



NDA 6-002/S-039

Sanofi-Synthelabo, Inc.
Attention: Andrea Czeizinger, J.D.
Manager, Drug Regulatory Affairs
90 Park Ave.
New York, NY 10016

Dear Ms. Czeizinger:

Please refer to your supplemental new drug application, dated December 21, 2001, received December 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

6-002	ARALEN [®] (chloroquine phosphate tablets, USP) ARALEN [®] Hydrochloride (chloroquine hydrochloride injection, USP)	S-039
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We acknowledge receipt of your submissions dated February 25, 2003; April 16, 2003; May 6, 2003; and May 29, 2003.

This “Changes Being Effected (CBE)” supplemental new drug application provides for the following revisions to the ARALEN[®] package inserts (additions are double underlined and deletions are ~~struck out~~). The labeling revisions for Aralen Tablets are listed on pages 1-7 of this letter, and the labeling revisions for Aralen Injection are listed on pages 7-10 of this letter. In addition, both package inserts are attached.

ARALEN TABLETS

1. The boxed warning at the beginning of the label was deleted as follows:

<p style="text-align: center;">WARNING: PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS LEAFLET BEFORE PRESCRIBING ARALEN.</p>
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2. DESCRIPTION

• The first sentence was revised to read:

~~ARALEN, phosphate, brand of chloroquine phosphate, USP, is a 4-aminoquinoline compound for oral administration.~~

- The word “phosphate” was deleted after the word “Aralen” each time it was mentioned in the package insert.

- A sentence was added after the chemical structure to read:

Each tablet contains 500 mg of chloroquine phosphate USP, equivalent to 300 mg chloroquine base.

3. CLINICAL PHARMACOLOGY

- This section was revised to read:

~~ARALEN phosphate has been found to be highly active against the erythrocytic forms of *Plasmodium vivax* and *Plasmodium malariae* and most strains of *Plasmodium falciparum* (but not the gametocytes of *P. falciparum*).~~

~~The mechanism of plasmodicidal action of chloroquine is not completely certain. While the drug can inhibit certain enzymes, its effect is believed to result, at least in part, from its interaction with DNA.~~

Microbiology

~~ARALEN has been found to be active against the erythrocytic forms of *Plasmodium vivax* and *malariae* and most strains of *Plasmodium falciparum* (but not the gametocytes of *P. falciparum*). It is not effective against exoerythrocytic forms of the parasite. The precise mechanism of action of the drug is not known.~~

~~In vitro studies with trophozoites of *Entamoeba histolytica* have demonstrated that ARALEN also possesses amebicidal activity comparable to that of emetine.~~

Mechanism of action: Chloroquine is an antimalarial agent. While the drug can inhibit certain enzymes, its effect is believed to result, at least in part, from its interaction with DNA. However, the mechanism of plasmodicidal action of chloroquine is not completely certain.

Activity in vitro and in vivo: Chloroquine is active against the erythrocytic forms of *Plasmodium vivax*, *Plasmodium malariae*, and susceptible strains of *Plasmodium falciparum* (but not the gametocytes of *P. falciparum*). It is not effective against exoerythrocytic forms of the parasite.

In vitro studies with trophozoites of *Entamoeba histolytica* have demonstrated that chloroquine also possesses amebicidal activity comparable to that of emetine.

Drug Resistance:

Resistance of *Plasmodium falciparum* to chloroquine is widespread and cases of *Plasmodium vivax* resistance have been reported.

4. WARNINGS

- The beginning of this section was revised to read:

In recent years it has been found that certain strains of *P. falciparum* have become resistant to 4-aminoquinoline compounds (including chloroquine and hydroxychloroquine) as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia. Treatment with quinine or other specific forms of therapy is therefore advised for patients infected with a resistant strain of parasites. Chloroquine resistance is widespread and, at present, is particularly prominent in various parts of the world, including sub-Saharan Africa, Southeast Asia, the Indian subcontinent, and over large portions of South America, including the Amazon basin¹.

Before using chloroquine for prophylaxis, it should be ascertained whether chloroquine is appropriate for use in the region to be visited by the traveler. Chloroquine should not be used for treatment of *P. falciparum* infections acquired in areas of chloroquine resistance or malaria occurring in patients where chloroquine prophylaxis has failed.

Patients infected with a resistant strain of plasmodia as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia should be treated with another form of antimalarial therapy.

- The last sentence in the paragraph before the new “*Usage in Pregnancy*” subsection was revised to read:

The drug should not be used in these conditions unless in the judgement of the physician the benefit to the patient outweighs the ~~possible hazzard~~ potential risks.

- A “*Usage in Pregnancy*” subsection was added to read:

Radioactively tagged chloroquine administered intravenously to pregnant pigmented CBA mice passed rapidly across the placenta and accumulated selectively in the melanin structures of the fetal eyes. It was retained in the ocular tissues for five months after the drug had been eliminated from the rest of the body². There are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women. Usage of chloroquine during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the potential risk to the fetus.

5. PRECAUTIONS

- The subsection “**General**” was changed to “**Hematological Effects/Laboratory Tests**” and was revised to read:

Complete blood cell counts should be made periodically if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuance of the drug should be considered.

~~Since this drug is known to concentrate in the liver, it should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs.~~

The drug should be administered with caution to patients having G-6-PD (glucose-6 phosphate dehydrogenase) deficiency.

Laboratory Tests

~~Complete blood cell counts should be made periodically if patients are given prolonged therapy.~~

- Six new subsections were added to read:

Auditory Effects

In patients with preexisting auditory damage, chloroquine should be administered with caution. In case of any defects in hearing, chloroquine should be immediately discontinued, and the patient closely observed (see ADVERSE REACTIONS).

Hepatic Effects

Since this drug is known to concentrate in the liver, it should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs.

Central Nervous System Effects

Patients with history of epilepsy should be advised about the risk of chloroquine provoking seizures.

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.

Pregnancy

See WARNINGS, Usage in Pregnancy.

Geriatric Use

Clinical studies of Aralen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are

more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

6. ADVERSE REACTIONS

- This section was revised to read:

~~Ocular reactions~~ 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.

~~Neuromuscular reactions; Convulsive seizures.~~

Auditory reactions: Nerve type deafness; tinnitus, reduced hearing in patients with preexisting auditory damage.

Musculoskeletal system: Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction, have been noted.

Gastrointestinal reactions system: Anorexia, nausea, vomiting, diarrhea, abdominal cramps.

Dermatologic reactions Skin and appendages: Pleomorphic skin eruptions, skin and mucosal pigmentary changes; lichen planus-like eruptions, pruritus, ~~and hair loss~~ photosensitivity and hair loss and bleaching of hair pigment.

Hematologic system: Rarely, aplastic anemia, reversible agranulocytosis, thrombocytopenia and neutropenia.

CNS reactions: Central Nervous System: Convulsive seizures. Mild and transient ~~psychic stimulation;~~ headache. Neuropsychiatric changes including psychosis, delirium, personality changes and depression.

Cardiovascular reactions system: Rarely, hypotension, electrocardiographic change (particularly, inversion or depression of the T-wave with widening of the QRS complex), and cardiomyopathy.

7. OVERDOSAGE

- The word “shock” was added to the fifth sentence in the first paragraph to read:

These consist of headache, drowsiness, visual disturbances, nausea and vomiting, cardiovascular collapse, shock and convulsions followed by sudden and early respiratory and cardiac arrest.

- The third paragraph was revised to read:

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.

8.DOSAGE AND ADMINISTRATION

- The first paragraph was revised to read:

The dosage of chloroquine phosphate is often expressed ~~or calculated as the~~ in terms of equivalent chloroquine base. Each 500 mg tablet of ARALEN ~~phosphate~~ contains the equivalent to 300 mg chloroquine base. In infants and children the dosage is preferably calculated ~~on the~~ by body weight.

- The “**Treatment of Acute Attack**” subsection was revised to read:

Adults: An initial dose of 1 g (=600 mg base) followed by an additional 500 mg (= 300 mg base) after six to eight hours and a single dose of 500 mg (= 300 mg base) on each of two consecutive days. This represents a total dose of 2.5 g chloroquine phosphate or 1.5 g base in three days.

The dosage for adults ~~may also be calculated on the basis of body weight; this method is preferred of low body weight and~~ for infants and children. ~~A total dose representing 25 mg of base per kg of body weight is administered in three days~~ should be determined as follows:

First dose: 10 mg base per kg (but not exceeding a single dose of 600 mg base)

Second dose: (6 hours after first dose) 5 mg base per kg (but not exceeding a single dose of 300 mg base) ~~6 hours after first dose~~.

Third dose: (24 hours after first dose) 5mg base per kg ~~18 hours after second dose~~.

Fourth dose: (36 hours after first dose) 5 mg base per kg ~~24 hours after third dose~~.

For radical cure of vivax and malariae malaria concomitant therapy with an 8-aminoquinoline compound is necessary.

- The following statement was added to the end of this section:

Geriatric Use

See PRECAUTIONS, Geriatric Use.

9.HOW SUPPLIED

- This section was revised to read:

~~Tablets of 500 mg (= 300 mg base), bottles of 25 (NDC 0024-0084-01).~~

~~Pink, film-coated convex tablet, 1/2 inch in diameter with an uncoated core, containing 500 mg chloroquine phosphate, equivalent to 300 mg of chloroquine base.~~

Tablets containing 500 mg chloroquine phosphate USP, equivalent to 300 mg of chloroquine base, bottles of 25 (NDC 0024-0084-01).

White, film-coated convex, discoïd tablet, 1/2 inch in diameter with an uncoated core, printed in black ink with a stylized “W” on one side and an “A77” on the other side.

Dispense in tight, light-resistant container as defined in the USP/NF.

Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature]

10. REFERENCES

• This new section was added to read:

1. Malaria Deaths Following Inappropriate Malaria Chemoprophylaxis – United States, 2001. MMWR Weekly, 2001; 50(28): 597-599.
2. Ullberg S, Lindquist N G, Sjostrand S E: Accumulation of chorioretinotoxic drugs in the foetal eye. Nature 1970; 227: 1257.

ARALEN INJECTION

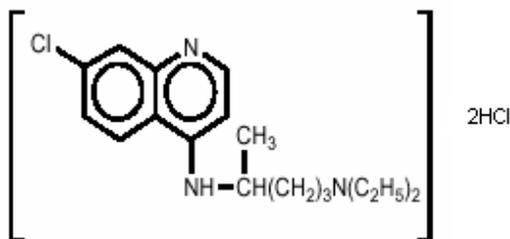
1. The boxed warning at the beginning of the label was deleted as follows:

<p>WARNING: PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS LEAFLET BEFORE PRESCRIBING ARALEN.</p>

2. DESCRIPTION

• The chemical name and chemical structure were revised as follows:

Chemically, ARALEN hydrochloride is ~~7-(Chloro-4-[[4-diethylamino)-1-methylbutyl] amino]-quinoline dihydrochloride~~ 7-chloro-4-[[4-(diethylamino)-1-methylbutyl]amino]quinoline dihydrochloride and has the following structural formula:



3. CLINICAL PHARMACOLOGY

• The first two sentences in this section were deleted:

~~ARALEN hydrochloride has been found to be highly active against the erythrocytic forms of *Plasmodium vivax* and *Plasmodium malariae* and most strains of *Plasmodium falciparum* (but not the gametocytes of *P. falciparum*).~~

~~The mechanism of plasmodicidal action of chloroquine is not completely certain. While the drug can inhibit certain enzymes, its effect is believed to result, at least in part, from its interaction with DNA.~~

- The **Microbiology** subsection was revised to read:

Microbiology

~~The compound is a highly active antimalarial and amebicidal agent.~~

~~*Plasmodium vivax* and *malariae* and most strains of *Plasmodium falciparum* (but not the gametocytes of *P. falciparum*). It is not effective against exoerythrocytic forms of the parasite. The precise mechanism of action of the drug is not known.~~

~~In vitro studies with trophozoites of *Entamoeba histolytica* have demonstrated that ARALEN also possesses amebicidal activity comparable to that of emetine.~~

Mechanism of action: Chloroquine is an antimalarial agent. While the drug can inhibit certain enzymes, its effect is believed to result, at least in part, from its interaction with DNA. However, the mechanism of plasmodicidal action of chloroquine is not completely certain.

Activity in vitro and in vivo: Chloroquine is active against the erythrocytic forms of *Plasmodium vivax*, *Plasmodium malariae*, and susceptible strains of *Plasmodium falciparum* (but not the gametocytes of *P. falciparum*). It is not effective against exoerythrocytic forms of the parasite.

In vitro studies with trophozoites of *Entamoeba histolytica* have demonstrated that chloroquine also possesses amebicidal activity comparable to that of emetine.

Drug Resistance:

Resistance of *Plasmodium falciparum* to chloroquine is widespread and cases of *Plasmodium vivax* resistance have been reported.

4. The **INDICATIONS** section is now called **INDICATIONS AND USAGE**. In this section, the following sentence was deleted:

~~Patients infected with a resistant strain of plasmodia as established by susceptibility testing, may have to be treated with another form of therapy.~~

5. WARNINGS

- The beginning of this section was revised to read:

Children and infants are extremely susceptible to adverse effects from an overdose of parenteral ARALEN and sudden deaths have been recorded after such administration. In no instance should the single dose of parenteral ARALEN administered to infants or children exceed 5 mg base per kg.

~~In recent years~~ It has been found that certain strains of *P. falciparum* have become resistant to 4-aminoquinoline compounds (including chloroquine and

hydroxychloroquine) as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia. Treatment with quinine or other specific forms of therapy is therefore advised for patients infected with a resistant strain of parasites. Chloroquine resistance is widespread and, at present, is particularly prominent in various parts of the world, including sub-Saharan Africa, Southeast Asia, the Indian subcontinent, and over large portions of South America, including the Amazon basin¹.

Before using chloroquine for prophylaxis, it should be ascertained whether chloroquine is appropriate for use in the region to be visited by the traveler. Chloroquine should not be used for treatment of *P. falciparum* infections acquired in areas of Chloroquine resistance or malaria occurring in patients where Chloroquine prophylaxis has failed.

Patients infected with a resistant strain of plasmodia as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia should be treated with another form of antimalarial therapy.

- The following sentence was revised to read:

All patients on long-term therapy with ~~this preparation~~ chloroquine should be questioned and examined periodically, including testing knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug.

- The “Use of Aralen in patients with psoriasis” paragraph was moved and is now the next-to-the-last paragraph in this section. The last sentence in this paragraph was revised to read:

The drug should not be used in these conditions unless in the judgement of the physician the benefit o the patient outweighs the ~~possible hazzard~~ potential risks.

- A new “*Usage in Pregnancy*” subsection was added to read:

Usage in Pregnancy: Radioactively tagged chloroquine administered intravenously to pregnant pigmented CBA mice passed rapidly across the placenta and accumulated selectively in the melanin structures of the fetal eyes. It was retained in the ocular tissues for five months after the drug had been eliminated from the rest of the body². There are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women. Usage of chloroquine during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the potential risk to the fetus.

6. PRECAUTIONS

- The changes in this section were identical to those in the Aralen Tablet label.

7. ADVERSE REACTIONS

- The changes in this section were identical to those in the Aralen Tablet label.

8. OVERDOSAGE

- This section was revised to read:

Symptoms: Toxic doses of chloroquine can be fatal. Doses should not exceed 5 mg base per kg. See WARNING concerning overdose in children. Toxic symptoms may occur within minutes. These consist of headache, drowsiness, nausea and vomiting, visual disturbances, cardiovascular collapse, shock, and convulsions followed by sudden and early respiratory and cardiac arrest. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

Treatment: Administer intravenous fluids. Peritoneal dialysis and exchange transfusions may be tried. Treat respiratory depression by artificial respiration, oxygen intubation or tracheostomy, if necessary. If present, convulsions due to cerebral stimulation may be treated with cautious administration of an ultra-short Oxygen and short-acting barbituates may be used to treat convulsions-acting barbiturate. If convulsions are due to anoxia, it should be corrected by oxygen administration and artificial respiration. Monitor ECG. In shock with hypotension, a potent vasopressor ~~such as NEO-SYNEPHRINE® hydrochloride~~ should be given intramuscularly in doses of 2 mg to 5 mg. Replace fluids and electrolytes as needed. Cardiac compressing or pacing may be indicated to sustain the circulation.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least six hours. Fluids may be forced, and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine to ~~help~~ promote urinary excretion in cases of both overdosage ~~or~~ and sensitivity.

9. DOSAGE AND ADMINISTRATION

- The following sentences were added to the end of this section:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Geriatric Use

See PRECAUTIONS, Geriatric Use.

10. HOW SUPPLIED

- This section was revised to read:

~~Clear ampuls of 5 mL (50 mg/mL), box of 5 (NDC 0024-0074-01)~~

Ampuls of 5 mL (250 mg/5 mL), box of 5 (NDC 0024-0074-01). Each mL contains 50 mg of the dihydrochloride salt equivalent to 40 mg of chloroquine base, in Water for Injection, USP.

Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature]

11. REFERENCES

- The addition of this section was identical to the Aralen Tablet label.

We have completed the review of this supplemental new drug application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended for use in the agreed upon labeling text. Accordingly, this supplemental new drug application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package inserts submitted May 29, 2003).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 6-002/S-039." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Robin Anderson, Labeling Reviewer at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

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

**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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