



NDA 06-002/S-042

sanofi-aventis U.S. Inc.
Attention: Ms. Debra L. Kolb
Base Business Product Support
U.S. Regulatory Affairs Marketed Products
55 Corporate Drive
P.O. Box 5925
Bridgewater, NJ 08807-0890

Dear Ms. Kolb:

Please refer to your supplemental new drug application dated December 11, 2008, received December 12, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aralen® (chloroquine phosphate, USP) Tablets, 500 mg.

This "Changes Being Effected" supplemental new drug application (sNDA) provides for revisions to the following sections of the Aralen® product labeling based on your review of your Company Core Data Sheet: **PRECAUTIONS/Drug Interactions, PRECAUTIONS/Nursing Mothers, ADVERSE REACTIONS/Special Senses: Ocular, ADVERSE REACTIONS/Gastrointestinal system, ADVERSE REACTIONS/Skin and appendages, ADVERSE REACTIONS/Hematologic system, ADVERSE REACTIONS/Central Nervous system, OVERDOSAGE/Symptoms, and OVERDOSAGE/Treatment.** Information at the end of the label has also been updated.

We have completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. This application provides for the following revisions to the content of labeling for the package insert (additions are noted with underline and deletions are noted with ~~strike through~~):

1. PRECAUTIONS

a. Drug Interactions

Antacids and kaolin: Antacids and kaolin can reduce absorption of chloroquine; an interval of at least 4 hours between intake of these agents and chloroquine should be observed.

Cimetidine: Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level. Concomitant use of cimetidine should be avoided.

Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability of ampicillin. An interval of at least two hours between intake of this agent and chloroquine should be observed.

Cyclosporine: After introduction of chloroquine (oral form), a sudden increase in serum cyclosporine level has been reported. Therefore, close monitoring of serum cyclosporine level is recommended and, if necessary, chloroquine should be discontinued.

Mefloquine: Co-administration of chloroquine and mefloquine may increase the risk of convulsions.

The blood concentrations of chloroquine and desethylchloroquine (the major metabolite of chloroquine, which also has antimalarial properties) were negatively associated with log antibody titers. Chloroquine taken in the dose recommended for malaria prophylaxis can reduce the antibody response to primary immunization with intradermal human diploid-cell rabies vaccine.

b. Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from chloroquine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the potential clinical benefit of the drug to the mother.

The excretion of chloroquine and the major metabolite, desethylchloroquine, in breast milk was investigated in eleven lactating mothers following a single oral dose of chloroquine (600 mg base). The maximum daily dose of the drug that the infant can receive from breastfeeding was about 0.7% of the maternal start dose of the drug in malaria chemotherapy. Separate chemoprophylaxis for the infant is required. See DOSAGE AND ADMINISTRATION.

2. ADVERSE REACTIONS

a. Special Senses: Ocular:

Special Senses: Ocular: Irreversible retinal damage in patients receiving long-term or high dosage 4-aminoquinoline therapy; visual disturbances (blurring of vision and difficulty of focusing or accommodation); nyctalopia; scotomatous vision with field defects of paracentral, pericentral ring types, and typically temporal scotomas, e.g., difficulty in reading with words tending to disappear, seeing half an object, misty vision, and fog before the eyes. Reversible corneal opacities have also been reported.

b. Gastrointestinal system:

Gastrointestinal system: Hepatitis, increased liver enzymes, Anorexia, nausea, vomiting, diarrhea, abdominal cramps.

c. **Skin and appendages:**

Rare reports of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and similar desquamation-type events. Pleomorphic skin eruptions, skin and mucosal pigmentary changes; lichen planus-like eruptions, pruritus, urticaria, anaphylactic/anaphylactoid reaction including angioedema, photosensitivity and hair loss and bleaching of hair pigment.

d. **Hematologic system:**

Rarely, pancytopenia, aplastic anemia, reversible agranulocytosis, thrombocytopenia and neutropenia.

e. **Central Nervous system:**

Convulsive seizures-, mMild and transient headache, polyneuritis. Neuropsychiatric changes including psychosis, delirium, anxiety, agitation, insomnia, confusion, hallucinations, personality changes, and depression.

3. **OVERDOSAGE:**

a. **Symptoms:**

Chloroquine is very rapidly and completely absorbed after ingestion. Toxic doses of chloroquine can be fatal. As little as 1 g may be fatal in children. Toxic symptoms can occur within minutes. These consist of headache, drowsiness, visual disturbances, nausea and vomiting, cardiovascular collapse, shock and convulsions followed by sudden and early respiratory and cardiac arrest. Hypokalemia has been observed with arrhythmias in cases of intoxication. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

b. **Treatment:**

Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital) or gastric lavage until the stomach is completely emptied. If finely powdered, activated charcoal is introduced by stomach tube, after lavage, and within 30 minutes after ingestion of the antimalarial, it may inhibit further intestinal absorption of the drug. To be effective, the dose of activated charcoal should be at least five times the estimated dose of chloroquine ingested.

Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultra short-acting barbiturate may be tried but, if due to anoxia, it should be corrected by oxygen administration and artificial respiration. Monitor ECG. In shock with hypotension, a potent vasopressor should be administered. Replace fluids and electrolytes as needed. Cardiac compressing or pacing may be indicated to sustain the circulation. Because of the importance of supporting

respiration, tracheal intubation or tracheostomy, followed by gastric lavage, may also be necessary. Peritoneal dialysis and exchange transfusions have also been suggested to reduce the level of the drug in the blood.

Intervention options can involve: diazepam for life-threatening symptoms, seizures and sedation, epinephrine for treatment of vasodilation and myocardial depression, potassium replacement with close monitoring of serum potassium levels.

4. **EDITORIAL REVISIONS** - Other editorial revisions proposed are as follows:

Revised ~~March 2007~~September 2008
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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> that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the national Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, "SPL for approved NDA 6-002/S-042."

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in SPL format to include the changes approved in these applications. Marketing the 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, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D.
Deputy Director for Safety
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
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/s/

Ozlem Belen
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