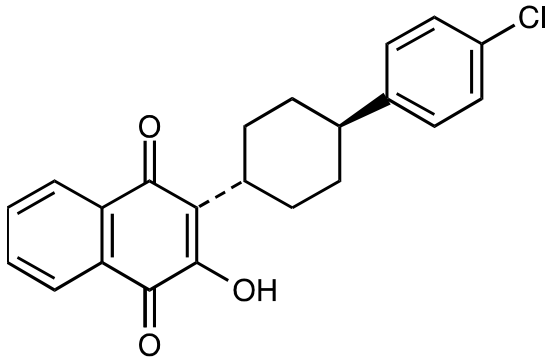
PRESCRIBING INFORMATION

MALARONE®
(atovaquone and proguanil hydrochloride)
Tablets

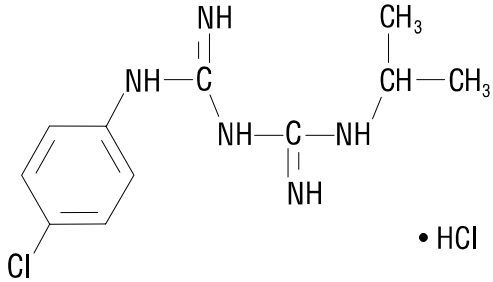
MALARONE®
(atovaquone and proguanil hydrochloride)
Pediatric Tablets

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 $C_{11}H_{16}ClN_5$•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 hypromellose, polyethylene glycol 400, polyethylene glycol 8000, red iron oxide, 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 non-immune 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. A population pharmacokinetic analysis demonstrated that the apparent volume of distribution of atovaquone (V/F) in adult and pediatric patients after oral administration is approximately 8.8 L/kg.

Proguanil is 75% protein bound. A population pharmacokinetic analysis demonstrated that the apparent V/F of proguanil in adult and pediatric patients >15 years of age with body weights from 31 to 110 kg ranged from 1,617 to 2,502 L. In pediatric patients ≤15 years of age with body weights from 11 to 56 kg, the V/F of proguanil ranged from 462 to 966 L.

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

Metabolism: In a study where ^{14}C-labeled 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 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.

A population pharmacokinetic analysis in adult and pediatric patients showed that the apparent clearance (CL/F) of both atovaquone and proguanil are related to the body weight. The values CL/F for both atovaquone and proguanil in subjects with body weight ≥11 kg are shown in Table 1.

Table 1. Apparent Clearance for Atovaquone and Proguanil in Patients as a Function of Body Weight

	Atovaquone		Proguanil	
Body Weight	N	CL/F (L/hr) Mean ± SD* (range)	N	CL/F (L/hr) Mean ± SD* (range)
11-20 kg	159	1.34 ± 0.63 (0.52-4.26)	146	29.5 ± 6.5 (10.3-48.3)
21-30 kg	117	1.87 ± 0.81 (0.52-5.38)	113	40.0 ± 7.5 (15.9-62.7)
31-40 kg	95	2.76 ± 2.07 (0.97-12.5)	91	49.5 ± 8.30 (25.8-71.5)
>40 kg	368	6.61 ± 3.92 (1.32-20.3)	282	67.9 ± 19.9 (14.0-145)

*SD = standard deviation.

The pharmacokinetics of atovaquone and proguanil in patients with body weight below 11 kg have not been adequately characterized.

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). In clinical trials, plasma trough levels of atovaquone and proguanil in pediatric patients weighing 5 to 40 kg were within the range observed in adults after dosing by body weight.

Geriatrics: In a single-dose study, the pharmacokinetics of atovaquone, proguanil, and cycloguanil were compared in 13 elderly subjects (age 65 to 79 years) to 13 younger subjects (age 30 to 45 years). In the elderly subjects, the extent of systemic exposure (AUC) of

cycloguanil was increased (point estimate = 2.36, CI = 1.70, 3.28). T_{max} was longer in elderly subjects (median 8 hours) compared with younger subjects (median 4 hours) and average elimination half-life was longer in elderly subjects (mean 14.9 hours) compared with younger subjects (mean 8.3 hours).

Hepatic Impairment: In a single-dose study, the pharmacokinetics of atovaquone, proguanil, and cycloguanil were compared in 13 subjects with hepatic impairment (9 mild, 4 moderate, as indicated by the Child-Pugh method) to 13 subjects with normal hepatic function. In subjects with mild or moderate hepatic impairment as compared to healthy subjects, there were no marked differences (<50%) in the rate or extent of systemic exposure of atovaquone. However, in subjects with moderate hepatic impairment, the elimination half-life of atovaquone was increased (point estimate = 1.28, 90% CI = 1.00 to 1.63). Proguanil AUC, C_{max}, and its $t_{1/2}$ increased in subjects with mild hepatic impairment when compared to healthy subjects (Table 2). Also, the proguanil AUC and its $t_{1/2}$ increased in subjects with moderate hepatic impairment when compared to healthy subjects. Consistent with the increase in proguanil AUC, there were marked decreases in the systemic exposure of cycloguanil (C_{max} and AUC) and an increase in its elimination half-life in subjects with mild hepatic impairment when compared to healthy volunteers (Table 2). There were few measurable cycloguanil concentrations in subjects with moderate hepatic impairment (see DOSAGE AND ADMINISTRATION). The pharmacokinetics of atovaquone, proguanil, and cycloguanil after administration of MALARONE have not been studied in patients with severe hepatic impairment.

Table 2. Point Estimates (90% CI) for Proguanil and Cycloguanil Parameters in Subjects With Mild and Moderate Hepatic Impairment Compared to Healthy Volunteers

Parameter	Comparison	Proguanil	Cycloguanil
$AUC_{(0\text{-inf})}$*	mild:healthy	1.96 (1.51, 2.54)	0.32 (0.22, 0.45)
C_{max}*	mild:healthy	1.41 (1.16, 1.71)	0.35 (0.24, 0.50)
$t_{1/2}$†	mild:healthy	1.21 (0.92, 1.60)	0.86 (0.49, 1.48)
$AUC_{(0\text{-inf})}$*	moderate:healthy	1.64 (1.14, 2.34)	ND
C_{max}*	moderate:healthy	0.97 (0.69, 1.36)	ND
$t_{1/2}$†	moderate:healthy	1.46 (1.05, 2.05)	ND

ND = not determined due to lack of quantifiable data.
*Ratio of geometric means.
†Mean difference.

Renal Impairment: In patients with mild renal impairment (creatinine clearance 50 to 80 mL/min), oral clearance and/or AUC data for atovaquone, proguanil, and cycloguanil are within the range of values observed in patients with normal renal function (creatinine clearance >80 mL/min). In patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min), mean oral clearance for proguanil was reduced by approximately 35% compared with patients with normal renal function (creatinine clearance >80 mL/min) and the oral

clearance of atovaquone was comparable between patients with normal renal function and mild renal impairment. No data exist on the use of MALARONE for long-term prophylaxis (over 2 months) in individuals with moderate renal failure. In patients with severe renal impairment (creatinine clearance <30 mL/min), atovaquone C_{max} and AUC are reduced but the elimination half-lives for proguanil and cycloguanil are prolonged, with corresponding increases in AUC, resulting in the potential of drug accumulation and toxicity with repeated dosing (see CONTRAINDICATIONS).

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** or **rifabutin** is known to reduce atovaquone levels by approximately 50% and 34%, respectively (see PRECAUTIONS: Drug Interactions). The mechanisms of these interactions are 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. Rare cases of anaphylaxis following treatment with atovaquone/proguanil have been reported.

MALARONE is contraindicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance <30 mL/min) (see CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment).

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.

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 take a dose as soon as possible if a dose is missed, then return to their normal dosing schedule. However, if a dose is skipped, the patient should not double the next dose.
- 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** or **rifabutin** is known to reduce atovaquone levels by approximately 50% and 34%, respectively. The concomitant administration of MALARONE and rifampin or rifabutin 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 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: No evidence of a carcinogenic effect was observed in studies conducted in CD-1 mice (doses up to 1.51 times the average systemic human exposure based on AUC) and in Wistar Hannover rats (doses up to 1.12 times the average systemic human exposure).

Proguanil 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.

Cycloguanil, the active metabolite of proguanil, was also negative in the Ames test, but was positive in the Mouse Lymphoma assay and the Mouse Micronucleus assay. These positive effects with cycloguanil, a dihydrofolate reductase inhibitor, were significantly reduced or abolished with folinic acid supplementation.

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: *Treatment of Malaria:* The efficacy and safety of MALARONE for the treatment of malaria have been established in controlled studies involving pediatric patients weighing 5 kg or more (see CLINICAL STUDIES). Safety and effectiveness have not been established in pediatric patients who weigh less than 5 kg.

Prophylaxis of Malaria: The efficacy and safety of MALARONE have been established for the prophylaxis of malaria in controlled studies involving pediatric patients weighing 11 kg or more (see CLINICAL STUDIES). Safety and effectiveness have not been established in pediatric patients who weigh less than 11 kg.

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, the higher systemic exposure to cycloguanil (see CLINICAL PHARMACOLOGY: Special Populations: Geriatrics), and the greater frequency of concomitant disease or other drug therapy.

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 (weighing 11 to 40 kg) 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%).

In a study of 100 pediatric patients (5 to <11 kg body weight) who received MALARONE for the treatment of uncomplicated *P. falciparum* malaria, only diarrhea (6%) occurred in ≥5% of patients as an adverse experience attributable to MALARONE. In 3 patients (3%), treatment was discontinued prematurely due to an adverse experience.

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% vs. 15.6%; AST 16.9% vs. 8.6%. By day 14 of this 28-day study, the frequency of transaminase elevations equalized across the 2 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 in placebo-controlled trials, adverse experiences occurred in similar proportions of subjects receiving MALARONE or placebo (Table 3). 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 3. Adverse Experiences in Placebo-Controlled Clinical Trials of MALARONE for Prophylaxis of Malaria

Adverse Experience	Percent of Subjects With Adverse Experiences (Percent of Subjects With Adverse Experiences Attributable to Therapy)				
	Adults			Children and Adolescents	
	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 experience	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.

In an additional placebo-controlled study of malaria prophylaxis with MALARONE involving 330 pediatric patients in a malaria-endemic area (see CLINICAL STUDIES), the safety profile of MALARONE was consistent with that described above. The most common treatment-emergent adverse events with MALARONE were abdominal pain (13%), headache (13%), and cough (10%). Abdominal pain (13% vs. 8%) and vomiting (5% vs. 3%) were reported more often with MALARONE than with placebo, while fever (5% vs. 12%) and diarrhea (1% vs. 5%) were more common with placebo. No patient withdrew from the study due to an adverse experience with MALARONE. No routine laboratory data were obtained during this study.

Among subjects who received MALARONE for prophylaxis of malaria in clinical trials with an active comparator, adverse experiences occurred in a similar or lower proportion of subjects receiving MALARONE than an active comparator (Table 4). The mean durations of dosing and the periods for which the adverse experiences are summarized in Table 4, were 28 days (Study 1) and 26 days (Study 2) for MALARONE, 53 days for mefloquine, and 49 days for chloroquine plus proguanil (reflecting the different recommended dosing regimens). Fewer neuropsychiatric adverse experiences occurred in subjects who received MALARONE than mefloquine. Fewer gastrointestinal adverse experiences occurred in subjects receiving MALARONE than chloroquine/proguanil. Compared with active comparator drugs, subjects receiving MALARONE had fewer adverse experiences overall that were attributed to prophylactic therapy (Table 4). Prophylaxis with MALARONE was discontinued prematurely due to a treatment-related adverse experience in 7 of 1,004 travelers.

Table 4. Adverse Experiences in Active-Controlled Clinical Trials of MALARONE for Prophylaxis of Malaria

Adverse Experience	Percent of Subjects With Adverse Experiences* (Percent of Subjects With Adverse Experiences Attributable to Therapy)			
	Study 1		Study 2	
	MALARONE n = 493	Mefloquine n = 483	MALARONE n = 511	Chloroquine plus Proguanil n = 511
Diarrhea	38 (8)	36 (7)	34 (5)	39 (7)
Nausea	14 (3)	20 (8)	11 (2)	18 (7)
Abdominal pain	17 (5)	16 (5)	14 (3)	22 (6)
Headache	12 (4)	17 (7)	12 (4)	14 (4)
Dreams	7 (7)	16 (14)	6 (4)	7 (3)
Insomnia	5 (3)	16 (13)	4 (2)	5 (2)
Fever	9 (<1)	11 (1)	8 (<1)	8 (<1)
Dizziness	5 (2)	14 (9)	7 (3)	8 (4)
Vomiting	8 (1)	10 (2)	8 (0)	14 (2)
Oral ulcers	9 (6)	6 (4)	5 (4)	7 (5)
Pruritus	4 (2)	5 (2)	3 (1)	2 (<1)
Visual difficulties	2 (2)	5 (3)	3 (2)	3 (2)
Depression	<1 (<1)	5 (4)	<1 (<1)	1 (<1)
Anxiety	1 (<1)	5 (4)	<1 (<1)	1 (<1)
Any adverse experience	64 (30)	69 (42)	58 (22)	66 (28)
Any neuropsychiatric event	20 (14)	37 (29)	16 (10)	20 (10)
Any GI event	49 (16)	50 (19)	43 (12)	54 (20)

*Adverse experiences that started while receiving active study drug.

In a third active-controlled study, MALARONE (n = 110) was compared with chloroquine/proguanil (n = 111) for the prophylaxis of malaria in 221 non-immune pediatric patients (see CLINICAL STUDIES). The mean duration of exposure was 23 days for MALARONE, 46 days for chloroquine, and 43 days for proguanil, reflecting the different recommended dosage regimens for these products. Fewer patients treated with MALARONE reported abdominal pain (2% vs. 7%) or nausea (<1% vs. 7%) than children who received chloroquine/proguanil. Oral ulceration (2% vs. 2%), vivid dreams (2% vs. <1%), and blurred vision (0% vs. 2%) occurred in similar proportions of patients receiving either MALARONE or

chloroquine/proguanil, respectively. Two patients discontinued prophylaxis with chloroquine/proguanil due to adverse events, while none of those receiving MALARONE discontinued due to adverse events.

Post-Marketing Adverse Reactions: In addition to adverse events reported from clinical trials, the following events have been identified during world-wide post-approval use of MALARONE. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to MALARONE.

Skin/Hypersensitivity: Cutaneous reactions ranging from rash, photosensitivity, angioedema, and urticaria to rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome.

Central Nervous System: Rare cases of seizures and psychotic events (such as hallucinations); however, a causal relationship has not been established.

OVERDOSAGE

There is no information on overdoses of MALARONE substantially higher than the doses recommended for treatment.

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 (1,825 mg/kg/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 1,500 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 experiences 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 5).

Table 5. 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 6).

Table 6. Dosage for Treatment of Acute Malaria in Pediatric Patients

Weight (kg)	Atovaquone/ Proguanil HCl Total Daily Dose	Dosage Regimen
5-8	125 mg/50 mg	2 MALARONE Pediatric Tablets daily for 3 consecutive days
9-10	187.5 mg/75 mg	3 MALARONE Pediatric Tablets daily for 3 consecutive days
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

MALARONE Tablets may be crushed and mixed with condensed milk just prior to administration for children who may have difficulty swallowing tablets.

Patients With Renal Impairment: MALARONE should not be used for malaria prophylaxis in patients with severe renal impairment (creatinine clearance <30 mL/min). MALARONE may be used with caution for the treatment of malaria in patients with severe renal impairment (creatinine clearance <30 mL/min), only if the benefits of the 3-day treatment regimen outweigh the potential risks associated with increased drug exposure (see CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment). No dosage adjustments are needed in patients with mild (creatinine clearance 50 to 80 mL/min) and moderate (creatinine

clearance 30 to 50 mL/min) renal impairment (see CLINICAL PHARMACOLOGY: Special Populations).

Patients With Hepatic Impairment: No dosage adjustments are needed in patients with mild to moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY: Special Populations: Hepatic Impairment).

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).

Unit Dose Pack of 24 (NDC 0173-0675-02).

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/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/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/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 7). Seven patients had a response of RI 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% (Table 7).

Table 7. 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) Cq and P/S	23 32	30.4% 87.5%
Peru	19	100.0%	Chloroquine P/S	13 7	7.7% 100.0%

*MALARONE = 1,000 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 7. 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 1,000 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 1,000 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.

The efficacy of MALARONE in treating acute uncomplicated *P. falciparum* malaria in children weighing ≥5 and <11 kg was examined in an open-label, randomized trial conducted in Gabon. Patients received either MALARONE (2 or 3 MALARONE Pediatric Tablets once daily depending upon body weight) for 3 days (n = 100) or amodiaquine (10 mg/kg/day) for 3 days (n = 100). In this study, the MALARONE Tablets were crushed and mixed with condensed milk just prior to administration. In the per-protocol population, adequate clinical response was obtained in 95% (87/92) of the pediatric patients who received MALARONE and in 53% (41/78) of those who received amodiaquine. A response of RI resistance (elimination of parasitemia but with recurrent parasitemia between 7 and 28 days after starting treatment) was noted in 3% and 40% of the patients, respectively. Two cases of RIII resistance (rising parasite count despite therapy) were reported in the patients receiving MALARONE. There were 4 cases of RIII in the amodiaquine arm.

Prevention of Malaria: MALARONE was evaluated for prophylaxis of malaria in 5 clinical trials in malaria-endemic areas and in 3 active-controlled trials in non-immune travelers to 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 8.

Table 8. Prevention of Parasitemia in Placebo-Controlled Clinical Trials of MALARONE for Prophylaxis of *P. falciparum* Malaria in Residents of Malaria-Endemic Areas

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

In another study, 330 Gabonese pediatric patients (weighing 13 to 40 kg, and aged 4 to 14 years) who had received successful open-label radical cure treatment with artesunate, were randomized to receive either MALARONE (dosage based on body weight) or placebo in a double-blind fashion for 12 weeks. Blood smears were obtained weekly and any time malaria was suspected. Nineteen of the 165 children given MALARONE and 18 of 165 patients given placebo withdrew from the study for reasons other than parasitemia (primary reason was lost to follow-up). In the per-protocol population, 1 out of 150 patients (<1%) who received MALARONE developed *P. falciparum* parasitemia while receiving prophylaxis with MALARONE compared with 31 (22%) of the 144 placebo recipients.

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.

Two active-controlled studies were conducted in non-immune travelers who visited a malaria-endemic area. The mean duration of travel was 18 days (range 2 to 38 days). Of a total of 1,998 randomized patients who received MALARONE or controlled drug, 24 discontinued from the study before follow-up evaluation 60 days after leaving the endemic area. Nine of these were lost to follow-up, 2 withdrew because of an adverse experience, and 13 were discontinued for other reasons. These studies were not large enough to allow for statements of comparative efficacy. In addition, the true exposure rate to *P. falciparum* malaria in both studies is unknown. The results are listed in Table 9.

Table 9. Prevention of Parasitemia in Active-Controlled Clinical Trials of MALARONE for Prophylaxis of *P. falciparum* Malaria in Non-Immune Travelers

	MALARONE	Mefloquine	Chloroquine plus Proguanil
Total number of randomized patients who received study drug	1,004	483	511
Failed to complete study	14	6	4
Developed parasitemia (*P. falciparum*)	0	0	3

A third randomized, open-label study was conducted which included 221 otherwise healthy pediatric patients (weighing ≥11 kg and 2 to 17 years of age) who were at risk of contracting malaria by traveling to an endemic area. The mean duration of travel was 15 days (range 1 to 30 days). Prophylaxis with MALARONE (n = 110, dosage based on body weight) began 1 or 2 days before entering the endemic area and lasted until 7 days after leaving the area. A control group (n = 111) received prophylaxis with chloroquine/proguanil dosed according to WHO guidelines. No cases of malaria occurred in either group of children. However, the study was not large enough to allow for statements of comparative efficacy. In addition, the true exposure rate to *P. falciparum* malaria in this study is unknown.

In a malaria challenge study conducted in healthy US volunteers, atovaquone alone prevented malaria in 6 of 6 individuals, whereas 4 of 4 placebo-treated volunteers developed malaria.

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 of 211 (11.4%) subjects who took placebo and 9 of 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.

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