



NDA 21-799/S-008

AR Holding Company, Inc.
Attention: Mr. Robert Dettery
Vice President, Regulatory Affairs
1100 Orthodox Street
Philadelphia, PA 19124

Dear Mr. Dettery:

Please refer to your supplemental new drug application dated and received October 22, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Quaalun (quinine sulfate) Capsules, 324mg.

We acknowledge receipt of your submissions dated May 13, 2008 (2), June 6, 2008, and July 1, 2008.

Your submission dated May 13, 2008 constituted a complete response to our Approvable letter dated April 22, 2008.

This supplemental new drug application provides for revisions to the **CLINICAL PHARMACOLOGY** and **PRECAUTIONS/Drug Interactions** sections of the package insert to add new information based on data from recently conducted *in vitro* studies of the hepatic metabolism of quinine and of the effect of quinine on inhibition of hepatic cytochrome P450 isoenzymes in human hepatocytes.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The final printed labeling (FPL) must be identical to the package insert submitted June 6, 2008.

The revisions to the package insert are as follows (additions are noted with underline and deletions noted with ~~strikethrough~~):

1. Under the **CLINICAL PHARMACOLOGY/Metabolism** subsection:

Metabolism: Quinine is metabolized almost exclusively *via* hepatic oxidative cytochrome P450 (CYP) pathways, resulting in four primary metabolites, 3-hydroxyquinine, 2'-quinone, Odesmethylquinine, and 10, 11-dihydroxydihydroquinine. Six secondary metabolites result from further biotransformation of the primary metabolites. The major metabolite, 3-hydroxyquinine, is less active than the parent drug. *In vitro* studies using human liver microsomes and recombinant P450 enzymes have shown that quinine is metabolized mainly by CYP3A4. Depending on the *in vitro* experimental conditions, other enzymes, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 were shown to have some role in the metabolism of quinine. ~~The CYP~~

~~isoenzyme pathways involved in quinine metabolism are not completely elucidated, but it is known that the formation of 3-hydroxyquinine is mediated mainly by CYP3A4 and to a minor extent, by CYP2C19. Therefore, co-administration of drugs that inhibit these enzymes may result in an increase in plasma quinine concentrations, whereas co-administration of drugs that induce these enzymes may decrease plasma quinine concentrations (See WARNINGS, PRECAUTIONS/Drug Interactions).~~

2. The heading of the **CLINICAL PHARMACOLOGY/Special Populations** subsection, Table 2, “Quinine Pharmacokinetic Parameters Following the First 10 mg/kg Quinine Sulfate Oral Dose in Pediatric Patients (age 1.5 to 12 years) with Acute Uncomplicated *P. falciparum* Malaria versus Healthy Pediatric Controls” was revised to read:

P. falciparum malaria pediatric patients
(n = 15)
Mean ± SD

3. Under the **PRECAUTIONS/Drug Interactions** subsection:

Effects of Drugs and Other Agents Substances on Quinine Pharmacokinetics

Drugs and other substances that alter the absorption, distribution, metabolism, and excretion of quinine may increase or decrease quinine concentrations (see CLINICAL PHARMACOLOGY).

Antacids: Antacids containing aluminum and/or magnesium may delay or decrease absorption of quinine. Concomitant administration of these antacids with Qualaquin should be avoided.

Cholestyramine: In 8 healthy volunteers who received quinine sulfate 600 mg with or without 8 grams of cholestyramine resin, no significant difference in quinine pharmacokinetic parameters was seen.

Cigarette Smoking (CYP1A2 Inducer): In healthy male heavy smokers, the mean quinine AUC following a single 600-mg dose was 44% lower, the mean C_{max} was 18% lower, and the elimination half-life was shorter (7.5 hours versus 12 hours) than in their non-smoking counterparts. However, in malaria patients who received the full 7-day course of quinine therapy, cigarette smoking produced only a 25% decrease in median quinine AUC and a 16.5% decrease in median C_{max}, suggesting that the already reduced clearance of quinine in acute malaria could have diminished the metabolic induction effect of smoking. Because smoking did not appear to influence the therapeutic outcome in malaria patients, it is not necessary to increase the dose of quinine in the treatment of acute malaria in heavy cigarette smokers.

Cimetidine, ranitidine (nonspecific CYP450 inhibitors): In healthy volunteers who were given a single oral 600 mg dose of quinine sulfate after pretreatment with cimetidine (200 mg three times daily and 400 mg at bedtime for 7 days) or ranitidine (150 mg twice daily for 7 days), the apparent oral clearance of quinine decreased and the mean elimination half-life increased significantly when given with cimetidine but not with ranitidine. Compared to untreated controls, the mean AUC of quinine increased by only 20% with ranitidine and by 42% with cimetidine (p<0.05) without a significant change in mean quinine C_{max}. When quinine is to be given concomitantly with a histamine H₂-receptor blocker, the use of ranitidine is preferred over cimetidine. Although cimetidine may be used concomitantly with Qualaquin, patients should be monitored closely for adverse events associated with quinine.

4. The following was added alphabetically to the **PRECAUTIONS/Drug Interactions/Effect of Quinine on the Pharmacokinetics of Other Drugs** subsection:

Atorvastatin (CYP3A4 substrate): Rhabdomyolysis with acute renal failure secondary to myoglobinuria was reported in a patient taking atorvastatin administered with a single dose of quinine. Quinine may increase plasma concentrations of atorvastatin, thereby increasing the risk of myopathy or rhabdomyolysis. Thus, clinicians considering combined therapy of Quinaldin with atorvastatin or other HMG-CoA reductase inhibitors (“statins”) that are CYP3A4 substrates (e.g., simvastatin, lovastatin) should carefully weigh the potential benefits and risks of each medication. If Quinaldin is used concomitantly with any of these statins, lower starting and maintenance doses of the statin should be considered. Patients should also be monitored closely for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during initial therapy. If marked creatine phosphokinase (CPK) elevation occurs or myopathy (defined as muscle aches or muscle weakness in conjunction with CPK values > 10 times the upper limit of normal) is diagnosed or suspected, atorvastatin or other statin should be discontinued.

5. Under the **PRECAUTIONS/Drug Interactions/Effect of Quinine on the Pharmacokinetics of Other Drugs** subsection:

Results of *in vivo* and *in vitro* drug interaction studies suggest that quinine has the potential to inhibit the metabolism of drugs that are substrates of CYP3A4 and CYP2D6, as well as, inhibit the biliary excretion of drugs like digoxin.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> so that it is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 21-799/S-008.**”

Marketing this product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

Letters To Health Care Professionals

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

Reporting Requirements

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Mrs. Melanie Brinkley, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure : Package Insert

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Renata Albrecht
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