Product Monograph

PrMALARONE®

(250 mg Atovaquone + 100 mg Proguanil Hydrochloride)
Tablets

PrMALARONE® PEDIATRIC

(62.5 mg Atovaquone + 25 mg Proguanil Hydrochloride)
Tablets

Antimalarial Agent

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ACTIONS AND CLINICAL PHARMACOLOGY

ACTIONS

The constituents of MALARONE® (a fixed combination product with each tablet containing atovaquone and proguanil hydrochloride), interfere with two different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication. The mechanism of action of atovaquone against *P.falciparum* is via inhibition of mitochondrial electron transport, at the level of the cytochrome bc_1 complex, and collapse of mitochondrial membrane potential. One mechanism of action of proguanil, via its metabolite cycloguanil, is inhibition of dihydrofolate reductase, which disrupts deoxythymidylate synthesis. Proguanil also has antimalarial activity independent of its metabolism to cycloguanil, and proguanil, but not cycloguanil, is able to potentiate the ability of atovaquone to collapse mitochondrial membrane potential in malaria parasites. This latter mechanism may explain the synergy seen when atovaquone and proguanil are used in combination.

Both atovaquone and proguanil are active against the hepatic stages of *P.falciparum* and against asexual blood stage malarial parasites.

CLINICAL PHARMACOLOGY

Pharmacokinetics

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose. A population pharmacokinetic analysis in adults and children was used to characterize the pharmacokinetics of atovaquone and proguanil. In clinical trials, trough levels of atovaquone, proguanil and cycloguanil in children (weighing 11-40 kg) are within the range observed in adults after adjusting for body weight.

Table 1 summarizes the pharmacokinetic parameters from an atovaquone-proguanil interaction study using dose levels of MALARONE® Tablets utilized in the treatment of malaria.

Table 1 Atovaquone, Proguanil and Cycloguanil Geometric Mean Parameters and Point Estimates for MALARONE® Tablets (4 x 250 mg Atovaquone / 100 mg Proguanil HCl) versus Atovaquone Tablets (4 x 250 mg) alone, and Proguanil HCl Tablets (4 x 100 mg) alone in Healthy Adults following Daily Administration for 3 Days in the Fed State

Parameter	Geometric Means		Combined/Alone ratio x 100 (%)	90% Confidence Interval (%)
	Combined	Alone		
Atovaquone				
AUC_{0-24} (h.µg/mL)[1]	193	180	108	(100, 116)
$AUC_{0-\infty}$ (h.µg/mL)[2]	510	549	93	(79, 110)
C_{max} (µg/mL)	11.5	10.5	110	(102, 118)
$t_{1/2}$ (h)	59	57.1	103	(96, 111)
Proguanil (PG)				
AUC_{0-24} (h.µg/mL)[1]	5.82	6.30	92	(86, 99)
$AUC_{0-\infty}$ (h.µg/mL)[2]	6.00	6.44	93	(84, 103)
C_{max} (µg/mL)	0.509	0.548	93	(87, 99)
$t_{1/2}$ (h)	14.5	13.7	106	(100, 113)
Cycloguanil (CG)				
AUC_{0-24} (h.µg/mL)[1]	1.19	1.30	92	(86, 98)
$AUC_{0-\infty}$ (h.µg/mL)[2]	1.20	1.36	89	(79, 99)
C_{max} (µg/mL)	0.0792	0.0821	97	(92, 101)
$t_{1/2}$ (h)	11.8	11.1	106	(93, 120)
AUC_{CG}/AUC_{PG}[3]	0.21	0.22	94	(86, 103)

[1] AUC_{0-24} : Trapezoidal area under plasma curve from last dose until 24h post dose.
[2] $AUC_{0-\infty}$:Trapezoidal area under plasma curve from last dose until final measured concentration, extrapolated from last concentration to infinity, corrected for concentration pre-dose. At true steady state, this is equivalent to $AUC_{0-\infty}$ for a single dose.
[3] Ratio of $AUC_{0-\infty}$ for cycloguanil to proguanil.

Absorption: Atovaquone is a highly lipophilic compound with low aqueous solubility. The pharmacokinetics of atovaquone are comparable between healthy subjects and HIV-infected patients. Although there are no absolute bioavailability data for atovaquone in healthy subjects, in HIV-infected patients the absolute bioavailability of a 750 mg single dose of atovaquone tablets taken with food is 21% (90% CI: 17% - 27%). Dietary fat taken with atovaquone increases the rate and extent of absorption. When taken with a standard breakfast containing 23 g of fat, AUC was increased 2-3 times and C_{max} 5 times compared to the fasting state. Patients should take MALARONE® with food or a milky drink (see DOSAGE AND ADMINISTRATION).

Proguanil hydrochloride is rapidly and extensively absorbed regardless of food intake.

Distribution: The apparent volume of distribution of atovaquone and proguanil is a function of body weight. Atovaquone is highly protein bound (> 99%) but does not displace other highly protein bound drugs *in vitro*, indicating that significant drug interactions arising from displacement are unlikely. The volume of distribution of atovaquone following oral administration in both adults and children is approximately 8.8 L/kg. Proguanil is 75% protein bound. The volume of distribution of proguanil following oral administration is 42 to 27 L/kg in adults (weighing 41-80 kg) and 42 to 20 L/kg in children (weighing 11-40 kg). In human plasma the binding of atovaquone and proguanil were unaffected by the presence of the other.

Metabolism: There is no evidence that atovaquone is metabolised and there is negligible excretion of atovaquone in urine with the parent drug being predominantly (> 90%) eliminated unchanged in faeces.

Proguanil hydrochloride is partially metabolised with less than 40% being excreted unchanged in the urine. Proguanil is metabolized to cycloguanil (primarily via CYP2C19) and 4-chlorophenylbiguanide, and these are also excreted unchanged in the urine.

Elimination: The oral clearance of atovaquone and proguanil is a function of body weight. The elimination half-life of atovaquone is about 2-3 days in adults and 1-2 days in children 6 to 12 years of age. The elimination half-lives of proguanil and cycloguanil are about 12-15 hours in both adults and children 6 to 12 years of age. Following oral administration, the clearance of atovaquone in adults and children (weighing 41-80 kg) is approximately 0.16 to 0.05 L/h/kg. In children (weighing 11-40 kg), the clearance is approximately 0.21 to 0.06 L/h/kg. Following oral administration, the clearance of proguanil in adults (weighing 41-80 kg) is 1.6 to 0.85 L/h/kg. In children (weighing 11-40 kg), the oral clearance is approximately 2.2 to 1.0 L/h/kg.

Special Populations

Renal Impairment: There are no studies in children with renal impairment. The effect of renal impairment was evaluated after single-dose oral administration of MALARONE® in adults. In patients with mild to moderate renal impairment, oral clearance and/or AUC data for atovaquone, proguanil, and cycloguanil are within the range of values observed in patients with normal renal function. In patients with severe renal impairment (creatinine clearance < 30 mL/min), atovaquone C_{max} and AUC are reduced, while the elimination half-lives for proguanil and cycloguanil are prolonged, with corresponding increases in AUC, resulting in the potential for drug accumulation with repeated dosing (see CONTRAINDICATIONS and PRECAUTIONS, Renal Impairment).

Hepatic Impairment: There are no studies in children with hepatic impairment. In a single-dose study, the pharmacokinetics of atovaquone, proguanil, and cycloguanil were compared in 13 adult patients with hepatic impairment (9 mild, 4 moderate, as indicated by the Child-Pugh method) with 13 adult subjects with normal hepatic function. In patients with mild or moderate hepatic impairment there were no marked differences in the rate or extent of systemic exposure to atovaquone (based on C_{max}, T_{max}, and AUC values). There was also no marked difference in the elimination half-life of atovaquone in these patients. There were no marked changes in the C_{max}, T_{max}, and elimination half-life of proguanil in patients with mild or moderate hepatic impairment. However, there was a marked increase (85%) in proguanil AUC in these patients, which is not considered to be clinically relevant due to proguanil's wide therapeutic range. Consistent with the increase in proguanil AUC, there were marked decreases in the

systemic exposure to cycloguanil (C_{max} and AUC). This was particularly evident in patients with moderate hepatic impairment, where few measurable cycloguanil concentrations were seen. The decrease in the systemic exposure to cycloguanil is unlikely to be clinically relevant based on evidence from *in vitro* and clinical data (in more than 100 patients), which indicate that phenotypic status of proguanil metabolism (i.e., low exposure to cycloguanil in poor metabolizers) does not influence the efficacy of MALARONE® (see PRECAUTIONS, Hepatic Impairment).

The pharmacokinetics of MALARONE® have not been studied in patients with severe hepatic impairment.

Elderly Subjects: A single oral dose pharmacokinetic study indicates that no dosage adjustments are needed in the healthy elderly. There is no clinically significant change in the average rate or extent of absorption of atovaquone or proguanil between healthy elderly and young patients. Systemic availability of cycloguanil is higher in the elderly compared to young subjects, but there is no clinically significant change in its elimination half-life. However, since geriatric patients may have reduced renal function, caution should be taken when treating geriatric patients with MALARONE® (see PRECAUTIONS, Use in Elderly and Renal Impairment, and CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment).

Pediatrics: The pharmacokinetics of atovaquone, proguanil, and cycloguanil were characterized following the daily oral administration of separate tablets of atovaquone and proguanil hydrochloride for 3 consecutive days. The dose was based on body weight. The pharmacokinetics of proguanil and cycloguanil were found to be similar in adult and pediatric patients. However, the elimination half-life of atovaquone was shorter in pediatric patients (1 to 2 days) than in adult patients (2 to 3 days), resulting in a lower C_{max} and AUC in children (i.e., lower systemic exposure to atovaquone in children than in adults). Clinical cure rates, however, were not affected.

Clinical Studies

The prophylaxis indication for adults weighing above 40 kg is based on 3 placebo-controlled studies of 10 to 12 weeks duration conducted in endemic areas with over 700 subjects and 2 active-controlled studies in non-immune travellers which enrolled more than 2000 non-immune travellers to a malaria-endemic country.

The prophylaxis indication for children weighing between 11 and 40 kg is based on 2 placebo-controlled studies of 12 weeks duration conducted in endemic areas with over 500 subjects aged 4 to 15 years, and 2 active-controlled studies in more than 180 non-immune travellers aged 2 to 14 years who visited a malaria-endemic country.

The treatment indication is based on 5 controlled clinical studies conducted in 466 patients (adults and children) receiving concurrent atovaquone and proguanil hydrochloride at the recommended dose (see DOSAGE AND ADMINISTRATION). Most of the patients were residents of malaria-endemic areas and may have had previous malaria infections that could have conferred a degree of immunity.

INDICATIONS AND CLINICAL USE

Prevention of Malaria: MALARONE® (atovaquone and proguanil hydrochloride) is indicated for the prophylaxis of *P. falciparum* malaria including areas where chloroquine resistance has been reported.

Treatment of Malaria: MALARONE® (atovaquone and proguanil hydrochloride) is indicated for the treatment of acute, uncomplicated *P.falciparum* malaria when oral treatment is appropriate.

MALARONE® has been shown to be effective in areas where *P. falciparum* may be resistant to some other antimalarials.

CONTRAINDICATIONS

MALARONE® (atovaquone and proguanil hydrochloride) is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation (see PHARMACEUTICAL INFORMATION, Composition).

MALARONE® is contraindicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30 mL/min). In patients with severe renal impairment, an alternative to MALARONE® should be recommended for treatment of *P. falciparum* malaria whenever possible (see CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment, and PRECAUTIONS, Renal Impairment).

WARNINGS

Serious hypersensitivity reactions, including angioedema and anaphylaxis, have been reported rarely following the use of MALARONE® (atovaquone and proguanil hydrochloride) for treatment and prophylaxis of malaria. These reactions may occur after the administration of the first dose. In this event, MALARONE® should be discontinued immediately and supportive medical treatment should be sought.

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

In the event of recrudescent infections due to *P. falciparum*, or failure of chemoprophylaxis, patients should be treated with a different antimalarial.

Absorption of atovaquone may be reduced in patients with diarrhoea or vomiting, but diarrhoea or vomiting was not associated with reduced efficacy in clinical trials of MALARONE® for malaria prophylaxis. Persons taking MALARONE® for prophylaxis or treatment of malaria should take a repeat dose if they vomit within 1 hour of dosing. In the event of diarrhoea, normal dosing should be continued. As with other antimalarial agents, patients with diarrhoea or vomiting should be reminded to continue to comply with personal protection measures (repellants, bednets).

In patients with acute malaria who present with diarrhoea or vomiting, alternative therapy should be considered. If MALARONE® is used to treat malaria in these patients, parasitemia should be closely monitored.

Parasitemia should be closely monitored in patients receiving concurrent tetracycline or metoclopramide (see PRECAUTIONS, Drug Interactions).

The concomitant administration of MALARONE® and rifampicin or rifabutin is not recommended (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS

General

Patients who have a history of epilepsy or psychiatric illness should take MALARONE® (atovaquone and proguanil hydrochloride) with caution. During clinical trials, one adult and one child receiving atovaquone/proguanil hydrochloride for the treatment of malaria had seizures; the child successfully continued treatment. Both subjects had a prior history of seizures and the investigators did not consider the events to be exacerbated by treatment with MALARONE®. Two adult subjects receiving atovaquone monotherapy experienced psychiatric symptoms. One subject had a history of psychiatric illness and the other a history of drug and alcohol abuse (see ADVERSE REACTIONS).

Absorption of orally administered atovaquone is significantly reduced when fasting. Therefore alternative therapy with other agents should be considered for patients who are not able to consume food (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

Parasite relapse occurred commonly when *P. vivax* malaria was treated with MALARONE® alone. Travellers with intense exposure to *P. vivax* or *P. ovale*, and those who develop malaria caused by either of these parasites, will require additional treatment with a drug, such as primaquine, that is active against hypnozoites.

Use in the Elderly

A single-dose pharmacokinetic study indicates that no dosage adjustments are needed in the healthy elderly (see CLINICAL PHARMACOLOGY, Special Populations, Elderly Subjects).

Use in Pregnant Women

There are no studies in pregnant women. The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human pregnancy has not been established. MALARONE® should be considered for use in pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Reproductive toxicity studies in animals did not indicate any teratogenic potential at dosages of atovaquone:proguanil hydrochloride of up to 50:20 mg/kg/day in the rat or 100:40 mg/kg/day in the rabbit. In rabbits given atovaquone alone at doses up to 1,200 mg/kg/day, an increased incidence of resorptions and decrease in length and weight of fetuses was noted. These effects were likely to be secondary to toxicity of atovaquone in maternal animals. However, animal studies are not always predictive of human response.

The proguanil component of MALARONE® acts by inhibiting parasitic dihydrofolate reductase. There are no clinical data indicating that folate supplementation diminishes drug efficacy. For women of childbearing age receiving folate supplements to prevent neural tube birth defects, such supplements may be continued while taking MALARONE®.

Use in Nursing Mothers

It is not recommended that mothers receiving MALARONE® breastfeed their babies. It is not known whether atovaquone is excreted in human milk. Proguanil is excreted in human milk in small quantities. In a rat study, the atovaquone concentrations in milk were 30% of the concurrent atovaquone concentrations in maternal plasma.

The amount of atovaquone or proguanil found in human breast milk would not provide adequate treatment for the infant against malaria.

Use in Children

Treatment of Malaria

MALARONE® is not recommended for treatment of acute, uncomplicated *P.falciparum* malaria in children under 3 years of age or who weigh less than 11 kg as safety and effectiveness has not been shown in this group of patients.

Prophylaxis of Malaria

Safety and effectiveness of MALARONE® for the prophylaxis of malaria have not been established in children who weigh less than 11 kg (see CLINICAL PHARMACOLOGY, Clinical Studies).

Renal Impairment

There are no studies in children with renal impairment (see CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment).

A single-dose pharmacokinetic study in adults indicates that no special precautions or dosage adjustments are needed in patients with mild to moderate renal impairment.

MALARONE® is not recommended in patients with severe renal impairment (see CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment, and CONTRAINDICATIONS).

Hepatic Impairment

There are no studies in children with hepatic impairment (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment).

A single dose pharmacokinetic study in adults indicates that 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).

Drug Interactions

General

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

Use with Anticoagulants

Proguanil may potentiate the anticoagulant effect of warfarin and other coumarin based anticoagulants. The mechanism of this potential drug interaction has not been established. Caution is advised when initiating or withdrawing malaria prophylaxis or treatment with atovaquone-proguanil in patients on continuous treatment with coumarin based anticoagulants.

Use with Efavirenz

Coadministration of efavirenz with MALARONE® resulted in a decrease in exposures to atovaquone and proguanil. When given with efavirenz or boosted protease-inhibitors, atovaquone concentrations have been observed to decrease as much as 75%. Since decreased concentrations of atovaquone and proguanil may result in a decrease of antimalarial efficacy, concomitant administration should be avoided whenever possible.

Use with Rifampicin, Rifabutin, Tetracycline or Metoclopramide

Parasitemia should be closely monitored in patients receiving tetracycline or metoclopramide concurrently with MALARONE®.

The concomitant administration of MALARONE® and rifampicin or rifabutin is not recommended.

Concomitant treatment with tetracycline, metoclopramide, rifabutin and rifampicin has been associated with significant decreases in plasma concentrations of atovaquone. Increased clearance of atovaquone when coadministered with tetracycline, leading to 40% lower atovaquone concentrations, has been observed. Concomitant administration of rifampicin or rifabutin is known to reduce atovaquone levels by approximately 50% and 34% respectively.

Use with Indinavir

Concomitant administration of atovaquone and indinavir results in a decrease in the C_{min} of indinavir (23% decrease; 90% CI 8-35%). Caution should be exercised when prescribing atovaquone with indinavir due to the decrease in trough levels of indinavir.

Use with Other Antimalarial Agents

MALARONE® should not be administered in combination with other antimalarial drugs. Interactions between MALARONE® and other antimalarial drugs have not been studied.

ADVERSE REACTIONS

As MALARONE® contains atovaquone and proguanil hydrochloride, the type and severity of adverse reactions associated with each of the compounds may be expected. At the doses employed for the treatment and prophylaxis of malaria, adverse reactions have generally been mild and of limited duration. There has been no evidence of increased toxicity following concurrent administration of the two compounds.

A summary of adverse events associated with the use of MALARONE®, atovaquone, or proguanil hydrochloride is provided below.

Blood and Lymphatic: Anemia, neutropenia. Pancytopenia in patients with severe renal impairment

Endocrine and Metabolic: Anorexia, hyponatremia

Gastrointestinal: Abdominal pain, nausea, vomiting, diarrhoea, gastric intolerance, oral ulceration, stomatitis

Hepatobiliary Tract and Pancreas: Elevated liver enzyme levels and reports of hepatitis, cholestasis, elevated amylase levels. Clinical trial data for MALARONE® indicated that abnormalities in liver function tests (elevated bilirubin and transaminases) were reversible and not associated with untoward clinical events.

Immune System/Hypersensitivity: Allergic reactions: including rash, urticaria, pruritus, angioedema, isolated reports of anaphylaxis, and vasculitis

Lower Respiratory: Cough

Neurology: Headache, insomnia, dizziness, asthenia

Non-Site Specific: Fever

Skin: Rash, hair loss

Other events seen in clinical trials with MALARONE® include:

Body as a Whole: Back pain, lethargy

Cardiovascular: Hypotension, palpitations

Erythropoietic: Splenomegaly

Gastrointestinal: Hepatomegaly, constipation, dyspepsia

Musculoskeletal: Myalgia

Neurology: Strange or vivid dreams, visual difficulties, depression, anxiety

Of the seven severe or treatment-limiting adverse experiences reported in clinical trials with atovaquone and proguanil hydrochloride, three were considered to be treatment related; two were reports of nausea and/or vomiting and one, a report of an anaphylactic reaction (see WARNINGS). Two subjects, one adult and one 4-year-old child, receiving atovaquone/proguanil hydrochloride for the treatment of malaria had seizures; the child successfully continued treatment. Both subjects had a prior history of seizures and the investigators did not consider the events to be exacerbated by treatment with MALARONE®. During clinical trials, two adult subjects receiving atovaquone monotherapy experienced psychiatric symptoms. One subject had a history of

psychiatric illness and the other a history of drug and alcohol abuse. Studies of this size and design would only be able to detect adverse events at a rate of 1:150 (95% CI).

Treatment

Table 2 provides a summary of the adverse events considered by investigators to be attributable to study medication and reported in clinical trials for the treatment of malaria with MALARONE® Tablets. Abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea, asthenia and abnormal liver function tests were the most commonly reported adverse experiences.

Table 2 Adverse Events Considered by Investigators to be Attributable to Study Medication, Occurring in ≥ 1% of Adults with Malaria in Completed Phase III Treatment Studies

Adverse Event	MALARONE® (n = 304)	PYR + S (n = 81)	MFQ (n = 91)	ADQ (n = 71)	C±PYR+S* (n = 55)
Gastrointestinal					
Abdominal Pain	15% (45)	21% (17)	0%	8% (6)	0%
Vomiting	12% (35)	15% (12)	0%	25% (18)	2% (1)
Nausea	11% (32)	14% (11)	2% (2)	21% (15)	2% (1)
Diarrhoea	8% (25)	11% (9)	0%	7% (5)	2% (1)
Anorexia	5% (15)	5% (4)	1% (1)	13% (9)	2% (1)
Hepatomegaly	2% (6)	6% (5)	0%	0%	0%
Constipation	1% (2)	0%	0%	0%	0%
Dyspepsia	1% (2)	0%	0%	0%	0%
Nervous/Psychiatric					
Headache	8% (25)	31% (25)	1% (1)	7% (5)	0%
Dizziness	3% (8)	11% (9)	0%	11% (8)	2% (1)
Insomnia	1% (3)	4% (3)	0%	25% (18)	0%
Body as a Whole					
Asthenia	7% (20)	16% (13)	0%	3% (2)	0%
Back Pain	1% (2)	4% (3)	0%	0%	0%
Abnormal liver function tests					
ALT	6% (18)	6% (5)	7% (6)	0%	0%
AST	5% (16)	5% (4)	7% (6)	0%	0%
Bilirubin	2% (7)	0%	1% (1)	0%	0%
Cardiovascular					
Hypotension, postural	2% (6)	17% (14)	0%	0%	0%
Palpitations	2% (5)	0%	0%	6% (4)	0%
Cutaneous					
Pruritus	2% (6)	2% (2)	0%	46% (33)	0%
Rash	1% (2)	0%	0%	0%	0%
Musculoskeletal					
Myalgia	3% (8)	6% (5)	0%	4% (3)	0%
Erythropoietic					
Splenomegaly	1% (4)	2% (2)	0%	0%	0%
Respiratory					
Coughing	1% (3)	0%	0%	2% (2)	0%

PYR = pyrimethamine S = sulfadoxine MFQ = mefloquine
ADQ = amodiaquine C= chloroquine
* Data for both comparator groups of chloroquine alone plus pyrimethamine and sulfadoxine.

A similar profile of clinical adverse events was reported in children with malaria treated with atovaquone and proguanil hydrochloride in phase III trials as occurred in the adult studies.

Prophylaxis

In clinical trials of MALARONE® for prophylaxis of malaria in adults weighing above 40 kg, the most commonly reported adverse events, independent of attributability, were headache, abdominal pain and diarrhoea, and were reported in a similar proportion of subjects receiving MALARONE® Tablets or placebo.

In clinical trials of MALARONE® for prophylaxis of malaria in children weighing between 11 and 40 kg, residents of malaria-endemic areas, the most commonly reported adverse events, regardless of drug relationship, were abdominal pain, headache, cough, vomiting and fever. Abdominal pain was reported more commonly in the children receiving MALARONE® PEDIATRIC Tablets than in the placebo group (21% versus 16%, respectively), whereas fever was reported more commonly in the placebo group than in the group receiving MALARONE® PEDIATRIC Tablets (11% versus 5%, respectively). The reported incidence of other events was identical or similar between the two groups.

Table 3 provides a summary of the most common drug-related adverse events reported in clinical trials of MALARONE® Tablets for the prophylaxis of malaria in non-immune travellers weighing above 40 kg.

Table 3 Common Drug-Related, Treatment-Emergent Adverse Events (≥5%) in Non-Immune Travellers Weighing Above 40 kg (MALARONE® Tablets vs Mefloquine and MALARONE® Tablets vs Chloroquine/Proguanil)

Adverse Event	MALARONE® [1] (n=993)		Mefloquine[2] (n=471)		Chloroquine[3]/ Proguanil[4] (n=511)	
	Active[5] n (%)	All[6] n (%)	Active[5] n (%)	All[6] n (%)	Active[5] n (%)	All[6] n (%)
Any Adverse Event	256 (26)	336 (34)	204 (43)	205 (44)	142 (28)	142 (28)
Digestive System	135 (14)	173 (17)	94 (20)	96 (20)	100 (20)	100 (20)
Neuro-Psychiatric*	117 (12)	165 (17)	139 (30)	139 (30)	53 (10)	54 (11)
Body as a Whole	55 (6)	84 (8)	58 (12)	58 (12)	34 (7)	34 (7)
Skin and Appendages	32 (3)	39 (4)	23 (5)	23 (5)	14 (3)	14 (3)

* Neuro-Psychiatric adverse events include strange or vivid dreams, dizziness, insomnia, visual difficulties, psychiatric depression and anxiety.
[1]1-2 days before travel until 7 days after travel.
[2]Weekly from 1-3 weeks before travel until 4 weeks after travel.
[3]1 week before until 4 weeks after travel.
[4]1-2 days before travel until 4 weeks after travel.
[5]Active - includes adverse events that occurred while the active study drug was being administered.
[6]All - includes adverse events that occurred while any study drug (active or placebo) was being administered.

In clinical trials of MALARONE® for prophylaxis of malaria in travellers to endemic areas, the most commonly (≥ 5%) reported adverse events, regardless of drug relationship, in children weighing between 11 and 40 kg receiving MALARONE® PEDIATRIC Tablets or chloroquine + proguanil were diarrhoea, fever, abdominal pain, nausea, vomiting and headache. Each of these events was reported in a similar or lower percentage of subjects who received MALARONE® PEDIATRIC Tablets than who received chloroquine + proguanil.

Table 4 provides a summary of the most common drug-related adverse events reported in clinical trials of MALARONE® PEDIATRIC Tablets for the prophylaxis of malaria in non-immune travellers weighing between 11 and 40 kg.

Table 4 Most Common[1] Drug-Related Adverse Events (> 1 subject) in Non-Immune Pediatric Travellers Weighing 11-40 kg

Adverse Event	11-20 kg		>20-30 kg		>30-40 kg		Total			
	MALARONE® (n=18)		MALARONE® (n=45)		MALARONE® (n=30)		MALARONE® (n=93)		chlor + prog (n=81)	
	T+7	RX	T+7	RX	T+7	RX	T+7	RX	T+7	RX
	n (%)		n (%)		n (%)		n (%)		n (%)	n (%)
At least one drug-related AE	2 (11)		3 (7)		4 (13)	5 (17)	9 (10)	10 (11)	7 (9)	13 (16)
Digestive system	2 (11)		3 (7)		2 (7)		7 (8)		6 (7)	12 (15)
Diarrhoea	2 (11)		2 (4)		0		4 (4)		2 (2)	3 (4)
Oral ulceration	0		1 (2)		1 (3)		2 (2)		2 (2)	
Vomiting	1 (6)		0		0		1 (1)		3 (4)	5 (6)
Abdominal pain	0		0		0		0		3 (4)	7 (9)
Nausea	0		0		0		0		2 (2)	7 (9)
Nervous system	0		1 (2)		2 (7)		3 (3)		1 (1)	
Dreams	0		1 (2)		2 (7)		3 (3)		0	
Skin and Appendages	0		0		2 (7)		2 (2)		1 (1)	
Pruritus	0		0		2 (7)		2 (2)		1 (1)	
Body as a whole	1 (6)		0		0	2 (7)	1 (1)	3 (3)	1 (1)	
Lethargy	0		0		0	2 (7)	0	2 (2)	0	
Special senses	0		0		0		0		2 (2)	
Visual impairment	0		0		0		0		2 (2)	

[1] Most common was defined as reporting in more than one subject in any treatment group.
prog = proguanil chlor = chloroquine
T+7 = Travel Period + 7 days (adverse events starting between start of travel and 7 days post travel)
RX = Treatment Period (MALARONE®: 1-2 days before travel until 7 days after travel; Chloroquine: 1 week before travel until 4 weeks after travel; Proguanil: 1-2 days before travel until 4 weeks after travel)

Over a similar duration of exposure, the reported incidence of drug-related adverse events was similar between groups (10% for those receiving MALARONE® PEDIATRIC

Tablets compared to 9% for those receiving chloroquine + proguanil). During the treatment period, the reported incidence was higher in subjects receiving chloroquine + proguanil than those receiving MALARONE® PEDIATRIC Tablets (16% versus 11%, respectively).

Post-Marketing Adverse Reactions: In addition to adverse events reported from clinical trials, the following events have been identified during worldwide 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: Cutaneous reactions ranging from rash, photosensitivity, and urticaria to cases of erythema multiforme and Stevens-Johnson syndrome.

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

Hypersensitivity: Allergic reactions: including rash, urticaria, pruritis, angioedema and isolated reports of anaphylaxis (see WARNINGS).

Hepatobiliary Tract and Pancreas: Elevated liver enzyme levels and reports of hepatitis, elevated amylase levels.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is limited information regarding overdosage from the administration of MALARONE® (atovaquone and proguanil hydrochloride). In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate.

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 atovaqone 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 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

Each MALARONE® (atovaquone and proguanil hydrochloride) Tablet contains 250 mg of atovaquone and 100 mg proguanil hydrochloride.

Each MALARONE® PEDIATRIC (atovaquone and proguanil hydrochloride) Tablet contains 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

The daily dose should be taken with food or a milky drink (to ensure maximum absorption) at the same time each day (see PRECAUTIONS, General). In the event of vomiting within 1 hour of dosing a repeat dose should be taken. Should vomiting continue, alternative therapy should be considered or the patient's parasitemia should be monitored.

MALARONE® Tablets (adult strength) and MALARONE® PEDIATRIC Tablets should preferably be swallowed whole. Either tablet may be crushed and mixed with condensed milk just prior to administration for children who may have difficulty swallowing tablets.

PROPHYLAXIS

Prophylaxis with MALARONE® should start 1 to 2 days before entering a malaria endemic area and any other non-endemic area where prophylaxis for malaria is recommended by international travel Health Authorities (such as PHAC, CDC, WHO, etc.). Prophylaxis should be continued daily throughout the stay and for 7 additional days after leaving the area of concern.

Dosage in Adults

One MALARONE® Tablet (adult strength = 250 mg atovaquone and 100 mg proguanil hydrochloride) daily.

Dosage in Children (see PRECAUTIONS, Use in Children, and CLINICAL PHARMACOLOGY, Special Populations, Pediatrics)

The dosage for prevention of malaria in children is based upon body weight.

11-20 kg body weight:	One MALARONE® PEDIATRIC Tablet daily.
21-30 kg body weight:	Two MALARONE® PEDIATRIC Tablets as a single dose daily.
31-40 kg body weight:	Three MALARONE® PEDIATRIC Tablets as a single dose daily.
> 40 kg body weight:	One MALARONE® Tablet (adult strength) daily.

MALARONE® is not recommended for malaria prophylaxis in children weighing less than 11 kg.

TREATMENT

Dosage in Adults

Four MALARONE® Tablets (adult strength) as a single dose for three consecutive days.

Dosage in Children (see PRECAUTIONS, Use in Children, and CLINICAL PHARMACOLOGY, Special Populations, Pediatrics)

The dosage for treatment of acute malaria in children is based upon body weight.

11-20 kg body weight:	One MALARONE® Tablet (adult strength) daily for three consecutive days.
21-30 kg body weight:	Two MALARONE® Tablets (adult strength) as a single dose for three consecutive days.
31-40 kg body weight:	Three MALARONE® Tablets (adult strength) as a single dose for three consecutive days.
> 40 kg body weight:	Dose as for adults.

SPECIAL POPULATIONS

Patients with Renal Impairment: There are no studies in children with renal impairment. However, pharmacokinetic studies in adults indicate that no dosage adjustments are needed in patients with mild to moderate renal impairment. MALARONE® should not be used for malaria **prophylaxis** in patients with severe renal impairment (creatinine clearance < 30 mL/min), and alternatives to MALARONE® should be recommended for **treatment** of acute *P. falciparum* malaria whenever possible (see CONTRAINDICATIONS, PRECAUTIONS, Renal Impairment, and CLINICAL PHARMACOLOGY, Special Populations).

Patients with Hepatic Impairment: There are no studies in children with hepatic impairment. However, a pharmacokinetic study in adults indicates that 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 PRECAUTIONS, Hepatic Impairment, and CLINICAL PHARMACOLOGY, Special Populations).

PHARMACEUTICAL INFORMATION

Drug Substance

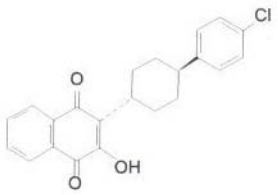
Proper Name: Atovaquone + Proguanil Hydrochloride

Chemical Name:

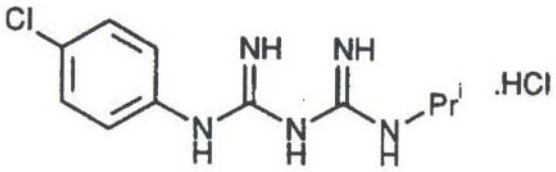
Atovaquone: trans-2-[4-(4-chlorophenyl)-cyclohexyl]-3-hydroxy-1,4-naphtalenedione

Proguanil Hydrochloride: 1-(4-chlorophenyl)-5-isopropyl-biguanide hydrochloride

Structural Formula:



Atovaquone



Proguanil Hydrochloride

Molecular Formula: Atovaquone: $C_{22}H_{19}Cl0_3$

Proguanil: $C_{11}H_{16}ClN_5.HCl$

Molecular Weight: Atovaquone: 366.84

Proguanil hydrochloride: 290.2

Description:

Atovaquone: Atovaquone is a yellow crystalline solid with a melting point of ≈ 221°C. It is practically insoluble in water (< 2 x 10^{-4} mg/mL) and in 0.1 M HCl (< 2 x 10^{-4} mg/mL), and slightly soluble in 0.1 M NaOH (1.7 mg/mL).

Proguanil Hydrochloride: A white crystalline powder, odorless or almost odorless with a melting point of 243°C to 244°C. It is slightly soluble in water, more soluble in hot water and sparingly soluble in 96% ethanol. It is practically insoluble in chloroform and in ether.

Composition

Each MALARONE® (atovaquone and proguanil hydrochloride) Tablet contains 250 mg of atovaquone and 100 mg proguanil hydrochloride (equivalent to 87.4 mg proguanil base).

Each MALARONE® PEDIATRIC (atovaquone and proguanil hydrochloride) Tablet contains 62.5 mg of atovaquone and 25 mg proguanil hydrochloride (equivalent to 21.86 mg proguanil base).

The non-medicinal ingredients in both tablets are low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, poloxamer 188, povidone K30 and sodium starch glycollate. The tablet coating contains hypromellose, macrogol 400, polyethylene glycol 8000, red iron oxide, and titanium dioxide.

Stability and Storage Recommendations

Store between 15°C - 30°C.

AVAILABILITY OF DOSAGE FORMS

MALARONE® (atovaquone and proguanil hydrochloride) Tablets are branded GX CM3, pink, round biconvex film-coated tablets available in blister packs of 12.

MALARONE® PEDIATRIC (atovaquone and proguanil hydrochloride) Tablets are branded GX CG7, pink, round, biconvex, film-coated tablets available in blister packs of 12. MALARONE® PEDIATRIC Tablets are smaller in size than MALARONE® Tablets (adult strength).

MALARONE®

INFORMATION FOR THE PATIENT

Please read this information carefully before taking your medication. If you have any questions ask your doctor or pharmacist.

What is malaria?

Malaria is a disease that is caused by the presence of very small organisms (malaria parasites called plasmodia) in the blood. Malaria is a serious but preventable disease spread by the bite of an infected mosquito. Anyone, of any age, can get malaria. Human malaria is caused by four species of protozoa belonging to the genus Plasmodium: *P. vivax, P. ovale, P. malariae* and *P. falciparum*. Malaria deaths are frequently the results of delays in the diagnosis and treatment of the infection.

Malaria is widespread in tropical and subtropical areas of Africa, Latin America, Asia and the Pacific. Several different types of malaria may exist within one area, each type requiring its own protective medication.

Malaria is characterized by fever and "flu-like" symptoms such as headache, abdominal and muscle pain, and malaise. Muscle rigidity (rigors) and chills often occur. Severe malaria due to *P.falciparum* may cause seizures, coma, and kidney and lung failure, and may lead to death.

To protect yourself against malaria, it is important to know the risks of acquiring malaria, apply measures to prevent being bitten, take preventative treatment where appropriate and seek early diagnosis and treatment if necessary.

What is MALARONE®?

MALARONE® belongs to a group of medicines called antimalarials. MALARONE® is used to treat and prevent malaria caused by *P. falciparum*, a parasite that is often resistant to other drugs. MALARONE® contains two active ingredients which kill the malarial parasites in your body to treat or prevent malaria.

Each MALARONE® Tablet contains the active ingredients atovaquone 250 mg and proguanil hydrochloride 100 mg.

Each MALARONE® PEDIATRIC Tablet contains the active ingredients atovaquone 62.5 mg and proguanil hydrochloride 25 mg.

The non-medicinal ingredients in both tablets are low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, poloxamer 188, povidone K30 and sodium starch glycollate. The tablet coating contains hypromellose, macrogol 400, polyethylene glycol 8000, red iron oxide, and titanium dioxide.

When MALARONE® should not be used:

Do not use MALARONE® if:

- You are allergic (hypersensitive) to atovaquone or proguanil hydrochloride or to any component of the formulation (see "What is MALARONE®?").
- You have severe kidney problems. Your doctor will assess this.

Before you take this medicine:

If you or your child answers "yes" to any of the following questions, tell your doctor about this before taking MALARONE®.

- Have you been told you are allergic to atovaquone, proguanil hydrochloride or any of the other ingredients in MALARONE® listed above?
- Have you been told that your malaria infection is severe and is affecting your lungs, kidneys and/or brain?
- Do you have a history of epilepsy or psychiatric illness?
- Have you ever had malaria before?
- Are you currently suffering from diarrhoea and/or vomiting?
- Are you fasting or unable to eat food?
- Is the medicine to be taken for the prevention of malaria in a child who weighs less than 11 kg?
- Is this medicine to be taken for the treatment of malaria by a child who weighs less than 11 kg or is under 3 years of age?
- Do you have kidney disease or any problems with your kidneys?

- Do you have liver disease or any problems with your liver?
- Are you pregnant or likely to become pregnant soon?
- Are you breastfeeding?

Your doctor will consider the benefit to you and the risk to your baby of taking MALARONE® while you're pregnant.

Breast-feeding is not recommended during treatment with MALARONE®. The ingredients can pass into the breast milk and so may harm your baby. Talk to your doctor about this.

What if I am taking other medicines?

Always tell your doctor about any other medicines you are taking, including tetracycline, metoclopramide, rifampicin, rifabutin, indinavir, efavirenz or highly active protease-inhibitors , anticoagulant medicines, and those you buy yourself (over-the-counter medicines). Some medicines can stop MALARONE® from working properly.

Proper use of MALARONE®:

Take MALARONE® as your doctor has advised you. The usual doses of MALARONE® are given below. If you are not sure, ask your doctor or pharmacist.

Prevention of malaria:

Adults:

One MALARONE® Tablet daily (250 mg atovaquone and 100 mg proguanil hydrochloride).

Children:

One, two or three MALARONE® PEDIATRIC Tablets (62.5 mg atovaquone and 25 mg proguanil hydrochloride) once a day depending on your child's weight (see table below). For children over 40 kg in weight, one MALARONE® Tablet (adult strength) once a day.

Dosage for Prevention of Malaria in Pediatric Patients

Weight (kg)	Dosage Regimen
11-20	1 MALARONE® PEDIATRIC Tablet daily
21-30	2 MALARONE® PEDIATRIC Tablets as a single dose daily
31-40	3 MALARONE® PEDIATRIC Tablets as a single dose daily
>40	1 MALARONE® Tablet (adult strength) daily

In order to prevent malaria, it is important that you take your MALARONE® every day. Start taking it 1 or 2 days before travelling to a country (or countries) where malaria is transmitted, continue daily dosing while you are there and for another 7 days after returning.

Don't stop MALARONE® without advice

For maximum protection you must take the full course of MALARONE®. Stopping early puts you at risk of getting malaria. It takes seven days to ensure that parasites sensitive to MALARONE® are killed.

MALARONE® is not recommended for malaria prevention in children weighing less than 11 kg.

At the end of this leaflet, there is other very important information on how, in addition to taking MALARONE®, you can protect yourself against malaria infection.

Treatment of malaria:

Adults:

Four MALARONE® Tablets (250 mg atovaquone and 100 mg proguanil hydrochloride) once a day for three days.

Children:

One, two or three MALARONE® Tablets (adult strength) once a day for three days depending on your child's weight (see table below). For children over 40 kg in weight, four MALARONE® Tablets (adult strength) once a day for three days.

Dosage for Treatment of Acute Malaria in Pediatric Patients

Weight (kg)	Dosage Regimen
11-20	One MALARONE® Tablet (adult strength) daily for three consecutive days
21-30	Two MALARONE® Tablets (adult strength) as a single dose daily for three consecutive days
31-40	Three MALARONE® Tablets (adult strength) as a single dose daily for three consecutive days
>40	Four MALARONE® Tablets (adult strength) as a single dose daily for three consecutive days

For effective treatment of malaria it is important that MALARONE® is taken exactly as directed over three days.

MALARONE® is not recommended for treatment of malaria in children under 3 years of age or weighing less than 11 kg.

How should MALARONE® be taken?

MALARONE® should be taken with food or a milky drink at the same time each day. MALARONE® should preferably be swallowed whole. The tablets may be crushed and mixed with condensed milk just prior to administration for children who may have difficulty swallowing tablets.

If you are taking MALARONE® to prevent malaria and you are sick (vomit) within one hour of taking your tablets, take another dose and then go on as before. If you do this you should contact your doctor for more MALARONE® tablets to replace those you brought up. It is important to take the full course of MALARONE®. If you have diarrhoea, continue taking MALARONE® as prescribed.

If you have been sick (vomited), MALARONE® may not be as effective so it is especially important to use extra protection, such as repellents and bednets.

If you are taking MALARONE® to treat an attack of malaria and you have diarrhoea or are sick (vomit), tell your doctor. Your doctor may want to check how well these tablets are working and if necessary may decide to change your treatment. A few days after finishing your treatment you should visit your doctor to check that your malaria has been fully treated.

If you feel ill again, particularly if you develop a fever at any time up to a month after finishing your tablets, see your doctor immediately.

There are no special doses for healthy elderly patients. If you have kidney or liver disease, you should inform your doctor.

What to do if you or your child takes too many tablets?

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What to do if you miss a dose?

If you forget to take a dose, take another as soon as possible and then take the next dose at the right time. Do not double dose. If you are not sure what to do, ask your doctor or pharmacist.

What are the possible side effects of MALARONE®?

Although most people find taking MALARONE® causes no problems, like all medicines MALARONE® can have side effects. The following side effects have been reported in persons taking MALARONE® or the active ingredients (atovaquone or proguanil). Most of these have been mild and have not lasted very long:

- Tiredness, weakness, giddiness or breathlessness. These symptoms may mean that you are suffering from a reduction in red blood cell count (anemia).
- A reduction in white blood cells (neutropenia)
- Disturbance of the salt balance of the body (hyponatremia)
- Loss of appetite, feeling sick (nausea) and/or being sick (vomiting), stomach pain, diarrhoea or constipation
- Mouth inflammation (swelling, redness, pain) and mouth ulcers
- Allergic reactions including rash, itching and swelling
- Headache, difficulty in sleeping (insomnia), raised body temperature, abnormal dreams, eyesight problems, depression, anxiety
- seeing or hearing things that are not there (hallucinations)
- Hair loss
- Fever
- Cough
- Dizziness
- Abnormal heartbeats
- Back pain, muscle pain
- Inflammation of the liver (hepatitis), yellow discoloration of the skin or eyes (jaundice)
- Inflammation of blood vessels (vasculitis) which may be visible as red or purple raised spots on the skin, but can affect other parts of the body

Dizziness may occur after using this medication. Make sure you know how you react to this medicine before you drive, operate machinery, or do anything requiring you to be alert.

STOP taking MALARONE® and seek medical attention immediately if you experience any of the following severe allergy symptoms after taking MALARONE®. Although they are rare, these symptoms could be serious.

- Sudden wheezing, tightness of the chest or throat, or difficulty breathing
- Swollen eyelids, face, lips, tongue or other part of the body
- Skin rash, which may blister and look like small targets (central dark spots surrounded by paler area with a dark ring around the edge [erythema multiforme])
- Widespread rash with blisters and peeling skin, particularly occurring around the mouth, nose, eyes and genitals (Stevens-Johnson Syndrome)

If you are having a blood test for any reason, tell the person who is taking your blood sample that you are receiving MALARONE®, or have recently taken MALARONE®, as it may affect your result. The following have been reported in persons taking MALARONE®:

- Blood tests showing a reduction in the number of red blood cells (anemia), white blood cells (neutropenia), and in people with severe kidney problems also a reduction in the number of platelets (cells necessary for blood clotting).
- Blood tests showing an increase in amylase, which is an enzyme produced by the pancreas, and an increase of enzymes produced by the liver.

Tell your doctor if you get any of these symptoms or any other side effects from your medicine which are not mentioned here.

Storing your medicine:

Store your tablets between 15°C - 30°C. Keep your tablets in a safe place where children cannot see or reach them.

Do not use your tablets after the expiry date shown on the pack.

If your doctor stops your treatment, do not keep any leftover tablets unless your doctor tells you to. Return any unused tablets to your pharmacist for safe disposal.

REMEMBER: This medicine is for you. Never give it to any one else. It may harm them even if they have the same symptoms as you.

How can you further protect yourself against malaria:

A few people may still get malaria despite taking the necessary precautions. Other types of malaria infection (*P. vivax and P. ovale* malaria) take a long time to cause symptoms, so the illness may not start until several days, weeks or even months after returning from an area which has malaria. If you develop symptoms similar to flu, such as high temperature, headache and tiredness while you are taking MALARONE® or within a few months after you have stopped, you should contact your doctor immediately.

If you have been treated for malaria you may develop the illness again in the future and need to be treated again. Contact your doctor for advice if the symptoms of malaria recur.

There are other precautions you can take to reduce the chance of being bitten by mosquitoes:

- Wear light-coloured clothing that covers most of the body, especially after sunset. In particular do not forget to cover your arms and legs.
- Use insect repellent on exposed areas of the skin.
- Sleep in a screened room or under a mosquito net impregnated with insecticide. If windows and doors are not screened close them at sunset.
- Consider the use of an insecticide to clear a room of insects before going to bed or to deter mosquitoes from entering the room.

Consult your doctor or local travel clinic for the best protection against malaria.

MICROBIOLOGY

Atovaquone has activity against *P. falciparum* (*in vitro* IC_{50} against *P. falciparum* 0.23-1.43 ng/mL).

Atovaquone has a unique mechanism of action and is not cross-resistant with any other antimalarial drugs in current use.

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC_{50} against various *P. falciparum* strains of 4-20 ng/mL; some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 600-3,000 ng/mL).

In *in vitro* studies of *P. falciparum* the combination of atovaquone and proguanil was shown to be synergistic.

Because *P. vivax* cannot be cultured, *in vitro* susceptibility cannot be determined. However, clinical studies have demonstrated that atovaquone/proguanil has activity against blood stages of *P. vivax*, but not against hypnozoites.

PHARMACOLOGY

Animals

In the rodent model, primary pharmacological studies have shown that the antimalarial effect of atovaquone and proguanil is unaffected when the two compounds are administered together.

Secondary pharmacology studies in conscious dogs examined the cardiovascular and behavioural effects (and pharmacokinetics), of orally administered atovaquone (20 mg/kg) and proguanil hydrochloride (8 mg/kg), given either alone or in combination. Their administration achieved plasma levels in the expected therapeutic range; such levels were well tolerated with no overt signs of clinically significant cardiovascular, central or autonomic nervous system or respiratory effects.

Human

In the fed state, atovaquone shows linear pharmacokinetic behaviour at doses up to 750 mg but less than dose proportional for doses greater than 750 mg. In a study, 15 to 20 patients were given atovaquone tablets once daily over 2 weeks in a cross-over design over the dose range of 750 to 3,000 mg. Main pharmacokinetic parameters were derived under steady-state conditions and are shown below.

Table 5 Mean ± SD Atovaquone Pharmacokinetic Parameter Estimates at Steady State

Parameter	750 mg qd (n=15)	1,500 mg qd (n=15)	3,000 mg qd (n=14)
AUC(0-24h) (µg.h/mL)	181 ± 84	253 ± 126	322 ± 135
C_{max} (µg/mL)	9.10 ± 3.99	13.2 ± 6.26	6.2 ± 6.56
C_{min} (µg/mL)	6.29 ± 3.13	9.03 ± 4.89	11.5 ± 5.20
CL/F (mL/min/kg)	1.34 ± 0.63	2.10 ± 1.55	2.96 ± 1.68

N= Number of evaluable subjects

The population estimate of oral clearance (CL/F) for atovaquone is 3.28 L/h in a typical 70 kg person. Food increases atovaquone C_{max} (5-fold) and AUC (2-fold) compared to fasted state. Population analysis showed that steady-state CL/F of atovaquone is linearly related to body weight with a population mean CL/F estimate of 1.65 L/h for a child with a mean body weight of 25 kg.

Proguanil exhibits linear pharmacokinetics with increase in dose from 100 mg to 400 mg and its systemic exposure is not dependent on food intake. As with atovaquone, the oral clearance of proguanil is dependent on body weight. The population estimates of CL/F for a typical 70 kg adult and 30 kg child are approximately 72 L/h and 45 L/h, respectively.

Average plasma concentrations of cycloguanil, the major metabolite of proguanil, is approximately 3-fold lower than for proguanil.

Bioavailability

In a comparative bioavailability study in healthy adult volunteers, MALARONE® administered as a single dose was bioequivalent to separate tablets of atovaquone 250 mg and proguanil 100 mg given concomitantly. In healthy adult subjects treated for 3 days, the pharmacokinetics of atovaquone and proguanil and its metabolite cycloguanil were not modified when atovaquone and proguanil were given alone or in combination as MALARONE®.

TOXICOLOGY

Acute Toxicity

At higher doses of proguanil in mice (30 mg/kg), ataxic and respiratory difficulties were seen after 2 to 4 hours and deaths 4 to 24 hours after dosing. In rats (dosed at 200 mg/kg), respiratory difficulties were followed by death 4 to 48 hours after dosing. In addition, surviving rats had slight body weight loss and decreased activity.

In the dog and rhesus monkey, proguanil appeared to be more toxic intramuscularly than orally. After oral doses of 200 and 400 mg/kg/day of proguanil, emesis was repeatedly observed 2 to 4 hours after dosing. There were no delayed signs of toxicity noted during the postdose observation period. Proguanil administration intramuscularly in monkeys and dogs resulted in mortalities at a dose of 160 mg/kg. Deaths occurred between 3 to 4 hours after dosing and were preceded by profound lethargy, slowing of heart rate, and respiratory difficulties ending in a coma. At a dose of 80 mg/kg, profound decreased activity lasting 8 to 12 hours postdose was reported.

Table 6 Acute Toxicity for Proguanil Hydrochloride

Species	Route of Administration	LD_{50} (mg/kg)
Mouse	oral intramuscular intraperitoneal intravenous	23 20 20 20
Rat	oral intraperitoneal intravenous	200 40 40
Rabbit	oral intraperitoneal	150 50
Dog	oral intramuscular	> 400 (no deaths) ≈120
Rhesus Monkey	oral intramuscular	> 400 (no deaths) ≈120

In acute toxicity experiments with atovaquone in rats and mice, the oral LD_{50} was in excess of 1,825 mg/kg, the highest dose tested. No deaths or other treatment-related effects were observed.

Multidose Toxicity

In 30-day studies in rats and dogs, primary drug-related effects were seen in animals given 40 mg/kg/day proguanil hydrochloride alone or in combination with 100 mg/kg/day atovaquone. These changes in the intestinal tract and bone marrow were essentially antiproliferative. In the intestine, the maturation arrest enteritis seen in the dog was similar to that described in dogs given dihydrofolate reductase inhibitors and nucleoside analogs. It was characterized by a blunting of the intestinal villi and flattening of the epithelium covering these blunted villi. This reflects a process whereby the normal turnover rate in the intestinal epithelium has been interfered with by the drug and the response is to try and cover the same amount of surface by using fewer cells than normal. Hence, the villi reduce in height and the covering cells flatten. In the rat, the effect was seen in the cecum only, but was not as severe. The bone marrow was hypocellular and there were fewer cells seen in the erythroid and myeloid series. Further, there was a decrease in maturation of the more immature erythroid and myeloid cells into mature erythrocytes and leucocytes.

Kidney changes consisted of acute tubular necrosis, basophilic (regenerative) tubular epithelium, and tubular dilatation. Renal changes were considered to be secondary to diarrhoea, inanition, and dehydration. Since these effects were seen in animals treated with proguanil hydrochloride either alone or in combination with atovaquone, the toxicities seen in the combination groups for rats and dogs were solely due to proguanil hydrochloride. These findings were fully reversible when the animals were evaluated after the drug-free recovery period.

The treatment of rats with proguanil hydrochloride for 6 months at dose levels up to 20 mg/kg/day, either alone or in combination with atovaquone, produced only very slight lesions in the caecum, which were reversible, or slight kidney tubular basophilia. Treatment with atovaquone alone at a dose level of 50 mg/kg/day produced no adverse effects, indicating that toxicity is proguanil related. These observations are consistent with the findings from the 1-month study in the rat, and are considered proguanil related.

In a 6-month repeat-dose toxicity study in dogs, with the exception of microscopic findings in the heart, liver, lungs and gall bladder, findings were consistent with those from the 1-month study. Slight changes in the liver and gall bladder were present at the low dose combination of 10 mg/kg/day atovaquone and 4 mg/kg/day proguanil hydrochloride at a systemic exposure approximately twice the exposures seen at the clinical dose in humans. Evidence of reversible biliary hyperplasia was seen in female dogs. The finding noted in the heart (atrial fibrovascular proliferation) is considered species-specific to the dog and is thus not of clinical relevance. In lungs, the observed interstitial pneumonia in the proguanil-treated groups was considered an exacerbation of a pre-existing condition. The toxicities observed following 6 months administration to dogs are considered proguanil related.

Table 7 Long Term Toxicity

Species	Male	Female	Dose Atovaquone:Proguanil HCl (mg/kg/day)	Route	Duration of Study	Observations
Rat	32	32	0:0	Oral (Gavage)	6 months	No adverse effects
	20	20	10:4			Microscopic findings of cecal hyperplasia. Emesis, salivation
	20	20	20:8			Decreased body weight in males. Microscopic findings of cecal hyperplasia.
	32	32	50:20			Decreased body weight in males. Microscopic findings of cecal hyperplasia and renal tubular basophillia.
	32	32	50:0			No drug related adverse effects were noted.
	32	32	0:20			Decreased body weight in males (recovery). Microscopic findings of cecal hyperplasia and renal tubular basophillia.
Dog	6	6	0	Oral (Capsule)	6 months	No adverse effects.
	4	4	10:4			Bile duct hyperplasia. Increase in background pneumonia. Gall bladder mucosal atrophy in females.
	4	4	20:8			Loose and liquid faeces. Transient decrease in red blood cell count. Dark area on the heart of a male. Microscopic findings in the kidney, bile duct, gall bladder and skin. Increase in pododermatitis and background pneumonia.

Table 7 Cont'd Long Term Toxicity

Species	Male	Female	Dose Atovaquone:Proguanil HCl (mg/kg/day)	Route	Duration of Study	Observations
Dog	6	6	30:12	Oral (Capsule)	6 months	2 males and 1 female killed in extremis, these animals had stress related microscopic findings. Emesis, salivation and diarrhoea, with associated decreased body weight and food consumption. Transient decrease in red blood cell count. Microscopic findings in the heart, bile duct, gall bladder, kidney. Increase in pododermatitis and background pneumonia.
	6	6	30:0			No adverse effects.
	6	6	0:12			3 male and 1 female died or killed in extremis, these animals had stress related microscopic findings. Emesis, salivation and diarrhoea, with associated decreased body weight and food consumption. Transient decrease in red blood cell count. Microscopic findings in the heart, bile duct, gall bladder, kidney and skin. Increase in pododermatitis and background pneumonia. Focal brain necrosis in a female.

Mutagenicity

A range of mutagenicity tests (Ames Test, mouse lymphoma assay and mouse micronucleus assay) have shown no evidence that atovaquone or proguanil up to a concentration of 74 mg/mL have mutagenic activity as single agents. Mutagenicity studies have not been performed with atovaquone in combination with proguanil.

Cycloguanil, the active metabolite of proguanil, was also negative in the Ames test, but was positive in the Mouse Lymphoma assay (0.075 µg/mL) and the Mouse Micronucleus assay (at ≥150 mg/kg). These positive effects with cycloguanil (a dihydrofolate antagonist) were reduced or abolished with folinic acid supplementation.

Carcinogenicity

Oncogenicity studies of atovaquone alone in mice showed a treatment-related increased incidence of hepatocellular adenomas and carcinomas at all dose levels tested (20, 50, 100, 200, 500 mg/kg/day) for a period up to 744 consecutive days. No such findings were observed in rats. These findings appear to be due to the inherent susceptibility of mice to atovaquone and are considered of no relevance in the clinical situation. Oncogenicity studies in proguanil alone showed no evidence of carcinogenicity in rats (at doses up to 20 mg/kg/day) and in mice (at doses up to 16 mg/kg/day).

In the pre-oncogenicity study in mice with proguanil hydrochloride alone, dosing at 40 mg/kg/day was not tolerated and administration was ceased on Day 12. Treatment-related microscopic changes were noted in the gall bladder, kidney and liver, and stress-related lymphoid depletion in various lymphoid tissues. Similar effects were seen following dosing at 8 and 20 mg/kg/day but with less severity and lower incidence. No adverse effects were noted at 4 mg/kg/day.

Teratology and Reproduction

In a teratology study conducted in rats, oral doses of up to 20 mg/kg/day proguanil hydrochloride alone or in combination with 50 mg/kg/day atovaquone were not teratogenic.

A study in male and female CD rats revealed no effect on fertility following oral dosing with proguanil hydrochloride alone at dose levels up to 16 mg/kg/day.

In a embryofetal development study carried out in rabbits, oral doses up to 100 mg/kg/day atovaquone or 40 mg/kg/day proguanil hydrochloride, either each component alone or in combination, was not toxic towards the rabbit fetus, and had no effect on the incidence of malformations or variations in this species. However, maternal toxicity was seen at 100:40 mg/kg/day atovaquone:proguanil hydrochloride, an effect enhanced by combined administration as compared to the administration of either drug alone.

In a pre- and post-natal toxicity study in the rat with proguanil hydrochloride alone at doses up to 16 mg/kg/day, there were no adverse effects on reproductive function in either the F0 or F1 generation, or on development or behaviour in F1 pups, although maternal toxicity (reduced body weight gain) was observed at the high dose.

Table 8 Teratology and Reproduction(Administration - Oral by gavage, once daily with each drug)

Parameter	Dose (atovaquone:proguanil HCl) mg/kg/day					
RATS						
Maternal	0	12.5:5	25:10	50:20	50:0	0:20
Evaluable pregnant females	23	28	26	25	27	24
Fetal						
Number of fetuses (litters) examined	354 (23)	396 (27)	348 (26)	401(25)	406 (27)	357 (24)
Number viable	Normal	Normal	Normal	Normal	Normal	Normal
Increased death/resorbed	No	No	No	No	No	No
Body weight/length	Normal	Normal	Normal	Normal	Normal	Normal
Increased malformations	No	No	No	No	No	No
Increased variations	No	No	No	No	No	Yes*
Distended Ureters						
Number of fetuses affected	3	14	7	14	5	12
Number of litters affected	2	7	5	5	4	10
RABBITS						
Maternal	0	25:10	50:20	100:40	100:0	0:40
Evaluable pregnant females	21	20	17	16	19	19
Clinical signs	No	No	No	YesH	No	No
Number deaths	0	0	4	10	1	2
Fetal						
Number of fetuses (litters) examined	109 (21)	116 (20)	82 (14)	50 (8)	102 (16)	99 (17)
Number viable	Normal	Normal	Normal	Normal	Normal	Normal
Increased death/resorbed	No	No	No	No	No	No
Body weight/length	Normal	Normal	Normal	Normal	Normal	Normal
Increased malformations	No	No	No	No	No	No
Increased variations	No	No	No	No	No	No

* Distended Ureter
H Decreased activity, prostration, loss of righting reflex, ataxia, red material around anal region

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