CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

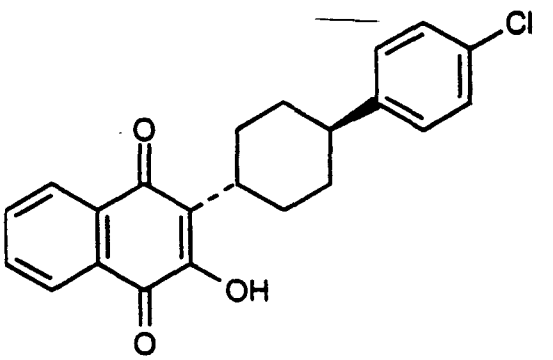
21-078

APPROVED LABELING

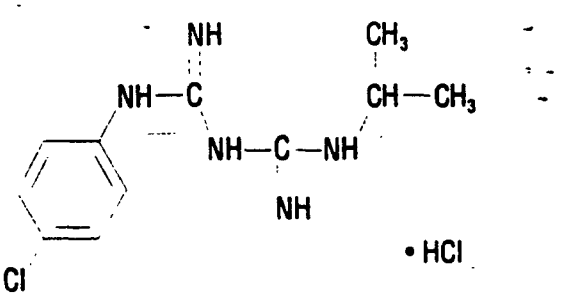
MALARONE™
(atovaquone and proguanil hydrochloride) Tablets

MALARONE™
(atovaquone and proguanil hydrochloride) Pediatric Tablets

DESCRIPTION: MALARONE (atovaquone and proguanil hydrochloride) is a fixed-dose combination of the antimalarial agents atovaquone and proguanil hydrochloride. The chemical name of atovaquone is *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione. Atovaquone is a yellow crystalline solid that is practically insoluble in water. It has a molecular weight of 366.84 and the molecular formula $C_{22}H_{19}ClO_3$. The compound has the following structural formula:



The chemical name of proguanil hydrochloride is 1-(4-chlorophenyl)-5-isopropyl-biguanide hydrochloride. Proguanil hydrochloride is a white crystalline solid that is sparingly soluble in water. It has a molecular weight of 290.22 and the molecular formula $C_{11}H_{16}ClN_5 \cdot HCl$. The compound has the following structural formula:



MALARONE Tablets and MALARONE Pediatric Tablets are for oral administration. Each MALARONE Tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride and

each MALARONE Pediatric Tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride. The inactive ingredients in both tablets are low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, poloxamer 188, povidone K30, and sodium starch glycolate. The tablet coating contains red iron oxide, polyethylene glycol 400, hydroxypropyl methylcellulose, polyethylene glycol 8000, and titanium dioxide.

CLINICAL PHARMACOLOGY:

Microbiology:

Mechanism of Action: The constituents of MALARONE, atovaquone and proguanil hydrochloride, interfere with 2 different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication. Atovaquone is a selective inhibitor of parasite mitochondrial electron transport. Proguanil hydrochloride primarily exerts its effect by means of the metabolite cycloguanil, a dihydrofolate reductase inhibitor. Inhibition of dihydrofolate reductase in the malaria parasite disrupts deoxythymidylate synthesis.

Activity In Vitro and In Vivo: Atovaquone and cycloguanil (an active metabolite of proguanil) are active against the erythrocytic and exoerythrocytic stages of *Plasmodium* spp. Enhanced efficacy of the combination compared to either atovaquone or proguanil hydrochloride alone was demonstrated in clinical studies in both immune and nonimmune patients (see CLINICAL STUDIES).

Drug Resistance: Strains of *P. falciparum* with decreased susceptibility to atovaquone or proguanil/cycloguanil alone can be selected in vitro or in vivo. The combination of atovaquone and proguanil hydrochloride may not be effective for treatment of recrudescent malaria that develops after prior therapy with the combination.

Pharmacokinetics:

Absorption: Atovaquone is a highly lipophilic compound with low aqueous solubility. The bioavailability of atovaquone shows considerable inter-individual variability.

Dietary fat taken with atovaquone increases the rate and extent of absorption, increasing AUC 2 to 3 times and C_{max} 5 times over fasting. The absolute bioavailability of the tablet formulation of atovaquone when taken with food is 23%. MALARONE Tablets should be taken with food or a milky drink.

Proguanil hydrochloride is extensively absorbed regardless of food intake.

Distribution: Atovaquone is highly protein bound (>99%) over the concentration range of 1 to 90 mcg/mL. The apparent volume of distribution of atovaquone after oral administration is approximately 3.5 L/kg.

Proguanil is 75% protein bound. The apparent volume of distribution is approximately 42 L/kg.

In human plasma, the binding of atovaquone and proguanil was unaffected by the presence of the other.

Metabolism: In a study where ^{14}C-labelled atovaquone was administered to healthy volunteers, greater than 94% of the dose was recovered as unchanged atovaquone in the feces over 21 days. There was little or no excretion of atovaquone in the urine (less than 0.6%). There is indirect evidence that atovaquone may undergo limited metabolism; however, a specific metabolite has not been identified. Between 40% to 60% of proguanil is excreted by the kidneys. Proguanil is metabolized to cycloguanil (primarily via CYP2C19) and 4-chlorophenylbiguanide. The main routes of elimination are hepatic biotransformation and renal excretion.

Elimination: The elimination half-life of atovaquone is about 2 to 3 days in adult patients. The mean oral clearance of atovaquone is approximately 0.04 L/h per kg.

The mean oral clearance of proguanil is 3.22 L/h per kg. The elimination half-life of proguanil is 12 to 21 hours in both adult patients and pediatric patients, but may be longer in individuals who are slow metabolizers.

Special Populations:

Pediatrics: The pharmacokinetics of proguanil and cycloguanil are similar in adult patients and pediatric patients. However, the elimination half-life of atovaquone is shorter in pediatric patients (1 to 2 days) than in adult patients (2 to 3 days).

Geriatrics: No studies have been carried out in geriatric patients to assess the pharmacokinetics in this patient population. Since geriatric patients may have reduced renal function, caution should be taken when treating geriatric patients with MALARONE (see Special Populations: Renal Impairment and PRECAUTIONS).

Hepatic Impairment: The pharmacokinetics of MALARONE have not been studied in patients with hepatic impairment. The effect of hepatic dysfunction on the conversion of proguanil to cycloguanil is unknown.

Renal Impairment: The pharmacokinetics of MALARONE have not been studied in patients with renal impairment. Since proguanil and cycloguanil are eliminated primarily via the renal route, the clinical implication of treating patients with severe renal dysfunction with MALARONE is unknown (see PRECAUTIONS: General).

Drug Interactions: There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose.

Concomitant treatment with **tetracycline** has been associated with approximately a 40% reduction in plasma concentrations of atovaquone.

Concomitant treatment with **metoclopramide** has also been associated with decreased bioavailability of atovaquone.

Concomitant administration of **rifampin** is known to reduce atovaquone levels by approximately 50% (see PRECAUTIONS: Drug Interactions). The mechanism of this interaction is unknown.

Atovaquone is highly protein bound (>99%) but does not displace other highly protein-bound drugs in vitro, indicating significant drug interactions arising from displacement are unlikely (see PRECAUTIONS: Drug Interactions). Proguanil is metabolized primarily by CYP2C19. Potential pharmacokinetic interactions with other substrates or inhibitors of this pathway are unknown.

INDICATIONS AND USAGE:

Prevention of Malaria: MALARONE is indicated for the prophylaxis of *P. falciparum* malaria, including in areas where chloroquine resistance has been reported (see CLINICAL STUDIES).

Treatment of Malaria: MALARONE is indicated for the treatment of acute, uncomplicated *P. falciparum* malaria. MALARONE has been shown to be effective in regions where the drugs chloroquine, halofantrine, mefloquine, and amodiaquine may have unacceptable failure rates, presumably due to drug resistance.

CONTRAINDICATIONS: MALARONE is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation. During clinical trials, one case of anaphylaxis following treatment with atovaquone/proguanil was observed.

PRECAUTIONS:

General: MALARONE has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including hyperparasitemia, pulmonary edema, or renal failure. Patients with severe malaria are not candidates for oral therapy.

Absorption of atovaquone may be reduced in patients with diarrhea or vomiting. If MALARONE is used in patients who are vomiting (see DOSAGE AND ADMINISTRATION), parasitemia should be closely monitored and the use of an antiemetic considered. Vomiting occurred in up to 19% of pediatric patients given treatment doses of MALARONE. In the controlled clinical trials of MALARONE, 15.3% of adults who were treated with atovaquone/proguanil received an antiemetic drug during that part of the trial when they received atovaquone/proguanil. Of these patients, 98.3% were successfully treated. In patients with severe or persistent diarrhea or vomiting, alternative antimalarial therapy may be required.

Parasite relapse occurred commonly when *P. vivax* malaria was treated with MALARONE alone.

In the event of recrudescent *P. falciparum* infections after treatment with MALARONE or failure of chemoprophylaxis with MALARONE, patients should be treated with a different blood schizonticide.

The concomitant administration of MALARONE and any other medication containing proguanil hydrochloride should be avoided. Because proguanil is eliminated by renal excretion, proguanil

hydrochloride, and hence MALARONE, should be administered with caution to patients with severe pre-existing renal failure.

Information for Patients: Patients should be instructed:

- to take MALARONE tablets at the same time each day with food or a milky drink.
- to take a repeat dose of MALARONE if vomiting occurs within 1 hour after dosing.
- to consult a healthcare professional regarding alternative forms of prophylaxis if prophylaxis with MALARONE is prematurely discontinued for any reason.
- that protective clothing, insect repellents, and bednets are important components of malaria prophylaxis.
- that no chemoprophylactic regimen is 100% effective; therefore, patients should seek medical attention for any febrile illness that occurs during or after return from a malaria-endemic area and inform their healthcare professional that they may have been exposed to malaria.
- that falciparum malaria carries a higher risk of death and serious complications in pregnant women than in the general population. Pregnant women anticipating travel to malarious areas should discuss the risks and benefits of such travel with their physicians (see Pregnancy section).

Drug Interactions: Concomitant treatment with **tetracycline** has been associated with approximately a 40% reduction in plasma concentrations of atovaquone. Parasitemia should be closely monitored in patients receiving tetracycline. While antiemetics may be indicated for patients receiving MALARONE, **metoclopramide** may reduce the bioavailability of atovaquone and should be used only if other antiemetics are not available.

Concomitant administration of **rifampin** is known to reduce atovaquone levels by approximately 50%. The concomitant administration of MALARONE and rifampin is not recommended.

Atovaquone is highly protein bound (>99%) but does not displace other highly protein-bound drugs in vitro, indicating significant drug interactions arising from displacement are unlikely.

Potential interactions between proguanil or cycloguanil and other drugs that are CYP2C19 substrates or inhibitors are unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Atovaquone: Carcinogenicity studies in rats were negative; 24-month studies in mice showed treatment-related increases in incidence of hepatocellular adenoma and hepatocellular carcinoma at all doses tested which ranged from approximately 5 to 8 times the average steady-state plasma concentrations in humans during prophylaxis of malaria. Atovaquone alone was negative with or without metabolic activation in the Ames *Salmonella* mutagenicity assay, the Mouse Lymphoma mutagenesis assay, and the Cultured Human Lymphocyte cytogenetic assay. No evidence of genotoxicity was observed in the in vivo Mouse Micronucleus assay.

Proguanil: Carcinogenicity studies with proguanil have not been completed. Proguanil was not genotoxic in in vitro or in vivo studies.

Proguanil alone was negative with or without metabolic activation in the Ames *Salmonella* mutagenicity assay and the Mouse Lymphoma mutagenesis assay. No evidence of genotoxicity was observed in the in vivo Mouse Micronucleus assay.

Genotoxicity studies have not been performed with atovaquone in combination with proguanil. Effects of MALARONE on male and female reproductive performance are unknown.

Pregnancy: Pregnancy Category C. Falciparum malaria carries a higher risk of morbidity and mortality in pregnant women than in the general population. Maternal death and fetal loss are both known complications of falciparum malaria in pregnancy. In pregnant women who must travel to malaria-endemic areas, personal protection against mosquito bites should always be employed (see Information for Patients) in addition to antimalarials.

Atovaquone was not teratogenic and did not cause reproductive toxicity in rats at maternal plasma concentrations up to 5 to 6.5 times the estimated human exposure during treatment of malaria. Following single-dose administration of ^{14}C-labeled atovaquone to pregnant rats, concentrations of radiolabel in rat fetuses were 18% (mid-gestation) and 60% (late gestation) of concurrent maternal plasma concentrations. In rabbits, atovaquone caused maternal toxicity at plasma concentrations that were approximately 0.6 to 1.3 times the estimated human exposure during treatment of malaria. Adverse fetal effects in rabbits, including decreased fetal body lengths and increased early resorptions and post-implantation losses, were observed only in the presence of maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of the concurrent maternal plasma concentrations..

The combination of atovaquone and proguanil hydrochloride was not teratogenic in rats at plasma concentrations up to 1.7 and 0.10 times, respectively, the estimated human exposure during treatment of malaria. In rabbits, the combination of atovaquone and proguanil hydrochloride was not teratogenic or embryotoxic to rabbit fetuses at plasma concentrations up to 0.34 and 0.82 times, respectively, the estimated human exposure during treatment of malaria.

While there are no adequate and well-controlled studies of atovaquone and/or proguanil hydrochloride in pregnant women, MALARONE may be used if the potential benefit justifies the potential risk to the fetus. The proguanil component of MALARONE acts by inhibiting the parasitic dihydrofolate reductase (see CLINICAL PHARMACOLOGY: Microbiology: Mechanism of Action). However, there are no clinical data indicating that folate supplementation diminishes drug efficacy, and for women of childbearing age receiving folate supplements to prevent neural tube birth defects, such supplements may be continued while taking MALARONE.

Nursing Mothers: It is not known whether atovaquone is excreted into human milk. In a rat study, atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma.

Proguanil is excreted into human milk in small quantities.

Caution should be exercised when MALARONE is administered to a nursing woman.

Pediatric Use: Safety and effectiveness for the treatment and prophylaxis of malaria in pediatric patients who weigh less than 11 kg have not been established.

Geriatric Use: Clinical studies of MALARONE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY: Special Populations: Geriatrics).

ADVERSE REACTIONS: Because MALARONE contains atovaquone and proguanil hydrochloride, the type and severity of adverse reactions associated with each of the compounds may be expected. The higher treatment doses of MALARONE were less well tolerated than the lower prophylactic doses.

Among adults who received MALARONE for treatment of malaria, attributable adverse experiences that occurred in ≥5% of patients were abdominal pain (17%), nausea (12%), vomiting (12%), headache (10%), diarrhea (8%), asthenia (8%), anorexia (5%), and dizziness (5%). Treatment was discontinued prematurely due to an adverse experience in 4 of 436 adults treated with MALARONE.

Among pediatric patients who received MALARONE for the treatment of malaria, attributable adverse experiences that occurred in ≥5% of patients were vomiting (10%) and pruritus (6%). Vomiting occurred in 43 of 319 (13%) pediatric patients who did not have symptomatic malaria but were given treatment doses of MALARONE for 3 days in a clinical trial. The design of this clinical trial required that any patient who vomited be withdrawn from the trial. Among pediatric patients with symptomatic malaria treated with MALARONE, treatment was discontinued prematurely due to an adverse experience in 1 of 116 (0.9%).

Abnormalities in laboratory tests reported in clinical trials were limited to elevations of transaminases in malaria patients being treated with MALARONE. The frequency of these abnormalities varied substantially across studies of treatment and were not observed in the randomized portions of the prophylaxis trials.

In one phase III trial of malaria treatment in Thai adults, early elevations of ALT and AST were observed to occur more frequently in patients treated with MALARONE compared to patients treated with an active control drug. Rates for patients who had normal baseline levels of these clinical laboratory parameters were: Day 7: ALT 26.7% versus 15.6%; AST 16.9% vs. 8.6%. By day 14 of this 28-day study, the frequency of transaminase elevations equalized across the two groups.

In this and other studies in which transaminase elevations occurred, they were noted to persist for up to 4 weeks following treatment with MALARONE for malaria. None were associated with untoward clinical events.

Among subjects who received MALARONE for prophylaxis of malaria, adverse experiences occurred in similar proportions of subjects receiving MALARONE or placebo (Table 1). The most commonly reported adverse experiences possibly attributable to MALARONE or placebo were headache and abdominal pain. Prophylaxis with MALARONE was discontinued prematurely due to a treatment-related adverse experience in 3 of 381 adults and 0 of 125 pediatric patients.

Table 1: Adverse Experiences in Clinical Trials of MALARONE for Prophylaxis of Malaria

	Percent of Subjects With Adverse Experiences (Percent of Subjects With Adverse Experiences Attributable to Therapy)				
	Adults			Children and Adolescents	
Adverse Event	Placebo (n = 206)	MALARONE* (n = 206)	MALARONE† (n = 381)	Placebo (n = 140)	MALARONE (n = 125)
Headache	27 (7)	22 (3)	17 (5)	21 (14)	19 (14)
Fever	13 (1)	5 (0)	3 (0)	11 (<1)	6 (0)
Myalgia	11 (0)	12 (0)	7 (0)	0 (0)	0 (0)
Abdominal pain	10 (5)	9 (4)	6 (3)	29 (29)	33 (31)
Cough	8 (<1)	6 (<1)	4 (1)	9 (0)	9 (0)
Diarrhea	8 (3)	6 (2)	4 (1)	3 (1)	2 (0)
Upper respiratory infection	7 (0)	8 (0)	5 (0)	0 (0)	<1 (0)
Dyspepsia	5 (4)	3 (2)	2 (1)	0 (0)	0 (0)
Back Pain	4 (0)	8 (0)	4 (0)	0 (0)	0 (0)
Gastritis	3 (2)	3 (3)	2 (2)	0 (0)	0 (0)
Vomiting	2 (<1)	1 (<1)	<1 (<1)	6 (6)	7 (7)
Flu syndrome	1 (0)	2 (0)	4 (0)	6 (0)	9 (0)
Any adverse event	65 (32)	54 (17)	49 (17)	62 (41)	60 (42)

*Subjects receiving the recommended dose of atovaquone and proguanil hydrochloride in placebo-controlled trials.
†Subjects receiving the recommended dose of atovaquone and proguanil hydrochloride in any trial.

OVERDOSAGE: There have been no reports of overdosage from the administration of MALARONE.

There is no known antidote for atovaquone, and it is currently unknown if atovaquone is dialyzable. The median lethal dose is higher than the maximum oral dose tested in mice and rats (1825 mg/kg per day). Overdoses up to 31,500 mg of atovaquone have been reported. In one such patient who also took an unspecified dose of dapsone, methemoglobinemia occurred. Rash has also been reported after overdose.

Overdoses of proguanil hydrochloride as large as 1500 mg have been followed by complete recovery, and doses as high as 700 mg twice daily have been taken for over 2 weeks without serious toxicity. Adverse events occasionally associated with proguanil hydrochloride doses of 100 to 200 mg/day, such as epigastric discomfort and vomiting, would be likely to occur with overdose. There are also reports of reversible hair loss and scaling of the skin on the palms and/or soles, reversible aphthous ulceration, and hematologic side effects.

DOSAGE AND ADMINISTRATION: The daily dose should be taken at the same time each day with food or a milky drink. In the event of vomiting within 1 hour after dosing, a repeat dose should be taken.

Prevention of Malaria: Prophylactic treatment with MALARONE should be started 1 or 2 days before entering a malaria-endemic area and continued daily during the stay and for 7 days after return.

Adults: One MALARONE Tablet (adult strength = 250 mg atovaquone/100 mg proguanil hydrochloride) per day.

Pediatric Patients: The dosage for prevention of malaria in pediatric patients is based upon body weight (Table 2).

Table 2: Dosage for Prevention of Malaria in Pediatric Patients

Weight (kg)	Atovaquone/Proguanil HCl Total Daily Dose	Dosage Regimen
11-20	62.5 mg/25 mg	1 MALARONE Pediatric Tablet daily
21-30	125 mg/50 mg	2 MALARONE Pediatric Tablets as a single dose daily
31-40	187.5 mg/75 mg	3 MALARONE Pediatric Tablets as a single dose daily
>40	250 mg/100 mg	1 MALARONE Tablet (adult strength) as a single dose daily

Treatment of Acute Malaria:

Adults: Four MALARONE Tablets (adult strength; total daily dose 1 g atovaquone/400 mg proguanil hydrochloride) as a single dose daily for 3 consecutive days.

Pediatric Patients: The dosage for treatment of acute malaria in pediatric patients is based upon body weight (Table 3).

Table 3: Dosage for Treatment of Acute Malaria in Pediatric Patients

Weight (kg)	Atovaquone/Proguanil HCl Total Daily Dose	Dosage Regimen
11-20	250 mg/100 mg	1 MALARONE Tablet (adult strength) daily for 3 consecutive days
21-30	500 mg/200 mg	2 MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days
31-40	750 mg/300 mg	3 MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days
>40	1 g/400 mg	4 MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days

HOW SUPPLIED: MALARONE Tablets, containing 250 mg atovaquone and 100 mg proguanil hydrochloride, are pink, film-coated, round, biconvex tablets engraved with "GX CM3" on one side.

Bottle of 100 tablets with child-resistant closure (NDC 0173-0675-01).

MALARONE Pediatric Tablets, containing 62.5 mg atovaquone and 25 mg proguanil hydrochloride, are pink, film-coated, round, biconvex tablets engraved with "GX CG7" on one side.

Bottle of 100 tablets with child-resistant closure (NDC 0173-0676-01).

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

ANIMAL TOXICOLOGY: Fibrovascular proliferation in the right atrium, pyelonephritis, bone marrow hypocellularity, lymphoid atrophy, and gastritis/enteritis were observed in dogs treated with proguanil hydrochloride for 6 months at a dose of 12 mg/kg per day (approximately 3.9 times the recommended daily human dose for malaria prophylaxis on a mg/m^2 basis). Bile duct hyperplasia, gall bladder mucosal atrophy, and interstitial pneumonia were observed in dogs treated with proguanil hydrochloride for 6 months at a dose of 4 mg/kg per day (approximately 1.3 times the recommended daily human dose for malaria prophylaxis on a mg/m^2 basis). Mucosal hyperplasia of the cecum and renal tubular basophilia were observed in rats treated with proguanil hydrochloride for 6 months at a dose of 20 mg/kg per day (approximately 1.6 times the recommended daily human dose for malaria prophylaxis on a mg/m^2 basis). Adverse heart, lung, liver, and gall bladder effects observed in dogs and kidney effects observed in rats were not shown to be reversible.

CLINICAL STUDIES:

Treatment of Acute Malarial Infections: In 3 phase II clinical trials, atovaquone alone, proguanil hydrochloride alone, and the combination of atovaquone and proguanil hydrochloride were evaluated for the treatment of acute, uncomplicated malaria caused by *P. falciparum*. Among

156 evaluable patients, the parasitological cure rate was 59/89 (66%) with atovaquone alone, 1/17 (6%) with proguanil hydrochloride alone, and 50/50 (100%) with the combination of atovaquone and proguanil hydrochloride.

MALARONE was evaluated for treatment of acute, uncomplicated malaria caused by *P. falciparum* in 8 phase III controlled clinical trials. Among 471 evaluable patients treated with the equivalent of 4 MALARONE Tablets once daily for 3 days, 464 had a sensitive response (elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days) (see Table 4). Seven patients had a response of R1 resistance (elimination of parasitemia but with recurrent parasitemia between 7 and 28 days after starting treatment). In these trials, the response to treatment with MALARONE was similar to treatment with the comparator drug in 4 trials, and better than the response to treatment with the comparator drug in the other 4 trials.

The overall efficacy in 521 evaluable patients was 98.7% (see Table 4).

Table 4: Parasitological Response in Clinical Trials of MALARONE for Treatment of *P. falciparum* Malaria

	MALARONE*		Comparator		
Study Site	Evaluable Patients (n)	% Sensitive Response**	Drug(s)	Evaluable Patients (n)	% Sensitive Response**
Brazil	74	98.6%	Quinine and tetracycline	76	100.0%
Thailand	79	100.0%	Mefloquine	79	86.1%
France†	21	100.0%	Halofantrine	18	100.0%
Kenya†‡	81	93.8%	Halofantrine	83	90.4%
Zambia	80	100.0%	Pyrimethamine/ sulfadoxine (P/S)	80	98.8%
Gabon†	63	98.4%	Amodiaquine	63	81.0%
Philippines	54	100.0%	Chloroquine (Cq)	23	30.4%
			Cq and P/S	32	87.5%
Peru	19	100.0%	Chloroquine	13	7.7%
			P/S	7	100.0%

*MALARONE = 1000 mg atovaquone and 400 mg proguanil hydrochloride (or equivalent based on body weight for patients weighing ≤40 kg) once daily for 3 days.
**Elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days.
†Patients hospitalized only for acute care. Follow-up conducted in outpatients.
‡Study in pediatric patients 3 to 12 years of age.

Eighteen of 521 (3.5%) evaluable patients with acute falciparum malaria presented with a pretreatment serum creatinine greater than 2.0 mg/dL (range 2.1 to 4.3 mg/dL). All were

successfully treated with MALARONE and 17 of 18 (94.4%) had normal serum creatinine levels by day 7.

Data from a phase II trial of atovaquone conducted in Zambia suggested that approximately 40% of the study population in this country were HIV-infected patients. The enrollment criteria were similar for the phase III trial of MALARONE conducted in Zambia and the results are presented in Table 4. Efficacy rates for MALARONE in this study population were high and comparable to other populations studied.

The efficacy of MALARONE in the treatment of the erythrocytic phase of nonfalciparum malaria was assessed in a small number of patients. Of the 23 patients in Thailand infected with *P. vivax* and treated with atovaquone/proguanil hydrochloride 1000 mg/400 mg daily for 3 days, parasitemia cleared in 21 (91.3%) at 7 days. Parasite relapse occurred commonly when *P. vivax* malaria was treated with MALARONE alone. Seven patients in Gabon with malaria due to *P. ovale* or *P. malariae* were treated with atovaquone/proguanil hydrochloride 1000 mg/400 mg daily for 3 days. All 6 evaluable patients (3 with *P. malariae*, 2 with *P. ovale*, and 1 with mixed *P. falciparum* and *P. ovale*) were cured at 28 days. Relapsing malarias including *P. vivax* and *P. ovale* require additional treatment to prevent relapse.

Prevention of Malaria: MALARONE was evaluated for prophylaxis of malaria in 4 clinical trials in malaria-endemic areas.

Three placebo-controlled studies of 10 to 12 weeks' duration were conducted among residents of malaria-endemic areas in Kenya, Zambia, and Gabon. Of a total of 669 randomized patients (including 264 pediatric patients 5 to 16 years of age), 103 were withdrawn for reasons other than falciparum malaria or drug-related adverse events. (Fifty-five percent of these were lost to follow-up and 45% were withdrawn for protocol violations.) The results are listed in Table 5.

Table 5: Prevention of Parasitemia in Controlled Clinical Trials of MALARONE for Prophylaxis of *P. falciparum* Malaria

	MALARONE	Placebo
Total number of patients randomized	326	341
Failed to complete study	57	44
Developed parasitemia (*P. falciparum*)	2	92

In a 10-week study in 175 South African subjects who moved into malaria-endemic areas and were given prophylaxis with 1 MALARONE Tablet daily, parasitemia developed in 1 subject who missed several doses of medication. Since no placebo control was included, the incidence of malaria in this study was not known. In a malaria challenge study conducted in healthy US volunteers, atovaquone alone prevented malaria in 6/6 individuals, whereas 4/4 placebo-treated volunteers developed malaria. Although these data suggest that MALARONE prophylaxis is

effective in both malaria-immune and nonimmune subjects, differences in the response rates may occur.

Causal Prophylaxis: In separate studies with small numbers of volunteers, atovaquone and proguanil hydrochloride were independently shown to have causal prophylactic activity directed against liver-stage parasites of *P. falciparum*. Six patients given a single dose of atovaquone 250 mg 24 hours prior to malaria challenge were protected from developing malaria, whereas all 4 placebo-treated patients developed malaria.

During the 4 weeks following cessation of prophylaxis in clinical trial participants who remained in malaria-endemic areas and were available for evaluation, malaria developed in 24/211 (11.4%) subjects who took placebo and 9/328 (2.7%) who took MALARONE. While new infections could not be distinguished from recrudescent infections, all but 1 of the infections in patients treated with MALARONE occurred more than 15 days after stopping therapy, probably representing new infections. The single case occurring on day 8 following cessation of therapy with MALARONE probably represents a failure of prophylaxis with MALARONE.

The possibility that delayed cases of *P. falciparum* malaria may occur some time after stopping prophylaxis with MALARONE cannot be ruled out. Hence, returning travelers developing febrile illnesses should be investigated for malaria.

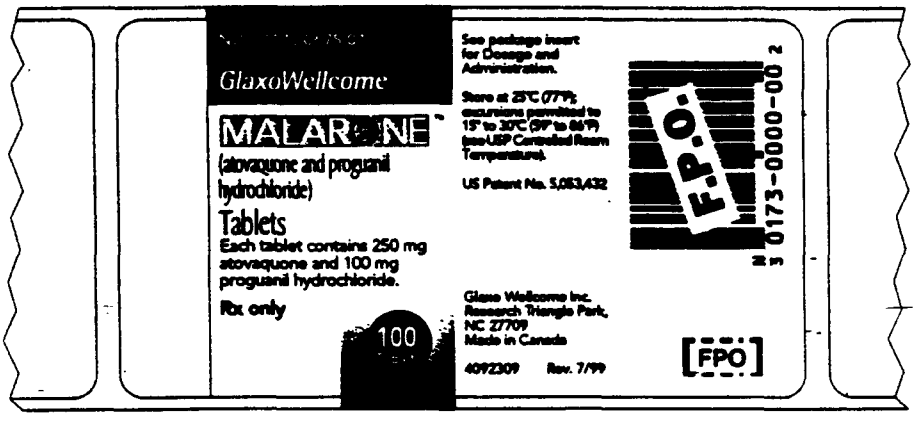
GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent Nos. 5,053,432 and 5,998,449

July 2000 RL-843

NDA 21-078
MALARONE™
(atovaquone and proguanil HCl)
Tablets
Label – Bottle x 100



NDA 21-078

MALARONE™
(atovaquone and proguanil HCl)
Pediatric Tablets
Label – Bottle x 100