Nigeria)     | Q7 (49)   | 35/49 (71.4%)            | 42.4 ± 31.6 [NR]               | 49 | 51.3 ± 25.6<br>[NR]               | 49 | 42 ± 22.8<br>[NR]                  | 49 |
|   | A5 (54)   | 43/54 (79.6%)            | 35.1 ± 27.1 [NR]               | 54 | 44.6 ± 26.6<br>[NR]               | 54 | 44.5 ± 26.6<br>[NR]                | 54 |
| Murphy <i>et al.</i> , 1996<br>(Kenya)        | Q3(71)  | 63/71 (88.7%)            | 13 ± NR [2.8 –<br>96]‡         | NR | 32 ± NR [4 –<br>96]‡              | NR | 48 ± NR [37<br>–56]‡               | NR |
|   | A33(89)   | 71/89 (79.8%)            | 12 ± NR [2.8 –<br>96]‡         | NR | 32 ± NR [4 –<br>86]‡              | NR | 39.5 ± NR<br>[24 – 45]‡            | NR |
| Karbwanget <i>et al.</i> , 1995<br>(Thailand) | Q7 (52)   | 31/50 (62%)              | NR                             | -- | 84 ± NR [36<br>– 144]             | 50 | 78 ± NR<br>[18-168]                | 50 |
|   | A7 (50)   | 41/46 (89%)††            | NR                             | -- | 79 ± NR [16–<br>147]              | 47 | 54 ± NR [30<br>–164]               | 47 |
| Karbwanget <i>et al.</i> , 1992<br>(Thailand) | Q7 (12)   | 7/12 (58%)               | NR                             | -- | 94 ± 34.7<br>[NR]                 | 12 | 61.6 ± 12.6<br>[NR]                | 12 |

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|  | Coma Recovery Time (hours) | Fever Clearance Time (hours)   | Parasite Clearance Time (hours) |
|--|----------------------------|--------------------------------|---------------------------------|
|  |                            |                                |                                 |
| A7 (14)                                    | NR                         | 64 ± 27.8 [NR]                 | 63.3 ± 30 [NR]                  |
| <b>INTRAMUSCULAR QUININE (N=1)</b>         |                            |                                |                                 |
| Van Hensbroek <i>et al.</i> , 1996(Gambia) | 226/288 (78.5%)            | 20 ± NR [12 - 43]              | 288                             |
| Q5 (288)                                   | 229/288 (79.5%)            | 26 ± NR [15 - 48]              | 288                             |
| A4 (288)                                   |                            | 33 ± NR [12 - 60] <sup>2</sup> | 14 ± NR [7 - 21]                |
|  |                            | 30 ± NR [16 - 48] <sup>2</sup> | 9 ± NR [7 - 16]                 |

Q=quinine; A=artemether or artemotil •The difference in mortality rate between the two treatment groups was not significant (P=0.16, Chi square) (Tran *et al.*, 1996)\*\* The difference in mortality rate between the two treatment groups was not significant (P=0.22, Chi square) (Newton *et al.*, 2003)†Mortality in the intention to treat population was statistically different (P < 0.05, Mantel-Haenszel test); however, after making a number of

exclusions (e.g., patients who did not meet criteria for cerebral malaria and those with other primary diagnoses), there was no difference (NS, Mantel-Haenszel test) (Murphy *et al.*, 1996)††The difference in mortality rate between the two treatment groups was statistically significant (P=0.013, Chi square) (Karbwang *et al.*, 1995);†The difference in mortality rate between the two treatment groups was not significant (P=0.96) (Thuma *et al.*, 2000)††The difference in mortality rate between the two treatment groups was not significant (P=0.5, Chi square or Fisher's Exact tests) (Van Hensbroek *et*

*al.*, 1996)‡Only 46 of the 54 patients randomized to quinine and 54 of 59 randomized to artesunate were found to have severe malaria 2Interquartile range 3Duration not specified but dependent on recovery (until the child was able to drink and parasitemia had cleared)4Intention to treat population.

**Medical Officer Comments:** *In these studies, the efficacy of parenteral quinine for severe malaria as determined by survival rate, was generally similar to artemisinin-based therapy, with the exception of 2 studies in Thailand (Karbwang, et al., 1992; Karbwang, et al., 1995) in which survival rates were higher with the artemisinin than the quinine treatment regimens.*

Parasitological response was evaluated in 6 of these studies. Parasitological response is shown in the table below for comparison with studies of oral quinine.

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**Table 27: Parasitological Response to Parenteral Quinine Therapy for Severe Malaria (applicant's table 10, ISE, modified to show percentage of evaluable patients)**

| Study  | Treatment/<br>Duration<br>Code (No.<br>Randomized) | No. Patients with<br>Recurrent<br>Parasitemia During<br>28-Day Follow-up<br>n/N (%) | Comment   |
|--|--|---|---|
| Newton <i>et al.</i> ,<br>2003<br>(Thailand)     | Q7 (54)  | 1/42 (2.4)  | 42 patients followed until discharge<br>RI=1<br>According to the authors, this patient had RII treatment failure, described as clearance of parasitemia at 48 hours, but reappearance on Day 5 of treatment. However, this more accurately fits the WHO definition of RI. |
|  | A7 (59)  | 0   | --  |
| Adam <i>et al.</i> ,<br>2002 (Sudan)             | Q7 (21)  | 1/15 (6.7)  | 15 patients with 28-day follow-up<br>RI=1 (recrudescence confirmed by PCR genotyping)   |
|  | A5 (20)  | 0   | --  |
| Faiz <i>et al.</i> ,<br>2001<br>(Bangladesh)     | Q7 (54)  | 1/50 (2.0)  | 50 patients appear to have been assessed for 28 days<br>RI=1  |
|  | A7 (51)  | 4/40 (10)   | 40 patients appear to have been assessed for 28 days<br>RI=4  |
| Moyou-Somo<br><i>et al.</i> , 2001<br>(Cameroon) | Q7(51)   | 13/37 (35.1)  | 37 patients with 28-day follow-up<br>RI=8<br>RII=5  |
|  | A (51)   | 11/41 (26.8)  | 41 patients with 28-day follow-up<br>RI=10<br>RII=1   |
| Olumese <i>et al.</i> ,<br>1999(Nigeria)         | Q7 (49)  | 0   | --  |
|  | A5 (54)  | 1/NA  | RI=1 (recrudescence occurred on Day 14 with fever)  |
| Taylor <i>et al.</i> ,<br>1998(Malawi)           | Q7 (88)  | 5/NA  | RI=5 (interpreted as RI since parasitemia cleared initially in all patients)  |
|  | A3 (95)  | 1/NA  | RI =1 (interpreted as RI since parasitemia cleared initially in all patients)   |

NA= not available

**Medical Officer Comments:** Parasitological cure rate at 28 days in these studies ranged from 65-98% for parenteral quinine monotherapy, which is similar to that observed in the studies which evaluated oral quinine monotherapy.

### 6.1.5 Clinical Microbiology

See Dr. Kalavati Suvarna's Microbiology Review for full details. Four species of *Plasmodium* (*falciparum*, *vivax*, *ovale*, and *malariae*) cause malaria. However, *P. falciparum* causes the most morbidity and mortality worldwide, and is the focus of this NDA.

The exact mechanism of quinine's antimalarial activity is unknown. Quinine acts primarily on the blood schizont form of *P. falciparum*; while it has no gametocidal activity; and has little effect on sporozoites or pre-erythrocytic forms.

The *in vitro* determination of *P. falciparum* susceptibility to antimalarial agents has not been standardized, and has not been correlated directly with *in vivo* failure. However, *in vitro* drug susceptibility testing has been used as an epidemiological tool to track emerging patterns of drug resistance.

*P. falciparum* is clinically resistant to chloroquine in most malarious areas except for Central America north and west of the Panama Canal, the Dominican Republic and Haiti, and some parts of the Middle East. High-level sulfadoxine-pyrimethamine resistance has been documented in most areas of Southeast Asia and in many areas of South America, and Africa; while mefloquine resistance has been reported mainly in Southeast Asia, particularly at the Thai-Cambodian and Thai-Myanmar border, as well as in some isolated regions of South America. Clinical quinine resistance has been reported in some areas of South America, Southeast Asia, and Bangladesh.

### Efficacy Conclusions

1. In studies which evaluated 7 days of quinine monotherapy, cure rates at 28 days post-treatment initiation ranged from 82-87% in evaluable populations in Southeast Asia and Africa, to 100% in Brazil in one study. Quinine monotherapy for  $\leq 3$  days in two studies resulted in unacceptable cure rates (32-38%).
2. Treatment with quinine in combination with an antimicrobial agent such as tetracycline or clindamycin for 7 days resulted in cure rates of 94-100% in evaluable populations in Thailand, and 100% in one Brazilian study.
3. Treatment with shorter courses (generally 3 days) of quinine in combination with tetracycline, clindamycin, or doxycycline resulted in cure rates ranged from 88-92% in evaluable populations in Brazil and Africa. No studies directly compared short-course (3-day) to 7-day quinine combination therapy.

**Medical Officer Comments:** *These studies support the use of oral quinine sulfate for the treatment of chloroquine-resistant uncomplicated P. falciparum malaria. The Clinical Studies section of the proposed label summarizes the efficacy of quinine monotherapy and combination therapy.*

## 7 INTEGRATED REVIEW OF SAFETY

Safety data for this NDA were obtained from the 2 pharmacokinetic studies sponsored by the applicant, including electrocardiographic data. Additionally, safety data were obtained from the randomized, controlled trials, and non-randomized studies of oral quinine for treatment of uncomplicated *P. falciparum* malaria, and from randomized, controlled studies of parenteral quinine for treatment of severe malaria. These data were limited, in that adverse events were not reported in all of the studies, and that adverse event monitoring was not described in most studies. In addition, there may have been reporting bias in some studies, as it appeared that not all adverse events were reported in some of the study publications. Most importantly, the incidence of adverse events was not reported in many of the studies, so the incidence of adverse events for this review, and for product labeling purposes, could only be estimated. Other sources of data on quinine safety for this review include postmarketing adverse event reports, reviews on quinine toxicity, and case reports of adverse events with quinine.

In general, quinine has been used safely for hundreds of years for treatment of *P. falciparum* malaria. The most common adverse events associated with quinine are a symptom complex called "cinchonism", which can be manifest as headache, nausea, tinnitus, mild hearing impairment, blurred vision, changes in color perception, dizziness or vertigo, sweating and flushing. Severe symptoms of cinchonism may include vomiting, diarrhea, abdominal pain, and rarely, blindness and deafness. According to multiple sources, some degree of cinchonism occurs in most patients treated with quinine for malaria. The symptoms of cinchonism are generally considered to be reversible with discontinuation of quinine.

Quinine has antiarrhythmic activity like its diastereomer, quinidine. One of the major safety issues with quinine is QTc prolongation, along with the associated risk of serious or potentially fatal cardiac arrhythmias such as torsades de pointes. Quinine is considered less potent than quinidine in this regard. Other safety issues with quinine include hypersensitivity reactions, such as rash, angioedema, or anaphylaxis, as well as reactions due to quinine-dependent antibodies, e.g. thrombocytopenia, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, blackwater fever (acute intravascular hemolysis, hemoglobinuria, and hemoglobinemia), and others. Quinine also has neuromuscular blocking activity, and may precipitate a myasthenic crisis in individuals with myasthenia gravis. Quinine also stimulates release of insulin from the pancreas, which may result in hypoglycemia. Pregnant women may be particularly susceptible to the latter.

Because quinine is metabolized exclusively in the liver by the cytochrome P450 system via the isozymes, CYP3A4, and to a lesser extent, CYP2D6, there are multiple possible pharmacokinetic interactions of quinine with other drugs, several of which have been characterized, and are discussed further in this review. Several important pharmacodynamic interactions between quinine and other drugs have been identified, and are discussed further in this review.

## 7.1 Methods and Finding

Safety data was obtained from the two pharmacokinetic studies sponsored by the Applicant, as well as from the published literature, postmarketing safety data, and labeling from other countries, as shown in the table below. The published clinical studies submitted for evaluation of quinine efficacy were also reviewed for safety for this review. The applicant performed a literature search in February 2004, for all side effects, adverse events, and drug reactions reported with quinine in humans, from 1966 to present, resulted in 2601 citations. Because of the large volume, the search was narrowed from 1993 to 2004, and 844 unique citations were identified. After review of titles and abstracts, 146 publications were reviewed. Another search was performed in June, 2004, resulting in 417 citations, of which 108 publications were fully reviewed. In total, 192 articles, and one review article (Taylor, and White, 2004), were used to provide safety information regarding quinine sulfate.

**Table 28: Sources of Safety Data (Applicant's Table 2, ISS)**

| Source   | Population                                     | N    | Data Source / Study Design   |
|--|--|------|--|
| <b>Mutual Pharma's-Sponsored Pharmacokinetic Studies</b>                           |  |      |  |
| RA3-085  | Healthy Adults                                 | 26   | Randomized, open-label, single-dose, three-way crossover study of quinine sulfate capsules under fasting and fed conditions  |
| R04-0376   | Healthy Adults                                 | 24   | Randomized, open-label, single-dose, two-way crossover study to compare the dose proportionality of 324 mg vs. 648 mg quinine sulfate capsules under fasted conditions |
| <b>Medical Literature</b>  |  |      |  |
| ORAL MONOTHERAPY: Patients with uncomplicated <i>P. falciparum</i> malaria         | Primary Studies in Adults and Children         | 504  | 11 Randomized studies  |
|  | Secondary Studies in Adults and Children       | 614  | 7 Nonrandomized studies  |
| ORAL COMBINATION THERAPY: Patients with uncomplicated <i>P. falciparum</i> malaria | Primary Studies in Adults and Children         | 975  | 16 Randomized studies  |
|  | Secondary Studies in Adults and Children       | 409  | 7 Nonrandomized studies  |
| PARENTERAL: Patients with severe, including cerebral, <i>P. falciparum</i> malaria | Primary Studies in Adults and Children         | 1125 | 14 Randomized studies  |
| Case Reports   | --   | --   | Additional case reports of adverse events  |
| <b>Postmarketing Safety Data</b>   |  |      |  |
| U.S. Food and Drug Administration  | Primarily U.S. but may include foreign reports | --   | 448 adverse event reports from 1969 through 30 June 2003   |
| World Health Organization  | 15 countries including the U.S.                | --   | 504 adverse event reports from 1968 – March 2004   |
| <b>Labeling Obtained from Other Countries</b>                                      |  |      |  |
| Other Countries  | --   | --   | Labeling for oral quinine obtained from Thailand, Taiwan, Australia, and South Africa  |

N= number of patients treated with quinine

The applicant's 120 day safety update included quinine labeling information from Australia, New Zealand, France, Denmark, the Netherlands, Germany, and Sweden. Additionally, the applicant performed another literature search on 30 December, 2004, which identified 895 unique citations, and of these, 11 articles ultimately provided additional safety information, which is included in this review of quinine safety.

*Medical Officer Comments: There are many limitations on the safety data on quinine sulfate provided for this NDA. The safety data from the bioequivalence studies submitted by the applicant, particularly the electrocardiographic data and QTc results were a valuable source of safety information for this review. However, the clinical trial safety data was limited in usefulness. Quinine safety was not evaluated in all of the studies, and in many cases, only selected adverse events were reported. Additionally, adverse event data was not always reported by treatment group. Because of these reporting issues, the incidence of adverse events associated with quinine treatment can only be estimated at best. In evaluating adverse events by organ system, the applicant, and this review have relied heavily on information supplied in case reports.*

*Cumulative adverse event data from postmarketing databases, including the FDA Adverse Event Reporting System (AERS) database and the World Health Organization (WHO) postmarketing adverse event database provided by the applicant were an important source of safety information regarding quinine. However, the incidence of adverse events cannot be determined from the postmarketing data because the denominator (number of patients who received the drug of interest) is not known. Additionally, from the data provided by the applicant it was not possible to look at the individual adverse events for a possible relationship to quinine. The Office of Drug Safety was consulted to review the AERS safety data on quinine, and information from their consultation has been incorporated into this review.*

#### **7.1.1 Deaths**

##### **Pharmacokinetic Studies**

No deaths were reported among the 51 subjects enrolled in the two pharmacokinetic studies sponsored by the Applicant and submitted with this NDA, studies RA3-085 and R04-0376.

##### **Clinical Studies**

In addition, no deaths were reported among 504 patients with uncomplicated malaria who received oral quinine monotherapy in the 11 published randomized, controlled studies provided for this NDA. Additionally, no deaths were reported among 975 patients with uncomplicated malaria who received oral quinine combination therapy in the 16 studies randomized, controlled studies submitted.

Studies evaluating efficacy and safety of parenteral quinine for treatment of severe malaria were also included for comparison in this NDA. The overall incidence of mortality in these studies in patients treated with parenteral quinine was 19.6% (216/1118 patients), ranging from 5 to 42%

across studies; while the overall incidence of mortality was 16.1% (180/1119 patients), ranging from 0 to 21% across studies, in patients treated with the comparator drugs (all artemisinin derivatives) as shown in the table below. The causes of death or relationship of death to study drug were not discussed in most of the individual studies; however, severe *P. falciparum* malaria is known to have a high rate of mortality despite appropriate treatment. The incidence of mortality in the randomized, controlled studies of parenteral quinine submitted in support of this NDA is shown in the following table.

**Table 29: Deaths in Patients with Severe *P. falciparum* malaria who received parenteral quinine in randomized studies (adapted from Applicant's table 9, ISS; and from references)**

| Study                             | Quinine<br>N | Deaths<br>n (%) | Comparator<br>N                           | Deaths<br>n(%) |
|-----------------------------------|--------------|-----------------|---|----------------|
| Singh, et al., 2000               | 26           | 4 (15.4)        | Artemether<br>26                          | 2 (7.6%)       |
| Newton, et al., 2003              | 54           | 12 (22%)        | Artesunate<br>59                          | 7 (11.9%)      |
| Satti, et al., 2002               | 39           | 2 (5.1%)        | Artemether<br>38                          | 3 (7.9%)       |
| Adam, et al., 2002                | 21           | 1(4.8%)         | Artemether<br>20                          | 0              |
| Faiz, et al., 2001                | 54           | 10 (18.5%)      | Artemether<br>51                          | 9 (18%)        |
| Thuma, et al., 2000               | 44           | 9 (20.5%)       | Artemotil<br>48                           | 10 (20.8%)     |
| Moyou-Somo, et al., 2001          | 51           | 14 (27.5%)      | Arteether<br>51                           | 8 (15.7%)      |
| Taylor, et al., 1998              | 81           | 12 (14.8%)      | Artemether<br>83                          | 10 (12.0%)     |
| Olumese, et al., 1999             | 49           | 14 (28.8%)      | Artemether<br>54                          | 11 (20.0%)     |
| Murphy, et al., 1996              | 71           | 8 (11.3%)       | Artemether<br>89                          | 18 (20.2%)     |
| Karbwang, et al., 1995            | 52           | 19 (36.5%)      | Artemether<br>50                          | 6 (12.0%)      |
| Karbwang, et al., 1992            | 12           | 5 (41.7%)       | Artemether<br>14                          | 1 (7.1%)       |
| Tran, et al., 1996b               | 276          | 47 (17.0%)      | Artemether<br>248                         | 36 (13%)       |
| Van hensbroek, et al., 1996       | 288          | 62 (21.5%)      | Artemether<br>288                         | 59 (20.5%)     |
| Total in all studies listed above | 1118         | 219 (19.6%)     | Total in all studies listed above<br>1114 | 180 (16.1%)    |

N= number of patients who received parenteral quinine or comparator  
 n (%) = number and proportion of patients who died in the study

**Medical Officer Comments:** *When the number of patients and number of deaths in the studies of parenteral quinine are combined, the overall incidence of mortality in the combined studies was 19.6% (216/1118) for quinine-treated and 16.1% (180/1119) for comparator-treated patients. However, because the study designs differ significantly between studies, pooling these results may not be valid, and most of these studies did not specify the cause of death. Published figures for mortality in severe malaria (particularly cerebral malaria) up to 40% despite appropriate treatment (WHO- 2000b); and presumably in these studies, most deaths were due to malaria and its' complications, rather than to drug-related adverse events.*

*One of the deaths in these studies was associated with a serious adverse event, blackwater fever following quinine administration in a pediatric patient (Moyou-Somo, et al., 2001). This patient was 13 months old, and had received quinine previously at the age of 9 months. The death, due to blackwater fever (acute intravascular hemolysis, hemoglobinemia and hemoglobinuria), occurred approximately 13 hours after quinine administration, despite discontinuation of quinine and a blood transfusion. No further information was provided in the publication, and it would be speculative to presume that the child was previously sensitized to quinine and the blackwater fever was a hypersensitivity reaction, although this has been reported in the literature. Because the proposed indication for quinine capsules in this NDA is treatment of uncomplicated malaria, which is generally not fatal, and no deaths occurred in the randomized studies of uncomplicated malaria, deaths in patients with severe malaria who received intravenous or intramuscular quinine may not be directly relevant to this safety analysis.*

#### **Postmarketing Data**

The applicant also reviewed the postmarketing data submitted to the FDA from 1969 to 31 December 2003 in the 120-day safety update. During that time frame, 487 adverse events, including 60 deaths associated with quinine use, were reported to the FDA. The causes of death were not summarized by the applicant. Additionally, the applicant provided postmarketing safety data reported to the World Health Organization (WHO) from 1968 to November, 2004. A total of 37 deaths among 1908 reports listing 4191 adverse events from 27 countries were listed in the WHO database, but the cause of death was not specifically reported, and the individual reports were not provided for review.

The Agency consulted with the Office of Drug Safety (ODS) to further review of the quinine postmarketing surveillance data submitted to the FDA AERS database. The full ODS consultation is attached to this review in the appendix (section 10. 3). ODS identified 642 adverse event reports in the AERS database through March 31, 2005. After further review, 537 unique cases with serious outcomes were identified. A sample of these (400 cases) were reviewed to determine the indication for quinine use; and it was determined that most (56%; 225/400) reports were from patients who used quinine for leg cramps; and only 4% (15/400) reports were from patients who were treated for malaria.

A total of 12.6% (81/642) of all cases had fatal outcomes. Nineteen of 81 (23.5%) deaths occurred in patients who received quinine for leg cramps, 10/81 (12.5%) occurred in patients who received quinine for malignant melanoma, 2/81 (2.5%) were in patients who received quinine for malaria, 1/81 (1.2%) occurred in a patient who received quinine for treatment of babesiosis, 36/81 (44.4%) were in patients with quinine overdose, and 1/81 (1.2%) was in a patient who received quinine for joint symptoms. The indication for quinine was not listed for 12 patients. Only 2/81 (2.5%) deaths were in patients who received intravenous rather than oral quinine. Both of these patients received quinine for treatment of malaria. In one of these patients, the cause of death was reported as suicide, which occurred 5 hours after quinine dosing in one patient who had been recently treated with chloroquine; in the other malaria patient who died, the cause of death was reported as disseminated fungal infection.

As reviewed by the ODS, most (42/81, 52%) deaths were in females, and most (63/81, 78%) were in patients from the U.S. The cause of death was reported in 53% (43/81) cases, and the most common cause of death was multiple drug overdose, reported in 32/43 (74%) cases in which the cause of death was reported. Other reported causes of death included thrombocytopenia (3/43, 7% cases), organ failure (2/43, 4.7% cases), and coronary artery disease, anemia, fungal infection, respiratory arrest, pulmonary embolism and suicide, each reported in 1 case. The youngest fatality occurred in a 2 year-old British child who experienced an arrhythmia and visual disturbance; however, no information was provided on the indication for quinine, the dose, or the cause of death. The table below obtained from the ODS consultation, summarizes the information regarding deaths associated with quinine use from the AERS database.

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**Table 30: Characteristics of AERS cases with fatal outcome (from Dr. Evelyn Farinas' ODS consultation)**

|  |                                  |      |
|--|----------------------------------|------|
| Total number of reports  | 81                               |      |
| Gender (n=77)  | Females                          | 42   |
|  | Males                            | 35   |
| Country (n=81)   | US                               | 63   |
|  | Foreign                          | 18   |
| Age in years (n=74)  | Average                          | 49   |
|  | Range                            | 2-85 |
| Indication or use (n=69)   | Overdose <sup>1</sup>            | 36   |
|  | Cramps                           | 19   |
|  | Malignant melanoma               | 10   |
|  | Protozoal infection              | 3    |
|  | Joint symptoms                   | 1    |
| # of cases reporting events associated with selected SOCs <sup>2</sup> | Hematologic events               | 23   |
|  | Neuro-psychiatric events         | 18   |
|  | Cardiac disorders                | 16   |
|  | Respiratory events               | 15   |
|  | Renal events                     | 10   |
|  | Hepatobiliary events             | 7    |
|  | Skin and hypersensitivity events | 5    |
| Identified cause of death (n=43)                                       | Overdose                         | 32   |
|  | Thrombocytopenia                 | 3    |
|  | Organ failure                    | 2    |
|  | Arteriosclerotic heart disease   | 1    |
|  | Anemia                           | 1    |
|  | Fungal infection                 | 1    |
|  | Respiratory arrest               | 1    |
|  | Pulmonary embolus                | 1    |
|  | Suicide by hanging               | 1    |

<sup>1</sup> Includes reports coded as overdose, accidental or intentional, as well as cinchonism, drug level increased, misuse and intentional misuse.

<sup>2</sup> One case may report events in more than one system organ class (SOC); thus one case may be included in more than one category.

*Medical Officer Comments: It is also significant that most of the deaths and adverse events associated with quinine reported in the AERS database occurred in patients who received oral, rather than intravenous quinine, and for the indication of leg cramps, rather than for malaria. The quinine dosage used for treatment of leg cramps (usually 260 to 300 mg daily) is generally lower than the proposed dose for uncomplicated malaria, 648 mg 3 times daily.*

### Labeling Issues

We have proposed a Warning in the final product label for the use of quinine sulfate in the treatment and prevention of leg cramps. Approximately one-quarter of the fatalities reported to the AERS database associated with quinine use, were in patients receiving quinine for leg cramps, most likely reflecting the high volume of off-label quinine use. However, the patients most likely to be receiving quinine for leg cramps are the elderly, and those with significant underlying conditions, such as diabetes, renal insufficiency, cardiac disease, or those taking

multiple concomitant medications. All of these factors may place patients at higher risk for quinine toxicity, particularly, QT prolongation.

The use of quinine for prevention or treatment of leg cramps was prohibited in the 1994 final rule. The 21 CFR 310.546 states: “The risk associated with the use of quinine sulfate, in the absence of evidence of its effectiveness, outweighs any potential benefit in treating/preventing this benign, self-limiting condition. Based on the adverse benefit-to-risk ratio, any drug product containing quinine or quinine sulfate cannot be considered generally recognized as safe for the treatment and/or prevention of nocturnal leg muscle cramps.”

### 7.1.2 Other Serious Adverse Events

#### Pharmacokinetic Studies

No serious adverse events were reported among the 51 subjects enrolled in the Applicant’s pharmacokinetic studies, RA3-085 and R04-0376.

#### Serious Adverse Events in Published Studies

In the randomized, controlled studies of oral quinine monotherapy submitted for review, no serious adverse events were reported among 504 patients who received quinine monotherapy. In the non-randomized studies of oral quinine for uncomplicated malaria, no serious adverse events were reported among 614 patients who received quinine alone. Additionally, no serious adverse events were reported among 975 patients who received quinine combination therapy for uncomplicated malaria.

In the randomized studies of parenteral quinine for severe malaria, 3 serious adverse events were reported among 1125 (0.3%) patients treated with quinine. As discussed in the previous section, in a study of cerebral malaria in pediatric patients Cameroon, 1 of 51 (2.0%) patients who received quinine developed blackwater fever and subsequently died following intravenous quinine administration (Moyou-Somo, et al., 2001); while in a study of Thai adults with severe malaria, 2 of 52 (3.8%) patients who received intravenous quinine developed severe, but transient hearing impairment (Karbwang, et al., 1995).

*Medical Officer Comments: Overall incidences for serious adverse events was not calculated because serious adverse events were not defined in all of the studies, nor were adverse events collected or reported systematically in each case.*

#### Adverse Events with Serious Outcomes Reported in Postmarketing Databases

In the postmarketing data summarized by the applicant from the FDA AERS database (1969 to December 31, 2003, outcomes for 487 adverse events reports with quinine listed as a suspect medication, are shown in the table below. This number may include duplicate reports and follow-up reports not linked to the initial report. Over this time period, a total of 60 deaths were reported. Because a total of 619 outcomes are listed in the table, presumably more than one outcome was listed for some adverse events.

**Table 31: Summary of Postmarketing Adverse Event Outcomes from FDA AERS Databases (Applicant's table 7 from 120-day safety update)**

| Adverse Event Outcome                                 | Count                                       |  |
|---|---|--|
|   | NDA 21-799<br>1969 to Jun 2003 <sup>1</sup> | Update<br>1969 to 31 Dec 2003 <sup>2</sup> |
| Hospitalization, initial or prolonged                 | 234   | 256  |
| Other   | 68  | 76   |
| Death   | 54  | 60   |
| Required intervention to prevent permanent impairment | 52  | 56   |
| Life-threatening                                      | 51  | 56   |
| Treated with prescription drug                        | 38  | 38   |
| Recovered   | 32  | 32   |
| None  | 25  | 25   |
| Disability  | 17  | 20   |

1. Source: FOI Report of Adverse Events with Quinine, 9 June 2004
2. Source: FOI Report of Adverse Events with Quinine Outcome Summary through 31 December 2003, the most current information available publicly as of 31 December 2004

*Medical Officer Comments: The applicant did not provide further analysis of adverse events with serious outcomes including death.*

The applicant did not summarize serious adverse events from the WHO postmarketing database which included 504 reports from 15 countries of 1195 adverse events from 1968 to March, 2004.

In their consultation report, the ODS found that 537/642 (83.6%) unique adverse events reported to AERS through March 31, 2005 had serious outcomes. The average age of patients with adverse events with serious outcomes was 56 years old, but age ranged from 20 months to 101 years old. The patient characteristics and the indication for quinine use in events with serious outcomes were summarized by ODS, as shown in the following table. Serious outcomes other than death were reported for 496 adverse events. Leg cramps was the most common indication for quinine use in this analysis.

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**Table 32: Summary of Adverse Events with Serious Outcomes (from Dr. Farinas' ODS consultation report)**

|  |  |                              |
|--|--|------------------------------|
| # of reports   | 537  |                              |
| Country (n=527)  | US   | 432                          |
|  | Foreign  | 95                           |
| Gender (n=511)   | Females  | 292                          |
|  | Males  | 219                          |
| Age (n=462)  | Average 56 years<br>Range 20 months to 101 years |                              |
| Outcome (n=537)  | Death  | 80                           |
|  | Hospitalization                                  | 293                          |
|  | Life threatening                                 | 21                           |
|  | Congenital anomaly                               | 1                            |
|  | Other serious outcomes*                          | 181                          |
| More frequent indications (> 13) (n=332, from manual inspection) | Cramps   | 228                          |
|  | Overdose   | 47                           |
|  | Malignant melanoma                               | 14                           |
|  | Malaria  | 15                           |
| IV Dosing (n=8)  | IV   | 8 (all protozoal infections) |

\* includes the remaining regulatory serious outcomes of disability, required intervention, and other

Among the 400 reports of adverse events with serious outcomes which were sampled for quinine indication, 225/400 (56%) were in patients who received quinine for leg cramps; 44/400 (11%) were in patients with quinine overdose, 15/400 (4%) were in patients treated for malaria, 11/400 (3%) were in patients who received quinine for malignant melanoma and 76/400 (19%) reports had no indication listed. Additionally, the ODS sampled 313 reports to assess the causality of adverse events with a serious outcome. In a total of 174/313 (56%) of these reports, quinine was considered probably related to the serious event by one or more of the following criteria: positive de-challenge, temporal association, positive or probable association statement by the reporter. In 103/313 (33%) reports, no association with quinine was found, and in 36/313 (11%) reports, no determination of possible relationship to quinine could be made from the information provided.

**Medical Officer Comments:** *It is noteworthy that most adverse events with serious outcomes reported to the AERS database were in patients who received quinine for treatment of leg cramps and only 4% were in patients who received quinine for malaria. In 1994, an FDA final rule prohibited marketing of quinine for treatment of nocturnal leg cramps because safety and efficacy of quinine for that indication has not been established. (59 FR 43252, Aug. 22, 1994; and . 21 CFR 310.546). The proposed indication for quinine sulfate oral capsules for this NDA is treatment of uncomplicated P. falciparum malaria. A drug utilization study requested by the Agency of the ODS DSRCs has shown however, that most quinine utilization in this country is for leg cramps and other off-label use rather than for treatment malaria (see attached DSRCs consultation report). We have proposed a statement in the INDICATIONS and USAGE section of the label stating that*

*“Quinine sulfate oral capsules have not been approved for the treatment or prevention of nocturnal leg cramps.”*

*Additionally, a Warning has been proposed regarding the use of quinine for treatment and prevention of leg cramps, as discussed in section 7.1.2 above.*

### **7.1.3 Dropouts and Other Significant Adverse Events**

#### **Pharmacokinetic studies**

In Mutual's study RA3-085, the bioavailability study, 25 of 27(92.6%) enrolled subjects completed the entire three-way crossover study. One patient was withdrawn due to positive pregnancy test, which was reported as an adverse event, and one withdrew for personal reasons. In the dose proportionality study, R04-0376, 23 of 24 (95.8%) subjects completed the study. One subject withdrew because he had to report to military active duty.

#### **Published Randomized, Controlled Trials**

This NDA submission is based mainly on data from published literature, and data regarding reason for dropout or discontinuation was not provided in most of the studies. However, the following tables show the rate of study completion for each study, as well as the overall rate of study completion for quinine monotherapy, and combination therapy regimens. Treatment discontinuation due to adverse events is summarized for individual studies below.

##### **7.1.3.1 Overall profile of dropouts**

Dropout rates in each of the randomized, controlled studies which evaluated quinine monotherapy are shown in the following table. In these studies, the overall dropout rate for patients treated with quinine was 71/504 (14.1%); while that for patients treated with the comparator was 150/1217 (12.3%) In most cases, the reasons for study drop-out were not provided in the publications.

**Table 33: Study Completion in Randomized, Controlled Trials of Quinine Monotherapy**

| Study                         | Duration of Follow-up (days) | Quinine n/N (%) | Duration of therapy (days) | Comparator (s)                      | Duration of therapy (days) | Comparator n/N (%) |
|-------------------------------|------------------------------|-----------------|----------------------------|-------------------------------------|----------------------------|--------------------|
| Watt, et al., 1988            | unknown                      | 10/10 (100)     | 5                          | chloroquine                         | 5                          | 10/10 (100)        |
| Pukrittayakamee, et al., 2004 | 28                           | 25/30 (83.3)    | 7                          | Quinine+ tetracycline               | 7                          | 22/30 (73.3)       |
|                               | --                           | --              |                            | Artesunate                          | 7                          | 21/23 (91.3)       |
| Mueller, et al., 2004         | 35                           | 34/48 (70.8)    | 7                          | Artemisia tea 5 g/day               | 7                          | 32/45 (71.1)       |
|                               | --                           | --              |                            | Artemisia tea 9 g/day               | 7                          | 30/39 (76.9)       |
| Ache, et al., 2002            | 28                           | 48/48 (100)     | 7                          | Sulfadoxine + pyrimethamine         | 1                          | 53/53 (100)        |
|                               | --                           | --              |                            | Chloroquine 25 mg/kg                | 3                          | 12/12 (100)        |
|                               | --                           | --              |                            | Chloroquine 40 mg/kg                | 4                          | 52/52 (100)        |
| Rahman, et al., 2001          | 28                           | 49/49 (100)     | 7                          | Quinine + sulfadoxine-pyrimethamine | Q3+ SP1                    | 145/145 (100)      |
|                               | --                           | --              |                            | Chloroquine                         | 3                          | 149/149 (100)      |
|                               | --                           | --              |                            | Mefloquine                          | 1                          | 70/70 (100)        |
| Pukrittayakamee, et al., 2000 | 28                           | 53/68 (77.9)    | 7                          | Quinine + clindamycin               | 7                          | 60/68 (88.2)       |
|                               | --                           | --              |                            | Quinine + tetracycline              | 7                          | 48/68 (70.6)       |
| McGready, et al., 2000        | 63                           | 42/42 (100)     | 7                          | Mefloquine + artesunate             | 3                          | 66/66 (100)        |
| De Vries, et al., 2000        | 28                           | 69/84 (82.1)    | 7                          | Quinine + artemisinin               | 3                          | 78/88 (88.6)       |
|                               | --                           | --              |                            | Quinine + artemisinin               | 5                          | 74/96 (77.1)       |
| Bich et al., 1996             | 28                           | 44/59 (74.6)    | 7                          | Quinine + artemisinin               | 3                          | 32/45 (71.1)       |
|                               | --                           | --              |                            | Artemisinin                         | 3                          | 42/53 (79.2)       |
| Metzger, et al., 1995         | 28                           | 37/40 (92.5)    | 1.5                        | Quinine + clindamycin               | 3                          | 36/40 (90.0)       |
|                               | --                           | --              |                            | Quinine + doxycycline               | 3                          | 35/40 (87.5)       |
| Segal, et al., 1974           | 28                           | 22/26 (84.6)    | 6                          | WR33063                             | 6                          | 25/25 (100)        |
| Overall Study Completion      | 504                          | 433 (85.9)      | --                         | All comparators                     | 1217                       | 1067 (87.7)        |

n/N = number of patients who completed study/number of patients enrolled

\* Study was an outpatient study

*Medical Officer Comments: The rate of study completion was similar overall for patients treated with quinine or comparator in these studies. Although 433/504 (85.9%) patients treated with quinine completed these studies, it is not clear whether the same proportion of patients completed the course of quinine. Reasons for study withdrawal were not reported in these studies. Studies that were outpatient studies would be expected to have a higher proportion of patients lost-to follow-up by the time of study completion than inpatient studies. Only 3 of these studies were conducted fully in the outpatient setting, McGready, et al. (2000), Ache, et al. (2002), and Metzger, et al. (1995). Interestingly, these 3 outpatient studies had the some of the highest rates of study completion.*

In the randomized, controlled trials of quinine combination therapy, overall study completion was 423/471 (89.8%) for patients who received a quinine-containing regimen, and 455/517 (88.0%) for those who received a comparator, as shown in the following table.

**Table 34: Study Completion in Randomized Controlled Trials of Quinine Combination Therapy\***

| Study                      | Duration of Follow-up (days) | Quinine Combination n/N (%)            | Duration of therapy (days) | Comparator (s)                        | Duration of therapy (days) | Comparator n/N (%) |
|----------------------------|------------------------------|--|----------------------------|---------------------------------------|----------------------------|--------------------|
| Duarte, et al., 1996       | 28                           | Quinine + tetracycline<br>69/88 (78.4) | 7                          | Artesunate + tetracycline             | 7                          | 72/88 (81.8)       |
| Fungladda, et al., 1998    |                              | Quinine + tetracycline<br>53/60 (88.3) | 7                          | Artesunate                            | 5                          | 61/77 (79.2)       |
| Salcedo, et al., 1997      | 28                           | Quinine + tetracycline<br>NR/14 **     | 3                          |                                       |                            |                    |
| De Alencar, et al., 1997   | 28                           | Quinine + tetracycline<br>77/77 (100)  | 7                          | Atovaquone + proguanil                | 3                          | 77/77 (100)        |
| Bunnag, et al., 1996       | 28                           | Quinine + tetracycline<br>40/42 (95.2) | 5                          | Quinine + tetracycline                | 7                          | 46/48 (95.8)       |
| Vanijanonta, et al., 1996  | 60                           | Quinine + chloroquine<br>18/25 (72.0)  | 7                          | Quinine + tetracycline                | 7                          | 18/25 (72.0)       |
| Looareesuwan, et al., 1994 | 28                           | Quinine + tetracycline<br>46/50 (92.0) | 7                          | Mefloquine + tetracycline             | 7                          | 47/52 (90)         |
| Karbwang, et al., 1994     | 28                           | Quinine + tetracycline<br>30/33 (90.9) | 7                          | Artesunate                            | 5                          | 30/31 (96.8)       |
| Kresmer, et al., 1988      | 28                           | Quinine + clindamycin<br>40/46 (87.0)  | 3                          | Quinine + sulfadoxine – pyramethamine | 3                          | 30/40 (75.0)       |

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

|                             |    |  |    |                 |    |                   |
|-----------------------------|----|--|----|-----------------|----|-------------------|
|                             |    | --   |    | Amodiaquine     | 3  | 25/29<br>(86.2)   |
| De Souza, et al.,<br>1985   | 42 | Quinine +<br>sulfadoxine –<br>pyramethamine<br>50/50 (100) | 3  | Mefloquine      | 1  | 49/50<br>(98.0)   |
| Overall Study<br>Completion | -- | 423/471 (89.8)   | -- | All comparators | -- | 455/517<br>(88.0) |

n/N = number of patients who completed study/number of patients enrolled; x= unknown

\* Includes only the studies not included in table 30 above for quinine monotherapy

NR= not reported

\*\* Salcedo, et al (1997) not included in total because no information on study completion was provided

*Medical Officer Comments: Similar overall rates of study completion were observed in patients who received a quinine-containing regimen or comparator. Although 423/471 (89.8%) patients who received quinine completed these studies, it is not clear whether the same proportion of patients completed the course of quinine. Reasons for study withdrawal were not reported in these studies. Studies that were outpatient studies would be expected to have a higher proportion of patients lost-to follow-up by the time of study completion than inpatient studies. Outpatient studies included Duarte, et al. (1996), Fungladda, et al. (1998), and Kremsner, et al. (1988), and rates of study completion in these studies did not differ significantly from the overall rates of study completion.*

In the studies of parenteral quinine therapy for severe malaria, the rate of study completion was somewhat lower than in the studies of oral quinine mono- or combination therapy, with approximately 77% of patients overall who received quinine, completing the studies, as shown in the following table. Study completion and duration of follow-up was not reported in a number of the studies listed below.

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**Table 35: Study Completion in Randomized Controlled Trials of Parenteral Quinine Therapy for Severe Malaria**

| Study                       | Duration of Follow-up (days) | Quinine n/N (%) | Duration of therapy (days) |
|-----------------------------|------------------------------|-----------------|----------------------------|
| Adam, et al., 2002          | 28                           | 15/21 (71.4)    | 7                          |
| Faiz, et al., 2001          | 28                           | 44/54 (81.5)    | 7                          |
| Karbwang, et al., 1992      | NR                           | NR/12*          | 7                          |
| Karbwang, et al., 1995      | NR                           | NR/52*          | 7                          |
| Moyou-Somo, et al., 2001    | 28                           | 37/51 (72.5)    | 7                          |
| Murphy, et al., 1996        | NR                           | NR/71*          | 7                          |
| Newton, et al., 2003        | NR                           | NR/54*          | 7                          |
| Olumese, et al., 1999       | 28                           | 35/49 (71.4)    | 7                          |
| Satti, et al., 2002         | 28                           | 26/39 (66.7)    | 7                          |
| Singh, et al., 2000         | NR                           | NR/26*          | 7                          |
| Taylor, et al., 1998        | 28                           | 69/88 (78.4)    | 7                          |
| Thuma, et al., 2000         | 28                           | 35/44 (79.5)    | 7                          |
| Tran, et al., 1996          | NR                           | NR/276*         | 7                          |
| Van Hensbroek, et al., 1996 | 28                           | 226/288 (78.5)  | 5                          |
| Overall study completion    | --                           | 487/634 (76.8)  | --                         |

NR= not reported

n/N = number of patients who completed study/number of patients enrolled

\*Not included in calculation of overall completion rate

*Medical Officer Comments: Although 487/634 (76.8%) patients completed these studies, it is not clear whether the same proportion of patients completed the course of quinine. Reasons for study withdrawal were not reported in these studies. However, mortality rates were higher in these studies than in those with oral quinine, and the lower rates of study completion in the setting of severe malaria may reflect patient deaths. All of these studies took place in the inpatient setting.*

### 7.1.3.2 Adverse events associated with dropouts

#### Pharmacokinetic Studies

In the pharmacokinetic study, RA3-085, 1/27 (3.7%) subjects were withdrawn from the study due to an adverse event. In this case, the adverse event was an unintended pregnancy. The applicant noted that this subject went on to terminate her pregnancy voluntarily. No subjects were withdrawn due to adverse events in study R04-076.

### **Published Clinical Studies**

In the randomized studies of quinine monotherapy, there were no treatment discontinuations due to adverse events among the 504 patients treated with quinine alone. In the randomized studies of oral quinine combination therapy for uncomplicated malaria, 5 of 975 (0.5%) patients discontinued treatment due to an adverse event, hemoglobinuria in 2 cases (De Vries, et al, 2000), and severe vomiting in 3 cases (Duarte, et al., 1996). Further details regarding these patients were not provided by the authors, except to note that the patients were withdrawn from the study and treated with artesunate.

*Medical Officer Comment: The overall incidence of discontinuation was not determined from these data because the reasons for discontinuation were not reported systematically in all of the studies. However, there was a low rate of quinine discontinuation due to adverse events in the randomized, controlled studies of both oral and parenteral quinine. Although many of these studies were performed in the inpatient setting, where drug discontinuation due to patient intolerance is less likely than the outpatient setting, it is notable that there were few treatment-limiting serious adverse events.*

#### **7.1.3.3 Other significant adverse events**

##### **Literature Review of Significant Adverse Events Associated with Quinine**

The safety profile of quinine has been well-characterized in a recent review of antimalarial drug safety by Taylor and White (2004). According to these authors, common adverse events associated with quinine include cinchonism, tinnitus, blurred vision, thrombocytopenia, granulomatous hepatitis, skin rash and acute interstitial nephritis. Some of the serious toxicities identified include thrombotic thrombocytopenic purpura or hemolytic uremic syndrome (TTP-HUS), disseminated intravascular coagulation (DIC), blindness, QT prolongation, and cardiac arrhythmias. Adverse events specifically associated with intravenous administration of quinine include potentially lethal hypotension with rapid (bolus) intravenous infusion of the drug, and hypoglycemia.

In this section, adverse events from case series, case reports, and clinical studies are reviewed by organ system, particularly with reference to a comparator where feasible, and with reference to the mechanism of toxicity, where known.

*Medical Officer Comments: Many of the adverse events discussed in this section were described only in case reports, case series, and/or reviews on quinine toxicity. Because adverse event information from the clinical studies submitted for this NDA was limited, it was necessary to rely on the applicant's literature review on quinine safety, supplemented by literature searches by the medical officer on specific adverse events.*

## 1. General

### Hypersensitivity Reactions

Angioedema, anaphylactoid reactions, drug-fever, lupus-like syndrome, hypersensitivity reactions including various rashes, photosensitization, pruritis, skin flushing, urticaria, thrombocytopenia, HUS, TTP, leukopenia, hemolysis, granulomatous hepatitis, have all been reported as immunologically-mediated reactions associated with quinine use. Most of these are described below.

Among the postmarketing adverse events reported in the AERS database, hypersensitivity reactions that occurred in patients who had a serious outcome included urticaria, rash, maculopapular rash, erythematous rash, blister, bullous dermatitis, erythema multiforme, exfoliative dermatitis, dermatitis, vasculitis, facial edema, tongue edema, pruritus, erythema, Stevens-Johnson syndrome, photosensitivity reactions, and fever.

### Cinchonism

This term is used to describe a spectrum of symptoms reported frequently in patients who receive quinine (a cinchona alkaloid). Mild symptoms include tinnitus, headache, nausea, dysphoria, mild high-tone hearing impairment and visual disturbances. More severe symptoms of cinchonism include vomiting, diarrhea, abdominal pain, vertigo, deafness, blindness, and disturbances of cardiac conduction or rhythm. The symptoms of cinchonism are generally considered to be reversible upon discontinuation of quinine.

Cinchonism, as such, was not reported as a serious adverse event in the AERS postmarketing database, as reviewed by ODS. However, a number of the individual manifestations of cinchonism were reported as individual adverse events.

Other serious adverse events reported in the AERS postmarketing safety database not reported in the other body systems below include asthenia, malaise, fatigue, chills, night sweats, sepsis, hyperhidrosis, cryoglobulinemia, systemic lupus erythematosus, positive antinuclear antibodies, and peripheral edema.

## **2. Cardiovascular system**

Quinine has been associated with significant effects on cardiac conduction, particularly QTC prolongation, with serious or fatal cardiac arrhythmias, and with hypotension, sometimes severe or fatal, as discussed further below.

### **ECG Changes and Cardiac Arrhythmias**

Quinine, like quinidine, its diastereomer, is a Class I antiarrhythmic, albeit less potent than quinidine (Tracy and Webster, 2001). Quinine blocks both sodium and potassium channels, delaying repolarization prolonging the action potential (Morrison, et al., 2003). Quinine also has a direct negative inotropic effect on the heart, decreases the rate of depolarization and conduction, increases the action potential and effective refractory period. ECG changes include sinus tachycardia, PR prolongation, widening of the QRS complex, an increased QT interval, T wave inversion, bundle branch block (Jaeger, et al., 1987). QT interval prolongation is concentration dependent with both quinine and quinidine; (White, et al., 1983; Touze, et al, 2002) however, approximately 3-4 fold more quinine than quinidine is required for similar effects on the QT interval (Karbwang, et al, 1993; White, et al., 1983a). It is estimated that 2-8% of patients develop marked QT prolongation and torsades de pointes with quinidine (Tracy and Webster, 2001), while the incidence is unknown with quinine. Cardiac arrhythmias are well-known manifestations of quinine overdose.

### **ECG Data from Applicant's Pharmacokinetic Studies**

See section 7.1.9 below.

### **ECG Data from Published Randomized, Controlled Studies**

Only one of the 21 studies submitted for evaluation of efficacy and safety of oral quinine mono- or combination therapy monitored ECG changes on treatment. In Vanijananta, et al. (1996), ECGs were obtained prior to treatment and 48 hours post-treatment with quinine combination regimen. The change in QTc in msec was not provided, but the median QTc prolongation in the quinine+chloroquine group was 11% (range -17% to 21%) and the median QTc prolongation in the quinine+tetracycline group was 7% (range -5% to 24%).

Among the supportive studies submitted for evaluation of parenteral quinine efficacy and safety, 6 monitored ECG changes during treatment, and QTc prolongation was reported in 2 of these studies, as summarized in the table below.

**Table 36: ECG Data from Pulished Randomized, Controlled Studies of parenteral Quinine Treatment of Severe P. falciparum Malaria (applicant's Table 27, ISS)**

| Study                                    | N<br>(Treatment/<br>Duration Code <sup>1</sup> ) | Abnormal ECG Findings  |
|--|--|--|
| <b>Intravenous</b>                       |  |  |
| <u>Faiz et al.</u><br>2001(Bangladesh)   | 54<br>(Q7)                                       | ECG was performed on Day 0, then daily for 3 days and on Days 7, 14, and 28. No abnormalities were reported.   |
| <u>Thuma et al.</u><br>2000(Zambia)      | 44<br>(Q7)                                       | The ECG schedule was not described. However, pre- and post-treatment ECGs were assessed for any arrhythmia or change in QT interval. No abnormalities were seen.   |
| <u>Taylor et al.</u><br>1988(Malawi)     | 88<br>(Q3 <sup>2</sup> )                         | ECGs (lead V2) were done on admission and at 6, 48, 54, and 96 hours after treatment started in the first 127 patients (the practice was then discontinued). More patients in the quinine group showed QTc prolongation after treatment as compared with IM artemether, but the difference was not statistically or clinically significant. No objective data are reported.  |
| <u>Karbwang et al.</u><br>1992(Thailand) | 52<br>(Q7)                                       | ECGs were obtained on admission and each day 2 hours after infusion of the first dose of the day until parenteral quinine was discontinued. QTc prolongation, notch and T wave changes were common in patients receiving quinine; however, no significant dysrhythmias were seen, despite the high concentrations of quinine in some patients who might have received quinine prior to admission.  |
| <u>Karbwang et al.</u><br>1992(Thailand) | 12<br>(Q7)                                       | ECGs were obtained on admission and each day 2 hours after infusion of the first dose of the day until parenteral quinine was discontinued. There were no significant drug-related ECG changes.  |
| <b>Intramuscular</b>                     |  |  |
| <u>Tran et al.</u><br>1996b(Vietnam)     | 276<br>(Q3 <sup>2</sup> )                        | After enrollment of 259 patients, the protocol changed to include an ECG with rhythm strip obtained before treatment, 12 hours after treatment was started, 4 hours after the last parenteral dose, and at discharge. There were no significant ECG abnormalities. 60 patients (45%) had QTc prolongation > 0.5 seconds and 12 patients (9%) had QTc prolonged by > 25%. QTc prolongation was not associated with any other clinical findings. |

Q=quinine

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

<sup>2</sup>Intravenous treatment was followed by treatment with one other oral antimalarial drug

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**Medical Officer Comments:** In Taylor, et al. (1988) QTc prolongation was noted, but not quantified. In Tran Hien, et al (1996b), 60 (45%) of monitored patients who received quinine, and while 38 (25%) of monitored patients who received artemether had QTc prolongation by > 500 msec according to the original publication. Although no cardiac adverse events were reported in this study, QTc prolongation > 500 msec is clinically significant.

A number of additional studies (other than those submitted for evaluation of safety and efficacy) submitted by the applicant evaluated ECG changes, including QTc prolongation and other cardiovascular effects with quinine. QTc interval prolongation occurred in both healthy subjects and in adults and children with malaria who received either oral or intravenous quinine; however, no serious cardiac arrhythmias were reported. Eleven studies in which systematic ECG monitoring was performed were summarized by the applicant and are described below.

### ECG Data in Healthy Subjects Exposed to Quinine

In 12 healthy Caucasian subjects who received a single dose of intravenous quinine (300 mg) over a 4 hour period, no changes in QTc were observed (Claessen, et al., 1998); while in 8 healthy Thai subjects who received a single infusion of quinine (10 mg/kg) over 1 hour, the mean QTc interval increased from 417± 14 milliseconds to 499 ± 31 milliseconds (mean change in QTc was 82 msec); while the mean QTc interval increased from 407± 20 milliseconds to 557± 70 milliseconds (mean change in QTc was 157 msec) after infusion of quinidine (10 mg/kg) over 1 hour in the same subjects at a different time (Karbwang, et al., 1993). In 7 healthy adults who received a single bolus intravenous dose of quinine (5 mg/kg), transient increases in QTc (maximum QTc was approximately 415 msec from a baseline of approximately 405) were observed, which corresponded to the distribution phase of quinine (White, et al., 1983b). The authors inferred from these data that because a measurable distribution phase adverse cardiovascular events are not observed after slow intravenous infusion of quinine, the latter is the preferred method of quinine administration. These data are summarized in Table 34 below.

**Table 37: Electrocardiographic changes associated with Intravenous Quinine in Healthy Subjects (Applicant's Table 12, ISS).**

TABLE 12  
 Electrocardiographic Changes Associated with Quinine in Published Studies

| Author, Year (Country)                  | N Population        | Dosage Regimen  | ECG Monitoring  | Findings  |
|---|---------------------|---|---|---|
| <b>Healthy Subjects</b>                 |                     |   |   |   |
| Claessen et al., 1998 (The Netherlands) | 12 healthy subjects | IV infusion (4 hours): 300 mg as a single dose        | Sequential (one-lead) ECG: Recorded several times during the 8-hour period post-dose  | No changes in QTc   |
| Karbwang et al., 1993 (Thailand)        | 8 healthy subjects  | Rapid IV infusion (1 hour): 10 mg/kg as a single dose | Sequential (12-lead) ECG: At baseline and 0.5, 1, 2, 4, 8, 12, and 24 hours post dose | <ul style="list-style-type: none"> <li>No serious cardiovascular adverse effects were noted.</li> <li>There was minimal prolongation of the QRS complex at the end of the infusion relative to baseline.</li> <li>The PR interval did not change.</li> <li>Mean QTc interval increased from 0.417 seconds to 0.499 seconds, reaching a maximum value at 1.5 hours (3 cases) or 2 hours (5 cases).</li> </ul>  |
| White et al., 1983b (Thailand)          | 7 healthy subjects  | Rapid IV bolus: A single 5 mg/kg dose over 5 minutes  | Sequential ECG: At 2-minute intervals for 18 minutes                                  | <ul style="list-style-type: none"> <li>Significant prolongation of QRS interval (change from baseline 0.087 seconds to 0.096 seconds) that was greatest 1 to 4 minutes after completion of the infusion and then returned to baseline (<math>P &lt; 0.001</math>, Student's t test).</li> <li>Significant prolongation of QTc interval was more variable with maximum values 1 to 4 minutes after completion of the infusion and then returned to baseline (from Figure 1, it appears that the mean QTc did not exceed 0.415 seconds).</li> </ul> |

**Medical Officer Comments:** Among the 27 healthy subjects who received intravenous quinine in the studies shown in the table above, no serious cardiac arrhythmias were observed. However, QTc prolongation was reported in 2 of the 3 studies. The mean change in QTc interval was 82 msec for quinine and 157 msec for quinidine in the study by Karbwang, et al. (1993), which suggests that in vivo, quinidine may be potent than quinidine with regard to the relative potential for QT prolongation. In the study by White, et al. (1983b), the mean maximum QTc did not exceed 415 msec.

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### ECG Data in Patients with Malaria

No serious cardiac arrhythmias were reported among 140 patients with *P. falciparum* malaria who received intravenous and/or oral quinine in the 8 studies cited in the table below; however, QTc interval prolongation was noted in several of these studies (Karbwang, et al, 1997; Classen, et al., 1998; Mehta, et al., 1994; White, et al., 1983; and Fulkerson, et al. 1970). QTc data was quantified in only 3 of these studies (Claessen, et al., 1998, Mehta, et al., 1994, and White, et al., 1983a).

In the study by White, et al. (1983a), 13 patients with uncomplicated *P. falciparum* malaria received a single dose of intravenous quinine followed by oral quinine sulfate or oral quinidinesulfate dosed at approximately 10 mg (salt)/kg every 8 hours, and 18 patients with severe malaria received intravenous quinine 10 mg/kg every 8 hours. In 31 quinine-treated patients (pooled patients with severe malaria and uncomplicated *P. falciparum* malaria), the maximum QTc prolongation was  $41 \pm 29$  msec, or  $10.3 \pm 7.7\%$  of pretreatment values; while in 14 oral quinidine-treated patients, maximum QTc prolongation was  $123 \pm 126$  msec, or  $24 \pm 8\%$  of baseline values. Thus, in this study, QTc prolongation was significantly longer in patients who received quinidine than in those who received quinine.

In the study by Claessen, et al. (1998), 10 patients with uncomplicated *P. falciparum* malaria received intravenous quinine, 600 mg 3 times per day. No cardiac adverse events were reported, but the mean QTc increased  $390 \pm 40$  msec, a  $20 \pm 11\%$  increase from baseline. In Mehta, et al. (1994), of 12 patients with cerebral malaria, 4 (33%) had QTc prolongation. The extent of QTc prolongation in this study did not exceed 15% of baseline, and normalized in all patients by day 6 of treatment.

**Table 38: Electrocardiographic changes associated with Intravenous Quinine (with loading dose) in Patients with Malaria (Applicant's Table 12 ISS)**

TABLE 38  
 Electrocardiographic Changes Associated with Quinine in Published Studies - continued

| Author, Year (Country)                       | N Population   | Dosage Regimen  | ECG Monitoring  | Findings   |
|--|--|---|---|--|
| <b>Patients with Malaria</b>                 |  |   |   |  |
| <b>Intravenous Quinine with Loading Dose</b> |  |   |   |  |
| Bragani <i>et al.</i> , 2003 (Tanzania)      | 10 children with severe <i>P. falciparum</i> malaria | IV loading dose: 20 mg/kg over 4 hours<br>IV maintenance dose: 10 mg/kg over 4 hours every 8 hours  | Continuous ECG monitoring for the first 24 hours  | No arrhythmias were observed; no PR or QT interval prolongation was recorded   |
| Karbwang <i>et al.</i> , 1997 (Thailand)     | 19 patients with severe <i>P. falciparum</i> malaria | IV loading dose: 20 mg/kg as an infusion (infusion time not stated)<br>IV maintenance dose: 10 mg/kg (infusion time not stated) every 8 hours, switching to oral quinine when tolerated for a total of 7 days of treatment      | Sequential ECG: At baseline and once daily (2 hours following the infusion of the first dose of the day) while on parenteral quinine                                | No arrhythmias were noted on ECG despite high plasma concentrations of quinine in some patients. QTc prolongation and notch- and T-wave changes were "common findings" after quinine treatment. 3 patients died but their ECGs were not significantly different from those who survived. |
| Bethell <i>et al.</i> , 1987 (Vietnam)       | 24 patients with severe <i>P. falciparum</i> malaria | Reported as total dose given during 24-hour ECG monitoring period: IV or IM, 30 to 40 mg/kg   | Continuous ECG: For 24-hours following admission  | No cardiac abnormalities were documented, either clinically or during 24-hour ECG monitoring.  |
| Davis <i>et al.</i> , 1990 (Thailand)        | 16 patients with severe <i>P. falciparum</i> malaria | Rapid IV loading dose: 7 mg/kg over 30 minutes<br>IV maintenance dose: Immediately following the loading dose, 10 mg/kg over 4 hours every 8 hours, switching to oral quinine when tolerated for a total of 7 days of treatment | Sequential ECG: Immediately before and at 5-minute intervals during the loading dose, and then at 15, 40, 60, and 90 minutes, during the first maintenance infusion | There was no evidence of arrhythmia. Changes in ECG indices were "similar to those reported" in other similar studies  |

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**Table 34:** (continued) Electrocardiographic changes associated with Intravenous and/or Oral Quinine in Patients with Malaria (Applicant's Table 12)

Table 12  
 Electrocardiographic Changes Associated with Quinine in Published Studies - continued

| Author, Year (Country)                             | N Population   | Dosage Regimen  | ECG Monitoring   | Findings   |
|--|--|---|--|--|
| <b>Patients with Malaria - continued</b>           |  |   |  |  |
| <b>Intravenous and/or Oral Quinine - continued</b> |  |   |  |  |
| Classen et al. 1982 (The Netherlands)              | 10 patients with uncomplicated <i>P. falciparum</i> malaria                | IV infusion (4 hours): 600 mg three times a day for 3 days  | Sequential (one lead) ECG: Recorded several times during the 3-day treatment period  | Mean ( $\pm$ SD) QTc increased from 0.390 $\pm$ 0.04 seconds to 0.470 $\pm$ 0.04 seconds (increase from baseline of 20 $\pm$ 11%)  |
| Mahta et al. 1994 (India)                          | 12 patients with severe <i>P. falciparum</i> malaria                       | IV loading dose: 20 mg/kg over 4 hours<br>IV maintenance dose: 10 mg/kg over 4 hours every 8 hours, switching to oral quinine when tolerated for a total of 7 days of treatment | Sequential ECG: At baseline and every 12 hours for the first 72 hours or as clinically warranted   | No arrhythmias or other serious effects were seen in any patient. QTc was prolonged in 4 of 12 patients (33%) but did not exceed 15% of baseline and normalized in all patients by Day 6.  |
|  | 11 patients (age and sex matched) with severe <i>P. falciparum</i> malaria | IV: 10 mg/kg over 4 hours every 8 hours, switching to oral quinine when tolerated for a total of 7 days of treatment  |  | No arrhythmias or other serious effects were seen in any patient. ECG findings in the group not administered a loading dose are not commented on.  |
| White et al. 1982a (Thailand)                      | 18 patients with severe <i>P. falciparum</i> malaria                       | IV: 10 mg/kg over 4 hours every 8 hours   | Sequential ECG: Before treatment and at hourly intervals after the start of treatment for 8 hours. In 10 patients with severe malaria, ECG was recorded at the beginning and end of the quinine infusion only. | <ul style="list-style-type: none"> <li>No arrhythmias were noted.</li> <li>There was no significant change in PR interval.</li> <li>QRS interval was slightly prolonged in 11 of 18 patients with severe malaria (mean 0.028 seconds) associated with plasma quinine concentrations exceeding 10 mg/L. Overall there was no significant prolongation of QRS interval in any patients with uncomplicated malaria.</li> <li>Pooled data show maximum mean (<math>\pm</math> SD) QTc prolongation of 0.041 <math>\pm</math> 0.029 seconds or 10% of pretreatment values.</li> </ul> |
|  | 13 patients with uncomplicated <i>P. falciparum</i> malaria                | One dose of IV quinine (10 mg/kg over 4 hours) followed by oral quinine 10 mg/kg every 8 hours  |  |  |

Electrocardiographic Changes Associated with Quinine in Published Studies - continued

| Author, Year (Country)                             | N Population   | Dosage Regimen   | ECG Monitoring   | Findings   |
|--|--|--|--|--|
| <b>Patients with Malaria - continued</b>           |  |  |  |  |
| <b>Intravenous and/or Oral Quinine - continued</b> |  |  |  |  |
| Fulkerson 1970 (U.S.)                              | 7 military patients with relapsing <i>P. falciparum</i> malaria    | IV: 1300 mg every 16 hours for 10 days (infusion period not stated)  | Sequential (12-lead) ECG before treatment and 3-lead ECGs daily at the same time every day | <ul style="list-style-type: none"> <li>One (IV) patient had multifocal ventricular extrasystoles when the infusion rate was erroneously increased approximately 3 times the prescribed rate to make up for a previous slower-than-prescribed infusion rate.</li> <li>One (oral) patient had a single premature ventricular contraction 6 hours after his first dose.</li> <li>Quinine produced measurable ECG changes in all but 1 patient and changes were similar in each group. PR, QRS, and QTc interval prolongations were seen. PR prolongation was longest 1 hour post-dose while QRS and QTc reached their longest value 6 hours post-dose. T wave depression was seen in 68% and reduction in P wave amplitude in 53%. U waves were seen in 30% of patients.</li> </ul> |
|  | 12 non-malarious convalescing post-surgical U.S. military patients | Oral: 650 mg every 8 hours for 10 days (two groups of 6 with each group receiving a different oral formulation of quinine sulfate) | Sequential (12-lead) ECG before treatment and 3-lead ECGs daily, 6 hours after a dose      |  |

**Medical Officer Comments:** It is somewhat reassuring that no serious cardiotoxicity was noted among 140 patients with malaria in the clinical studies shown in the table above, despite mild-moderate QTc prolongation (approximately 10-20% increase from baseline) observed in patients with malaria. However, uncommon cardiac adverse events such as serious arrhythmia or syncope may not have been detected in this small patient population in these studies.

In a prospective study of 60 African patients with *P. falciparum* malaria, randomized a single oral to quinine, mefloquine, artemether or halofantrine, significant QTc prolongation was observed with halofantrine, but not with quinine, mefloquine, or artemether. However, QTc dispersion, a

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marker of the heterogeneity of ventricular repolarization, was increased in patients who received oral quinine (25 mg/kg daily in 3 doses), but no value exceeded 65 msec, which was considered the pathologic threshold; while in those who received halofantrine (1500 mg daily in 3 doses), 5 of 15 patients had QTc dispersion values of > 100 msec. (Touze, et al., 2002). QTc dispersion was defined as the difference between the shortest and longest QTc interval measured at baseline, 9 hours, and 24 hours post-exposure.

**Table 39: Electrocardiographic changes associated with Oral Quinine in Patients with Malaria (Applicant's Table 12)**

Electrocardiographic Changes Associated with Quinine in Published Studies - continued

| Author, Year (Country)            | N Population  | Dosage Regimen                                     | ECG Monitoring   | Findings   |
|-----------------------------------|---|--|--|--|
| Patients with Malaria - continued |   |  |  |  |
| Oral Quinine                      |   |  |  |  |
| Touze et al., 2002 (France)       | 15 patients with uncomplicated <i>P. falciparum</i> malaria | Orally, 25 mg/kg/day in 3 divided doses for 5 days | 12-lead ECG: Recorded upon admission and at 9 and 24 hours after the start of treatment.<br><br>Continuous ECG (Ambulatory): Recording started on the morning of Day 1 | <ul style="list-style-type: none"> <li>Slight lengthening of the QTc interval and a moderate increase in QTc dispersion, with no value higher than 0.065 seconds</li> <li>Holter recordings: Ventricular arrhythmia was not detected.</li> </ul> |

*Medical Officer Comments: This study suggests the potential for QT prolongation is greater with halofantrine than with quinine. Halofantrine carries a prominent Black Box Warning for QTc interval prolongation and rare reports of serious ventricular dysrhythmias sometimes associated with death (Halfan® final product label, August, 2002). In one in vitro study, mefloquine, quinine, quinidine, and ketoconazole were shown to inhibit metabolism of halofantrine in human liver microsomes (Baune, et al., 1999). We have proposed a Warning in the final product label regarding concomitant use of quinine and halofantrine due to the risk for potentiation of halofantrine cardiotoxicity with quinine.*

**Summary of Quinine's Potential to cause QT Prolongation**

The following table summarizes the information regarding the potential for quinine to cause QT prolongation. The preclinical data indicates that quinine is approximately 10-fold less potent than quinidine in blocking HERG channels (Sanchez-Chapula, et al., 2003). Similar to quinidine, quinine interacts with open K+ channels, inactivates Ca 2+ channels, blocks sodium and potassium conductance, and induces the opening of hemi-gap junctional channels. A major electrophysiological effect of both quinine and quinidine is prolongation of conduction time, while only quinidine prolongs action potential duration in vitro (Sheldon, et al., 1990) and repolarization in vivo (Jurkiewicz, et al., 1985). In healthy volunteers in the applicant's bioequivalence study, QTc prolongation following a single 324 mg or 648 mg of oral quinine sulfate was only 10- 12 msec over baseline. In comparison, in published studies of healthy volunteers who received IV quinine sulfate, the ΔQTc was 82 msec (Karbwang, et al., 1993); while in another study the mean maximal QTc was 415 msec (White, et al., 1983b). In patients with malaria who received intravenous quinine, the mean maximal ΔQTc increased 20% (Claessen, et al., 1998), 15% (Mehta, et al., 1994), and 10% (White, et al., 1983a) from baseline.

In one study in patients with malaria who received oral quinine sulfate at a dose of 25 mg/kg/day in 3 doses (similar to the proposed dose for this application), the QTc dispersion increased to 65 msec with quinine in comparison to >100 msec with halofantrine, an antimalarial agent with well-recognized potential for QT prolongation, and fatal cardiac arrhythmias, including torsades de pointes. Other clinical studies reported no change in QT interval in malaria patients treated with quinine as shown in the tables above. These data are summarized in the following table.

**Table 40: Summary of Data describing Quinine’s Potential for QT Prolongation**

| Preclinical Data   | Healthy Volunteers   | Patients with Malaria  |
|--|--|--|
| Quinine inhibits HERG channels <i>in vitro</i> less than quinidine (Sanchez-Chapula, et al., 2003)   | Mean QTc increased 10-12 msec after single dose oral quinine sulfate (324 mg and 648 mg) (Mutual’s bioequivalence studies) | $\Delta$ QTc 80 msec (increased approximately 20% from baseline) in patients who received quinine 600 mg IV 3 times daily (Claessen, et al., 1998)   |
| Quinine blocks K <sup>+</sup> and Ca <sup>+</sup> channels <i>in vitro</i> (Clark, et al., 1995; del Pozo, et al., 1996; Michel, et al., 2002) | No change in QTc after single dose 300 mg IV quinine (Claessen, et al., 1998)  | $\Delta$ QTc 15% over baseline with IV quinine 20 mg/kg loading dose, then 10 mg/kg every 8 hours, followed by oral quinine sulfate when tolerated (Mehta, et al., 1994)                                     |
| Quinine and quinidine prolong conduction time <i>in vivo</i> (Sheldon, et al., 1990; Jurkiewicz, et al., 1985)                                 | $\Delta$ QTc 82 msec with rapid IV infusion of single 10 mg/kg dose quinine (Karbwan, et al., 1993)                        | $\Delta$ QTc 10% over baseline (mean maximal QTc prolongation of 41 msec) with IV quinine (10 mg/kg) followed by oral quinine (10 mg/kg every 8 hours) (White, et al., 1983a)                                |
|  | Mean maximal QTc 415 msec with rapid IV infusion of 5 mg/kg quinine (White, et al., 1983)                                  | Slight increase in QTc dispersion to 65 msec in patients treated with oral quinine sulfate 25 mg/kg 3 times daily; compared to increase in QTc dispersion with halofantrine > 100 msec (Touze, et al., 2002) |

**Medical Officer Comments:** *These data collectively confirm quinine’s potential for QT prolongation. In general, it would appear that quinine may be less potent in this regard than either quinidine or halofantrine. As discussed below, we have proposed both Contraindications and Warnings regarding QT prolongation in the final product label for quinine sulfate.*

Although QTc prolongation with quinine is not uncommon in healthy subjects and patients, reports of serious cardiac arrhythmias in patients who received quinine for treatment of malaria have been infrequent. In a retrospective review of 452 patients treated for malaria between 1980 and 1990 in a German hospital, 3 of 100 (3.0%) patients who received quinine (with or without doxycycline) developed ECG changes or arrhythmias (not further described), which resolved after quinine was stopped, and were attributed to quinine (Weinke, et al., 1992).

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

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**Table 41: Case Reports of Serious Cardiac Arrhythmias associated with Quinine (Applicant's Table 13, ISS)**

**Published Case Reports of Serious Quinine-Associated Cardiotoxicity**

| Author, Year(Country)         | N | Adverse Event  | Dosage Regimen / Route / Indication  |
|-------------------------------|---|--|--|
| Bonington et al., 1996 (U.K.) | 1 | Ventricular fibrillation / death   | Intravenous loading dose of 1.4 grams of quinine (20 mg/kg) infused over 4 hours, followed 8 hours later by an i.v. dose of quinine 600 mg for treatment of <i>P. falciparum</i> malaria |
| Iyegb et al., 2001 (India)    | 2 | Tachycardia, irregular rhythm, unifocal premature ventricular contractions, nodal escape beats following the PVCs, and U waves | Intravenously, 600 mg i.v. over 4 hours for treatment of <i>P. falciparum</i> malaria  |
| Kachar et al., 1998 (India)   | 1 | Prolonged QTc interval and multiple ventricular premature beats, followed by ventricular fibrillation                          | Intravenously, 7 mg/kg loading dose, followed by 600 mg over 3 to 4 hours 3 times a day for treatment of <i>P. falciparum</i> malaria  |
| Wainke et al., 1992 (Germany) | 3 | Arrhythmia (not otherwise specified)   | "Usual doses" of quinine, often initiated intravenously and later switched to oral drug for treatment of <i>P. falciparum</i> malaria  |
| Martin et al., 1997 (U.S.)    | 1 | Torsades de pointes  | A single 260-mg dose of oral quinine sulfate for leg cramps concurrently with astemizole 10 mg (Hismanal <sup>®</sup> )  |

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In the case reported by Bonington, et al. (1996), a 71 year-old female missionary from Zambia with no significant past medical history, received intravenous quinine for *P. falciparum* malaria (20 mg/kg loading dose administered over 4 hours; followed by 600 mg administered every 8 hours for two doses). The patient then developed ventricular tachycardia unresponsive to lidocaine, followed by ventricular fibrillation. The patient was initially resuscitated, but later developed asystole and died. This patient had a prolonged QTc interval (490 msec) on admission. However, during quinine treatment, the QTc interval increased to 593 msec noted approximately 10 hours after the second maintenance dose of quinine, then 657 msec 4 hours later. The free (unbound) quinine levels were determined to be elevated in this patient (up to 9 mg/L at 26.5 hours after the first dose of quinine), despite normal total plasma quinine levels (10-20 mg/L). Free quinine levels are generally expected to range from 5-10% of the total quinine level in patients with malaria because of increased  $\alpha$ 1-glycoprotein, the major protein responsible for plasma binding of quinine. The only other medication the patient received prior to the QTc prolongation and ventricular arrhythmias was cefotaxime, which has not been associated with QT prolongation. Quinine was considered the likely cause for these events. It was not clear, however, why free quinine levels were elevated in this patient relative to total quinine.

**Medical Officer Comments:** *This patient had QT prolongation at baseline, and congenital QT syndrome or other baseline QTc prolongation is a known risk factor for the development of torsades de pointes, which was not described in this case. We have proposed a CONTRAINDICATION in the final product label as follows:*

***"Prolonged QT Interval***

*Quinine sulfate is contraindicated in patients with a prolonged QT interval. One case of a fatal ventricular arrhythmia was reported in an elderly patient with a prolonged QT*

*interval at baseline, who received quinine sulfate intravenously for P. falciparum malaria. (See WARNINGS.)”*

Tigga, et al. (2001) reported two cases of cardiac arrhythmias in young men with *P. falciparum* malaria, who were treated with standard doses (10 mg/kg every 8 hours) of intravenous quinine. The first case involved a 23 year-old man who developed an irregular heart rate and “uneasiness in the chest” after his third dose of quinine (600 mg). ECG showed a heart rate of 105 bpm and ventricular bigeminy, with normal PR, QRS, and QT intervals. Quinine was stopped and replaced with sulfadoxine-pyramethamine, and ECG changes resolved within 48 hours of stopping quinine. The second case involved a 20 year-old male who initially received quinine at a dose of 600 mg every 8 hours for 48 hours, then every 12 hours. An irregular heart rate was noted on the fourth day of quinine therapy, and an ECG showed a heart rate of 65 bpm, multiple unifocal PVCs, and U waves, but normal PR, QRS and QTc intervals. Serum sodium and potassium were normal. Quinine was stopped and replaced with sulfadoxine-pyramethamine, and ECG changes resolved 3 days after quinine discontinuation. Because QTc intervals were not prolonged in either patient, the investigators considered the cardiovascular toxicity in these cases was due to an idiosyncratic response.

*Medical Officer Comments: The temporal relationship of these cardiac arrhythmias and resolution upon quinine discontinuation suggest a causal relationship to quinine. Although these arrhythmias did not result in a serious outcome, because they occurred in young, presumably healthy individuals, suggests that the cardiac effects of quinine are not limited to elderly patients with multiple co-morbidities.*

As reported by Kochar, et al., (1998), a 46 year-old Indian female with no history of cardiovascular or peripheral vascular disease developed bilateral gangrene of the feet with *P. falciparum* malaria. The patient had intermittent fever, chills and rigors for 1 month, nausea and vomiting for 10 days, and bluish/blackened feet for 5 days prior to the diagnosis of malaria. Although she had received antibiotics and antipyretics, she had not received antimalarial treatment prior to quinine. The patient was treated with intravenous quinine (7 mg/kg loading dose, then 600 mg three times daily), administered over 3-4 hours for each dose. Pre-treatment ECG was normal. She developed syncope on the second day of treatment, recovered with cardiopulmonary resuscitation, but again had a syncopal episode on the third day. At that time, the ECG showed a prolonged QTc interval (not quantified) and multiple ventricular premature beats. Quinine was stopped and replaced with chloroquine, but the patient developed multiple episodes of ventricular fibrillation which resolved with cardioversion, and infusion of potassium and magnesium. The QTc prolongation and ventricular arrhythmias resolved after 48 hours of quinine discontinuation. The patient recovered and was discharged from the hospital.

*Medical Officer Comments: The temporal relationship to quinine and resolution of QTc prolongation and ventricular arrhythmias upon quinine discontinuation suggest a causal relationship of quinine to these events. We have proposed a WARNING statement in the final product labeling regarding QT prolongation and ventricular arrhythmias as follows:*

***“QT Prolongation and Ventricular Arrhythmias***

*QT interval prolongation has been a consistent finding in studies which evaluated electrocardiographic changes with oral or parenteral quinine administration, regardless of age, clinical status, or severity of disease. The maximum increase in QT interval has been shown to correspond with peak quinine plasma concentration. (See Clinical Pharmacology/Electrocardiogram.) Quinine sulfate has been rarely associated with potentially fatal cardiac arrhythmias, including torsades de pointes.”*

Martin, et al. (1997) reported a case of syncope and torsades de pointes in a 42 year-old female after a single dose of Quinamm® (260 mg quinine sulfate) for severe leg cramps. This patient had been taking daily astemizole (10 mg) for allergies in addition to triamterene plus hydrochlorothiazide, isradipine, oral potassium, alprazolam and fluoxetine. ECG on hospital admission showed torsades de pointes, with a QT interval of > 680 msec. The patient had mildly decreased serum potassium and magnesium on admission. The arrhythmia eventually resolved with a number of different treatments, and the ECG normalized over the next 3 days.

***Medical Officer Comments:*** *This case occurred prior to the time that astemizole was removed from the market for potential effects on the QT interval. The temporal relationship between the torsades de pointes and administration of quinine, suggests a causative role for quinine, although astemizole is known to cause QT prolongation itself. Because astemizole is a CYP3A4 substrate, higher astemizole plasma levels could result with concomitant quinine because the latter is a CYP3A4 inhibitor. Torsades de pointes has also been described in association with quinine and astemizole in 2 cases identified in the AERS postmarketing database. None of these cases were fatal.*

We have proposed a Warning regarding concomitant use of quinine sulfate and astemizole, and similar drugs which are CYP3A4 substrates known to prolong the QT interval, as follows:

***“QT Prolongation and Ventricular Arrhythmias”***

*“... Quinine may also inhibit the metabolism of other drugs that are CYP3A4 substrates known to cause QT prolongation, such as astemizole, cisapride, terfenadine, pimozone, halofantrine and quinidine. Torsades de pointes has been reported in patients who received concomitant quinine and astemizole. Therefore, concurrent use of quinine sulfate with these medications, or drugs with similar properties, should be avoided (See **PRECAUTIONS/Drug Interactions**).”*

In addition, we have proposed a WARNING against concomitant use of quinine sulfate with class IA and III antiarrhythmic agents, also known to prolong QT intervals. The proposed wording is as follows:

*“Quinine sulfate is not recommended for use with other drugs known to cause QT prolongation, including Class IA antiarrhythmic agents (e.g. quinidine, procainamide, disopyramide), and Class III antiarrhythmic agents (e.g. amiodarone, sotalol, dofetilide).”*

Another WARNING was proposed for the concomitant use of macrolide antibiotics such as erythromycin, because of its potential to increase quinine exposure, and because of a postmarketing adverse event reported to AERS in which an elderly patient died after receiving quinine, erythromycin and dopamine, and developing torsades de pointes. This proposed WARNING states:

*“The use of macrolide antibiotics such as erythromycin should be avoided in patients receiving quinine sulfate. Fatal torsades de pointes was reported in an elderly patient who received concomitant quinine, erythromycin, and dopamine. Although a causal relationship between a specific drug and the arrhythmia was not established in this case, erythromycin is a CYP3A4 inhibitor and could potentially increase quinine plasma levels when used concomitantly. A related macrolide antibiotic, troleandomycin, has been shown to increase quinine exposure in a pharmacokinetic study (See **PRECAUTIONS/Drug Interactions**).”*

Additionally, the antimalarial agent halofantrine has known cardiotoxicity, including QT prolongation (Halfan® label), and in vitro pharmacokinetic studies have shown that halofantrine levels may increase when given with quinine. Similarly, pharmacokinetic studies have shown that concomitant mefloquine and quinine may result in QT prolongation. Because patients receiving quinine may have recently received mefloquine or halofantrine, we have proposed a WARNING regarding concomitant use of quinine and halofantrine or mefloquine as follows:

*“Concomitant administration of quinine sulfate with the antimalarial drugs, mefloquine or halofantrine, may result in electrocardiographic abnormalities, including QT prolongation, and increase the risk for torsades de pointes or other serious ventricular arrhythmias. Concurrent use of mefloquine and quinine may also increase the risk of seizures (See **PRECAUTIONS/Drug Interactions**).”*

We have also proposed the following WARNING regarding use in quinine in patients with risk factors for QT prolongation:

*“Quinine sulfate should be also be avoided in patients with known prolongation of QT interval (See **CONTRAINDICATIONS**), in elderly patients, and in patients with clinical conditions known to prolong the QT interval, such as uncorrected hypokalemia, bradycardia, and certain cardiac conditions.”*

#### **Hypotension associated with use of Quinine**

Administration of intravenous quinine, particularly by bolus injection, has been associated with severe, sometimes fatal hypotension, as reviewed by White, (1996). Quinine, like quinidine, may decrease vagal tone, resulting in vasodilatation and hypotension. However, hypotension is also frequently observed in patients with severe malaria prior to the receipt of any antimalarial treatment, making assessment of causality difficult for this adverse event. In a study involving 7 healthy volunteers reported by White, et al. (1983), who received a rapid intravenous infusion of quinine at a concentration of 1 mg/kg over 5 minutes, blood pressure, recorded at 2 minute intervals over an 18 minute period was decreased in 5/7 (71.4%) subjects, but only by < 10 mm

(systolic). Karbwang, et al. (1993) reported mild, transient hypotension in two of 8 healthy male subjects who received 10 mg/kg quinine by intravenous infusion over 1 hour.

In a study of 16 Thai adult patients with severe malaria, only 1/16 (6.3%) patients developed significant hypotension requiring dopamine, during the intravenous quinine infusion of 7 mg/kg over 30 minutes, followed by 10 mg/kg over 4 hours (Davis, et al., 1990). Mehta, et al., (1994) reported no significant hypotension in 24 patients with severe malaria treated with either a loading dose of quinine (20 mg/kg infused over 4 hours, followed by 10 mg/kg every 8 hours) or with the standard dose of 10 mg/kg every 8 hours, without the loading dose. However, in a study comparing quinine (initially administered intravenously 10 mg/kg every 8 hours followed by oral quinine as soon as oral medication was feasible) with intramuscular artemether, 160 mg loading dose, followed by 80 mg daily, in patients with severe malaria, hypotension was observed in 13/19 (68.4%) patients who received quinine, and in 2/31 (6.5%) patients who received artemether (. Although, the degree of hypotension was not further characterized, this difference was statistically significant ( $p=0.007$  by Fisher's exact test) (Karbwan, et al., 1997). In a report by Fulkerson, et al., (1970), hypotension was reported in 11/12 (91.7%) subjects (post-surgical patients without malaria) who received oral quinine 650 mg every 8 hours for 10 days. The mean maximum decrease in systolic blood pressure at some time during the course of quinine was 16 to 18 mm in these patients, and was associated with a concomitant increase in heart rate of 23-24 bpm on average.

***Medical Officer Comment:** Severe hypotension has been associated with rapid infusion of quinine or quinine overdose, but has been observed less consistently with slow intravenous administration. Whether hypotension is associated with oral quinine in therapeutic doses is not as clear. Only one of the studies cited by the applicant (Fulkerson, et al., 1970) evaluated blood pressure systematically in a small number of patients who received oral quinine, and noted mild-moderate decreases in blood pressure at some point during the 10 day course of quinine, as described above. However, this was not a randomized, controlled study, and concomitant medications or other conditions that contributed to hypotension were not discussed. Hypotension was not reported as an adverse event by the applicant in the two pharmacokinetic studies of oral quinine in approximately 50 subjects, performed for this NDA.*

Hypotension was not reported as an adverse event in the pharmacokinetic studies sponsored by the applicant or in any of the randomized, controlled studies which evaluated oral quinine monotherapy or combination therapy for treatment of uncomplicated *P. falciparum* malaria. In the studies submitted for evaluation of parenteral quinine treatment of severe *P. falciparum* malaria, hypotension was reported in one study (Singh, et al., 2000). In this study, hypotension was reported in 3/26 (11.5%) patients treated with intravenous quinine, and in none of the 26 patients treated with intramuscular artemether. The degree of hypotension or outcome of these patients was not reported.

In the AERS postmarketing database, ODS found 19 unique reports which described hypotension or syncope. Among these reports, 10 had serious outcomes, 3 deaths, and 7 hospitalizations. The average patient age was 53, and the most common indication was

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leg/muscle cramps (in 13/19 cases). None of these cases noted intravenous administration of quinine, and presumably these events occurred in patients taking oral quinine. In 17/19 reports, hypotension had a positive association with quinine use.

**Cardiovascular Adverse Events-Postmarketing Data from AERS Database**

As reviewed by the ODS, there were 63 unique cardiac adverse events reported in the AERS database. Most of these events had serious outcomes, including 12 cardiac deaths, 36 hospitalizations, and 11 other serious outcomes. Most cases were among females (34) and patients from the U.S. The average patient age was 59 years. In 5 cases, ODS determined a positive association of the adverse event with quinine. Cardiac adverse events are shown in the table below.

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**Table 42: Cardiac Adverse Events in the AERS Postmarketing Database for Quinine (from ODS consultation report)**

| Adverse Event                                | Number of Unique Events<br>N             | Cardiac<br>Deaths<br>N | Indication for Quinine Use   |
|--|--|------------------------|--|
| Total  | 63                                       | 12                     | --   |
| Torsades de pointes                          | 11                                       | 1                      | Leg cramps: 7 Unknown:4  |
| Overdosage                                   | 11                                       | 7                      | Suicide/intentional:7<br>Accidental: 4 (3 of which were for<br>"leg pain or pain") |
| Palpitations                                 | 5  | 0                      | Leg cramps: 3<br>Arthritis:1<br>Unknown:1  |
| Chest pain                                   | 7  | 1                      | Leg cramps: 5<br>Unknown: 2  |
| Arrhythmia                                   | 6  | 0                      | Leg cramps:1<br>Restless leg syndrome:1;<br>Unknown:4                              |
| Tachycardia                                  | 5  | 1                      | Leg cramps/muscle spasms:2;<br>malaria:1<br>Multiple myeloma: 1<br>Unknown: 1      |
| Congestive heart failure<br>(CHF), worsening | 4  | 1                      | Unknown:4  |
| Ventricular tachycardia                      | 3  | 0                      | Leg cramps:2; restless leg syndrome:1  |
| Syncope                                      | 4  | 0                      | Leg cramps:1<br>Unknown: 3   |
|  |  |                        |  |
| Atrial fibrillation                          | 2  | 0                      | Unknown:2  |
| Cardiac arrest                               | 2  | 1                      | Unknown:2  |
| Abnormal ECG                                 | 2 (A-V block, and T-wave<br>abnormality) | 0                      | Leg cramps: 1<br>Unknown:1   |
| Bradycardia                                  | 1  | 0                      | Unknown:1  |
| Total  | 63                                       | 12                     |  |

As reviewed by ODS, among the 11 cases of torsades de pointes, the median patient age was 75 (range 41 to 93 years old). Serious outcomes were noted among all of these cases, including one death which occurred in an 83 year old female who was receiving erythromycin and dopamine for an unknown indication. Two non-fatal cases of torsades de pointes involved concomitant administration of astemizole, a drug with known potential for QT prolongation. In another case, an 83 year-old female with a history of chronic atrial fibrillation and chronic furosemide use experienced QT prolongation and torsades de pointes after a single quinine dose. A 72 year-old male with pre-existing hypertension, diabetes, and renal failure, requiring hemodialysis, experienced torsades de pointes after 1 week of quinine use. This latter patient was also taking digoxin. Six additional patients with torsades de pointes had other serious underlying medical conditions or multiple concomitant medications. A positive association between quinine use and torsades de pointes was noted in 2 of these reports.

The median age was 58 (range 16 to 78 years old) for patients with arrhythmia reported as an adverse event. Four patients were female, 1 male, and gender was not specified in one case. One case of arrhythmia was reported in a 65 year-old female with atrial fibrillation, who had a cardiac pacemaker, and who was receiving the antiarrhythmic drug, dofetilide. Three cases involved quinine overdose. Each of these cases had a serious outcome, not further described.

Among the 3 reports of ventricular tachycardia, 2 were females; one was male, with a median age of 78, ranging from 50 to 80 years old. One case was confounded by the concomitant use of cisapride, which is known to cause QT prolongation. In the second case, the patient was receiving concomitant ibutilide, an antiarrhythmic agent, for atrial fibrillation, and in the third case, the patient had underlying cardiovascular disease with an automatic implantable cardiac defibrillator, and had received concomitant propafenone, and an unintentional overdose of meclizine. All three of these patients had received quinine for leg cramps or restless leg syndrome. Each of these cases had a serious outcome, not further described.

Among the 4 cases of syncope reviewed by ODS, 2 patients were male, and 1 was female, (gender not reported in one case. Median age was 58 years (range 56-60). Syncope resulted in hospitalization in 3 of the 4 cases.

Among the 6 cases of tachycardia reviewed by ODS, the median age was 51 years (range 34 to 72 years). The one death in this category occurred in a 34 year-old female with a previous history of quinine-induced adverse events. This patient had a previous diagnosis of systemic lupus erythematosus, and was on hemodialysis. Death was due to cardiac arrest.

Among the 7 cases of chest pain reviewed by ODS, the median age was 73 years. There was one fatality in a 65 year-old female with diabetes, angina and CHF. In addition to the report of chest pain, she was noted to be jaundiced and thrombocytopenic, requiring a platelet transfusion.

In addition to those listed above, other cardiac adverse events reported in the AERS postmarketing safety database included ventricular extrasystoles, supraventricular tachycardia, atrioventricular block (first degree and complete), nodal arrhythmia, decreased heart rate, chest discomfort, hypertension, hypotension, orthostatic hypotension, flushing, cyanosis, circulatory collapse, ventricular hypertrophy, and myocarditis. These events were not reviewed specifically for possible relationship to quinine.

***Medical Officer Comments:*** *Although no serious cardiac adverse events were reported among the published randomized, controlled studies submitted for evaluation of oral quinine safety and efficacy, a number of case series, case reports, in addition to postmarketing data confirm the potential of quinine to cause QT prolongation, and potentially fatal cardiac arrhythmias, particularly in patients with other risk factors for these events or with concomitant use of medications known to cause QT prolongation. As discussed above, we have proposed a Warning regarding the potential of quinine for prolongation of the QTc interval and increased risk for fatal torsades de pointes. Additionally, a Contraindication is proposed for patients with known prolonged QT syndrome, as described previously.*

### 3. Gastrointestinal Adverse Events with Quinine

Gastrointestinal adverse events, including nausea, vomiting, diarrhea and abdominal pain are commonly generally considered part of the spectrum of cinchonism observed with quinine, and are a prominent feature of quinine overdose. The applicant referred only to the review by Bateman and Dyson (1986) on quinine toxicity in describing adverse events associated with quinine. These events are thought to be due to a local irritant effect on the gastrointestinal tract, as well as central effects of quinine on the chemoreceptor trigger zone.

*Medical Officer Comments: Adverse events associated with antimalarial therapy were documented by Weinke, et al. (1992) in a retrospective study of 452 patients with malaria. Abdominal pain was the most common drug-related adverse event and was reported in 7% of 100 patients with malaria who received quinine, 4.7% of 301 patients who received chloroquine, 26% of patients who received mefloquine, and 13.3% of 15 patients who received Fansidar® (sulfadoxine-pyramethamine).*

Serious postmarketing gastrointestinal adverse events included diarrhea, paralytic ileus, tenesmus, nausea, vomiting, dysphagia, odynophagia, esophageal ulcer, esophagitis, hematemesis and gastrointestinal hemorrhage. These events, however, were not reviewed individually to attribute causality.

*Medical Officer Comments: The most commonly cited gastrointestinal adverse events will be listed in the ADVERSE EVENTS section of the final product labeling.*

### 4. Hepatic Adverse Events with Quinine

Severe hepatic impairment and fulminant hepatic failure have been reported with severe *P. falciparum* malaria (Srivastava, et al., 1996), and hepatic adverse events related to quinine have been reported only infrequently in the literature. Granulomatous hepatitis has been reported previously with quinidine (Bramlet, et al., 1980). More recently, a number of case reports have described granulomatous hepatitis with quinine use for nocturnal leg cramps. The mechanism of hepatic toxicity with quinine and quinidine is considered to be an antibody-mediated hypersensitivity reaction (Bramlet, et al., 1980). The case reports provided by the applicant are summarized in the table below. In the case described by Hou, et al. (1997), in addition to granulomatous hepatitis, the patient also developed thrombocytopenia and leukopenia, and quinine-dependent antibodies to platelets, neutrophils and lymphocytes were detected, and were considered evidence of quinine-induced thrombocytopenia and leukopenia. However, the mechanism of hepatotoxicity in this case was not determined, but a similar hypersensitivity-type mechanism was proposed. One additional report indicating hypersensitivity as a possible mechanism was found on review of the literature. In this case, a 35 year-old female with relapsing fevers, leukopenia, myalgias, headache, and elevated transaminases was found to have hepatic granuloma on liver biopsy after consumption of > 1 liter/week of tonic water (Schlegel, A, 2004).

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**Table 43: Summary of Case Reports of Granulomatous Hepatitis with Quinine**

| Case Report                 | Patient age and gender | Indication for Quinine | Dose               | Symptoms  | Laboratory abnormalities   | Liver biopsy-confirmed | Effect of quinine discontinuation              | Effect of quinine re-challenge                 |
|-----------------------------|------------------------|------------------------|--------------------|---|--|------------------------|--|--|
| Katz, et al., 1983          | 65F                    | Nocturnal leg cramps   | Not specified      | Fever, malaise, nausea, vomiting, and polyarthralgia  | Elevated AST, ALT, sedimentation rate                                      | Yes                    | Symptoms resolved                              | Symptoms recurred                              |
| Mathur, et al., 1990        | 67M                    | Muscle cramps          | 300 mg daily       | Fever, and polyarthralgia, vasculitic rash  | Elevated AST, AP, GGT  | Yes                    | Symptoms resolved                              | Not performed                                  |
| Punukollu, RC, et al., 1990 | 37F                    | Leg cramps             | 300 mg twice daily | Fever, chills, headache, photophobia, blurred vision, arthralgias, myalgias, nausea, abdominal pain, and diarrhea | Decreased platelet count, elevated AST, ALT, AP, and bilirubin             | No                     | Symptoms resolved                              | Symptoms and laboratory abnormalities recurred |
| Perez, et al., 1994         | 74M                    | Leg cramps             | 260 mg daily       | Fever, back pain, right upper quadrant abdominal pain and jaundice  | Elevated AST, ALT, alkaline phosphatase, bilirubin, and sedimentation rate | Yes                    | Yes  | Not performed                                  |
| Farver, and Lavin, 1999     | 57F                    | Nocturnal leg cramps   | 260 mg daily       | Nausea, vomiting, myalgia, headache, fever, chills, rigors  | Elevated AST, ALT, AP, GGT, and sedimentation rate                         | No                     | Symptoms and laboratory abnormalities resolved | Not performed                                  |
| Hou, et al., 1997           | 58M                    | Not specified          | Not specified      | Fever, vomiting, diarrhea   | Mild thrombocytopenia, leukopenia, and elevated AST and ALT                | Yes                    | Symptoms not specified                         | Symptoms and laboratory abnormalities recurred |

AST= aspartate aminotransaminase; ALT= alanine aminotransferase; AP= alkaline phosphatase; GGT=  $\gamma$ -glutamyl transferase

*Medical Officer Comments: Although uncommon, hepatic toxicity in the form of granulomatous hepatitis, presumably due to a hypersensitivity reaction to quinine can occur with relatively low doses of quinine in comparison to those proposed for the treatment of uncomplicated malaria in this NDA. Most of the patients described in these reports were receiving low doses of quinine for treatment of leg cramps. Symptoms and laboratory abnormalities abated upon discontinuation of quinine, and in several cases, recurred upon rechallenge, clearly indicating a drug-related effect. Notably, no cases of severe hepatic impairment or hepatic failure have been attributed to quinine in the published literature. Although no cases of granulomatous hepatitis have been reported in patients with malaria, the non-specific symptoms documented in these case reports could be mistaken for symptoms of cinchonism.*

Postmarketing hepatobiliary adverse events reported to the AERS database included abnormal hepatic function, hepatitis, hepatic failure, hyperbilirubinemia, jaundice, cholestatic jaundice, abnormal liver function tests, cholestasis, increased AST, alkaline phosphatase, gammaglutamyl transferase, and bilirubin. These events however were not reviewed individually to determine a potential causal relationship to quinine.

#### **5. Hematological Adverse Events with Quinine**

Quinine has been associated with a variety of hematological adverse events including thrombocytopenia, immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), hemolysis, hemolytic anemia, blackwater fever, disseminated intravascular coagulation (DIC), leukopenia, neutropenia, agranulocytosis, pancytopenia, lupus anticoagulant, and hypoprothrombinemia. These events were reviewed by the applicant, as summarized below.

##### **Thrombocytopenia**

Quinine and quinidine are one of the most common drugs associated with immune-mediated thrombocytopenia (George, et al., 1998). The applicant has provided a number of case reports describing severe thrombocytopenia, particularly after intermittent ingestion of quinine for leg cramps (Hawthorne, et al., 2000; Reddy, et al., 2004; Kojouri, et al., 2000), but also in association with ingestion of quinine-containing beverages such as tonic water. The mechanism appears to involve binding of quinine-dependent antibodies to specific platelet membrane glycoproteins, resulting acutely in increased platelet destruction and uptake by the reticuloendothelial system (Burgess, et al., 1998; Asvadi, et al., 2003). The clinical picture associated with drug-induced thrombocytopenia includes thrombocytopenia, purpura, petechiae, and occasionally serious bleeding complications.

*Medical Officer Comments: The over-the-counter (OTC) use of quinine was prohibited by the Agency in 1994 because of the concern regarding hematological adverse events associated with quinine, including thrombocytopenia hypersensitivity reactions. (59 FR 43252 and 21 CFR 310.546). We have proposed a CONTRAINDICATION and*

*WARNING regarding potential hypersensitivity reactions including thrombocytopenia for the final product labeling.*

### **Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)**

Thrombotic microangiopathy includes both TTP and HUS, and has multisystemic manifestations resulting from platelet aggregation in the arterial microvasculature. A specific clinical entity of TTP-HUS associated with quinine-dependent antibodies has been described in a number of case reports (Glynne, et al. 1999; McDonald, 1997; Gottshall, 1994; Baliga, and Wingo, 2003). This syndrome encompasses a constellation of signs and symptoms including thrombocytopenia, microangiopathic hemolytic anemia, acute renal failure, purpura, and neurologic abnormalities in some instances. In one case, distal digital necrosis was reported in a patient with quinine-associated TTP-HUS (Agarwal, and Cherascu, 2002). In a retrospective study of 225 patients referred for plasma exchange with suspected TTP-HUS, quinine was the most common cause of drug-associated TTP-HUS, with 17/225 (7.6%) cases associated with quinine use for nocturnal leg cramps (Kojouri, et al., 2001). The most common presenting symptoms in this series included abdominal pain, nausea, vomiting and diarrhea, sometimes with fever and chills. Sepsis was a common initial diagnosis. In this series, 3/17 (17.6%) patients died during their initial hospitalization for this diagnosis, and 8/14 (57%) survivors developed chronic renal failure. Thus, this clinical entity carries significant morbidity and mortality. A hypersensitivity reaction involving anti-platelet antibodies (discussed above) is thought to be the mechanism of TTP-HUS pathogenesis. Anti-endothelial cell antibodies associated with quinine have also been described (Spearing, et al., 1990), and may contribute to immune-mediated endothelial damage, development of microangiopathic hemolytic anemia and nephropathy (Baliga and Wingo, 2003).

*Medical Officer Comments: Some of these cases developed after ingestion of only a single quinine tablet many years after initial exposure to quinine. In the proposed labeling, the applicant listed prior thrombotic thrombocytopenia with quinine as a contraindication to quinine use. We have proposed adding a CONTRAINDICATION and in the final product labeling regarding the potential for hypersensitivity reactions with quinine, including TTP-HUS.*

### **Disseminated Intravascular Coagulation (DIC)**

DIC is a coagulopathy resulting in consumption of platelets and clotting factors, resulting in diffuse bleeding or hemorrhage. Other clinical manifestations of DIC include thrombosis and peripheral acrocyanosis. Laboratory abnormalities in DIC include thrombocytopenia, abnormal PT and/or PTT, decreased fibrinogen, elevated fibrin split products, and schistocytes (fragmented red blood cells).

Knower, et al. (2003) summarized 15 cases of quinine-associated DIC reported in the literature. Most of the patients were female, all had thrombocytopenia, and increased fibrin degradation (split) products or D-dimer and coagulopathy. Most patients, 12/15 (80%), were female, and most presented with gastrointestinal complaints, including nausea, vomiting, abdominal pain, diarrhea, hematemesis, or melena. Some patients also developed hemolysis, renal impairment, and lactic acidosis. Most patients had detectable anti-platelet antibodies; while some also had anti-leukocyte and/or anti-erythrocyte antibodies. Spearing, et al. (1990) suggested that quinine-

dependent antibody binding of a specific endothelial cell antigen results in activation of coagulation and subsequent DIC.

*Medical Officer Comments: There appears to be considerable overlap between antibody-mediated quinine-dependent thrombocytopenia, quinine-associated TTP-HUS, and DIC, as described in these cases. All appear to involve some type of antibody-mediated hypersensitivity reaction. We have proposed CONTRAINDICATIONS and PRECAUTIONS in the final product label for potential quinine hypersensitivity reactions.*

#### **Quinine-Associated Leukopenia, Neutropenia or Pancytopenia**

The applicant described one case report of severe neutropenia in a 64 year-old male who received quinine for leg cramps (Sutherland, 1977). Additionally, neutropenia or leukopenia has been described in association with quinine use in patients who also had thrombocytopenia, anemia, or in those with HUS, or DIC (Maguire, et al., 1993). Quinine-induced neutropenia, and anemia like thrombocytopenia, are thought to be due to an immune (antibody) -mediated process (Stroncek, et al., 1992).

#### **Hemolysis, Hemolytic Anemia and Blackwater Fever associated with Quinine**

Blackwater fever, a syndrome of acute intravascular hemolysis, hemoglobinuria (black or red urine), and fever, sometimes accompanied by renal failure, is associated with recent or current *P. falciparum* malaria, and quinine use (Bruneel, et al., 2001). However, acute hemolysis may also occur in patients with *P. falciparum* malaria without exposure to quinine (Rogier, et al., 2003). The incidence of blackwater fever declined in Africa when chloroquine was introduced in 1950, and has increased recently with increased use of quinine, and the related amino-alcohol drugs, mefloquine and halofantrine for treatment of chloroquine-resistant malaria (Bruneel, et al., 2001). In the absence of high levels of parasitemia, the mechanism of hemolysis in blackwater fever may involve immune-mediated lysis of erythrocytes sensitized by quinine, halofantrine, or mefloquine in patients chronically exposed to *P. falciparum*, and there may be cross-reactivity among these antimalarial agents (Bruneel, et al., 2001). Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency has also been implicated as a factor in hemolysis in some patients who received quinine for malaria (Tran Hien, et al., 1996).

The incidence of blackwater fever in a randomized, controlled trial of intramuscular artemether or quinine in Vietnamese adults with severe falciparum malaria was 7/284 (2.5%) in patients treated with artemether, and 4/276 (1.4%) among those who received quinine (Tran Hien, et al., 1996). This difference was not statistically significant (p=0.11)

*Medical Officer Comments: We have proposed a CONTRAINDICATION in the final product labeling regarding use of quinine sulfate in the setting of G-6-PD deficiency. Additionally, a CONTRAINDICATION and PRECAUTION is proposed regarding potential hypersensitivity reactions with quinine, including blackwater fever.*