

**MALARONE™**  
(atovaquone and proguanil HCl)  
Tablets

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Pediatric Tablets

***Prevention and  
Treatment of Malaria***

## Malaria



- World's most important parasitic disease
- Parasite transmitted by mosquitoes
  - female *Anopheles* mosquito
- *P. falciparum* parasite causes most severe morbidity and mortality
  - responsible for 40-60% of world's malaria
  - responsible for 95% of deaths from malaria

Hoffman SL. *Med Clin No Am* 1992;76:1327.



Malaria is caused by parasites transmitted through the bite of the female *anopheles* mosquito. The *P. falciparum* parasite causes acute, fatal malaria, and is responsible 90% of clinical cases in Africa, and 50% in Southeast Asia and South America. This parasite is also responsible for the vast majority of deaths associated with the disease.

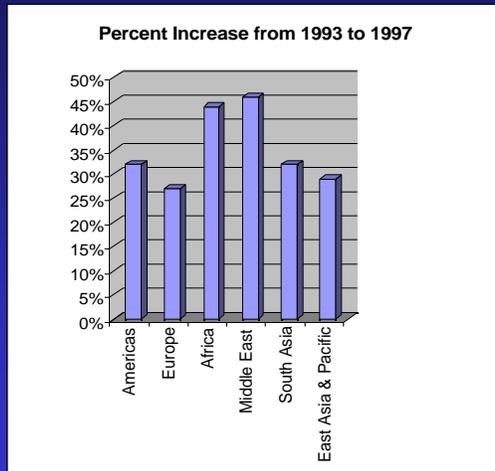
Malaria bouts are cyclical; fever alternates with freedom from symptoms about every 48 hours. This corresponds with the cycle of replication and eruption of the parasite from red blood cells in the patient. Initial symptoms include fever, headache, malaise, fatigue, nausea, muscle pains, and mild diarrhoea, which are often mistaken for influenza or gastrointestinal infection. Patients can rapidly progress from an uncomplicated stage to a severe and complicated stage, leading to delirium, impaired consciousness and generalised convulsions, followed by coma and death. Severe cases, including cerebral malaria, require hospital care.

Morbidity is very high as each disease episode may last several days, and repeat infections coupled with poor nutrition leads to anaemia and debilitation.

## Frequent Flyers

### Most Popular Air Routes Between Continents 1997

- Americas
- Europe
- Africa
- Middle East
- South Asia
- East Asia & Pacific



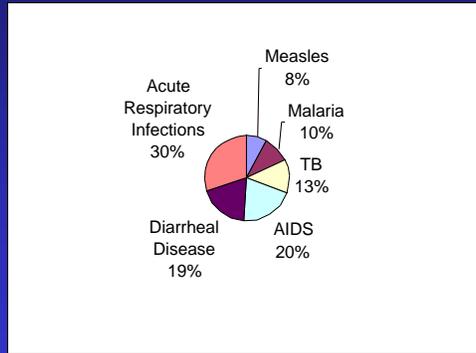
World Traveler Report WHO 1997.

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# Leading Infectious Disease Killers

Leading Infectious Disease Killers by Cause.  
11.5 millions deaths in 1998

- 300 million cases of malaria reported each year
- 1.1 million deaths in 1998
- Compared with 2.3 million deaths from AIDS



WHO Infectious Diseases Report 1999.

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## Diseases Affecting Tourists

Exiting tourists with infectious diseases, Thailand 1995

- Diarrheal Diseases (64%)
- Respiratory Infections (8%)
- Fever - cause unknown (6%)
- **Malaria (4%)**
- Hepatitis (4%)
- Gonorrhoea (4%)
- Other (10%)

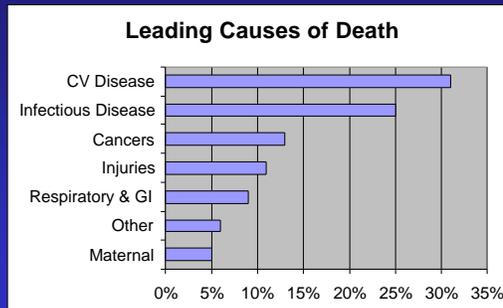
WHO Annual Report - Thailand, 1998.



## Leading Causes of Death

53.9 million from all causes, worldwide, 1998

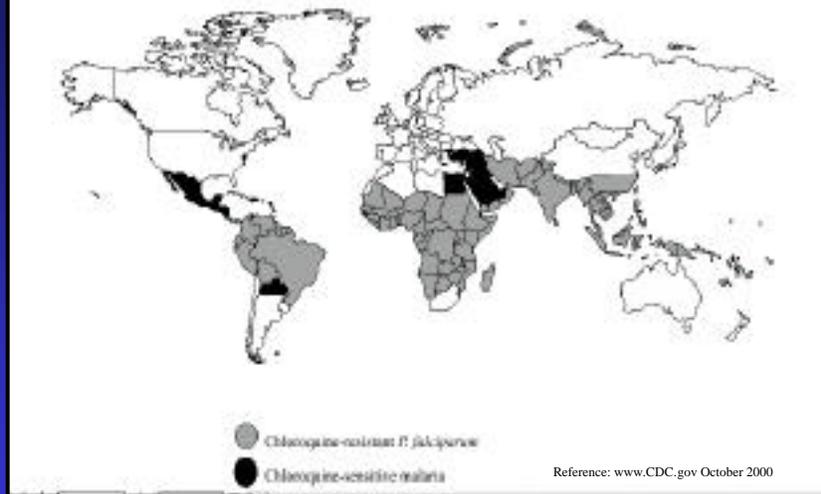
- CV Disease (31%)
- Infectious Disease (25%)
- Cancers (13%)
- Injuries (11%)
- Respiratory & GI (9%)
- Other (6%)
- Maternal (5%)



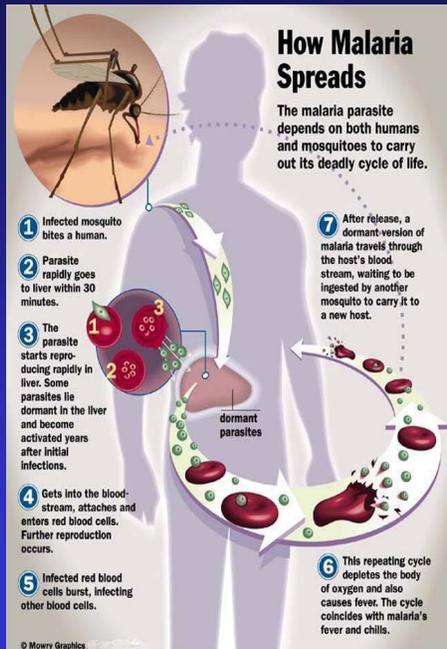
WHO Infectious Diseases Report 1999.

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Distribution of Malaria and Chloroquine-Resistant *Plasmodium falciparum*, 1997



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## Life Cycle of Malaria

1. Sporozoites injected by female mosquito
2. Rapid localization in hepatocytes (30 min)
3. Transform, multiply and develop into tissue schizonts (pre-erythrocytic stage of infection ---> 5 -16 days)
4. Tissue schizonts rupture, releasing merozoites which go into bloodstream; merozoites invade erythrocytes (erythrocytic stage)
5. Rupture of infected erythrocytes - febrile attacks every 48 hours
6. Repeating cycle
7. Continued transmission

Taylor TE. Malaria. In: *Hunter's Tropical Medicine and Emerging Infectious Diseases*, 8th ed., 2000.



## Symptoms of Malaria

- Malaria bouts are cyclical
  - fever alternates with freedom from symptoms every 48 hours
- Initial symptoms include fever, headache, malaise, fatigue, nausea, muscle pains, and mild diarrhea
- Severe malaria characterized by delirium, impaired consciousness and generalized convulsions, followed by coma and death

Taylor TE. Malaria. In: *Hunter's Tropical Medicine and Emerging Infectious Diseases, 8th Ed., 2000.*



## Control Measures

- Malaria deaths can be decreased with currently available interventions
  - vector control measures
  - bednets to reduce mosquito bites
  - early diagnosis of malaria
  - access to affordable, effective treatments
  - access to preventative treatments
- Countries most affected lack sufficient resources to control malaria

Taylor TE. Malaria. In: *Hunter's Tropical Medicine and Emerging Infectious Diseases*, 8th Ed., 2000.



# Resistance

- Increasing due to widespread uncontrolled and unregulated drug distribution
- Improper usage of drugs
- Renders available drugs ineffective and new closely related drugs show reduced efficacy
- Few effective antimalarial drugs available
- Insufficient research in novel drug targets
- Emergence of resistance to DDT and other insecticides

Taylor TE. Malaria. In: *Hunter's Tropical Medicine and Emerging Infectious Diseases*, 8th Ed., 2000.



Drug resistance - increasing rapidly due to widespread uncontrolled and unregulated drug distribution.

Resistance renders available drugs ineffective and new closely related drugs show reduced efficacy.

Improper usage of the drugs - subcurative doses, non-compliance with complete course of therapy

Few effective anti-malarial drugs available - most tropical countries still rely on chloroquine (low cost and no alternatives)

Insecticide programs - emergence of resistance to DDT and other insecticides.

Insufficient research in novel drug targets

## MALARONE™

### – **Prevention of Malaria:**

- *MALARONE* is indicated for the prophylaxis of *P. falciparum* malaria, including in areas where chloroquine resistance has been reported.

### – **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 chloroquine, halofantrine, mefloquine, and amodiaquine may have unacceptable failure rates, presumably due to drug resistance.



Enter Malarone. Malarone is a combination of atovaquone, an old anti-malarial treatment, and proguanil, used to prevent malaria. Because these two drugs act on very different pathways involved in the replication of the malaria parasite, they are almost 100% effective in treating and preventing malaria.

Malarone is currently approved in many countries around the world, for treatment of *P. falciparum* malaria. The treatment dose is four tablets, once a day, for three days. So far, resistance is minimal; therefore, Malarone is currently effective against parasites that have developed resistance to older medicines.

Prevention studies are underway in travellers, and Glaxo Wellcome is also studying Malarone for effectiveness against another form of the malaria parasite - *p. vivax*.

# MALARONE™

## ***Contraindications:***

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



# MALARONE™

## ***Contraindications (cont):***

*MALARONE* is contraindicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance <30 mL/min).

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(atovaquone and proguanil HCl)  
Tablets

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## ***Precautions:***

*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.

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## ***Precautions (cont):***

In patients with severe renal impairment (creatinine clearance <30 mL/min), alternatives to *MALARONE* should be recommended for treatment of acute *P. falciparum* malaria whenever possible.

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## ***Drug Interactions:***

- Reduced plasma concentrations of atovaquone:
  - **Rifampin or Rifabutin** - concomitant administration with *MALARONE* *not recommended*
  - **Tetracycline** - parasitemia should be closely monitored
  - **Metoclopramide** - should be used only if other antiemetics are not available



# MALARONE™

## Clinical Pharmacology

- **MOA:** Interferes with 2 different pathways involved in biosynthesis of pyrimidines required for nucleic acid replication
  - *Atovaquone* - Inhibitor of parasite mitochondrial electron transport
  - *Proguanil* - Active metabolite cycloguanil - inhibits parasitic dihydrofolate reductase disrupting deoxythymidylate synthesis
- **Activity *In Vitro* and *In Vivo*:**
  - Atovaquone and cycloguanil are active against the exo-erythrocytic and erythrocytic stages of *Plasmodium* spp
  - Enhanced efficacy of the combination compared to either agent alone demonstrated in clinical trials



# MALARONE™

## *Summary of Prevention Trials*

- Three randomized, placebo-controlled studies
  - Two Adult
  - One Pediatric
- One open-label study in nonimmune military personnel

Shanks GD. *J Travel Med* 1999;6:S21-27.



# MALARONE™

## ***Controlled Clinical Trials for Prevention of Malaria***

- Evaluated prophylactic activity of atovaquone + proguanil in subjects who did not have malaria parasitemia
- Required patients in malaria-endemic areas to take a curative course of antimalarial treatment QD x 3d
  - (1000 mg atovaquone + 400 mg proguanil)
- Primary endpoint: proportion of subjects who remained free of malaria parasitemia
  - 10 - 12 week period (Kenya, Zambia, Gabon)

Shanks GD. *J Travel Med* 1999;6:S21-27.



# MALARONE™

## *Prevention of Malaria (Kenya)*

- R, DB, PC trial in healthy adult volunteers (17 - 55 yo)
  - MALARONE - 1 tab (250 mg atovaquone/ 100 mg proguanil) daily
  - MALARONE - 2 tabs (500 mg atovaquone/ 200 mg proguanil) daily
  - Placebo
- Treated with MALARONE (4 tabs QD x 3d) to clear pre-existing malaria
- Directly observed administration of drug daily for 10 wks
- Blood films weekly or for symptoms
- 205 enrolled in the study; 162 completed the study

Shanks GD , et al. *Clin Infect Dis* 1998;27:494-499.



# MALARONE™

## *Prevention of Malaria (Kenya)*

	Enrolled	Completed	Developed patasitemia	Efficacy
Placebo	68	54	28	
MALARONE	70	54	0	100%

Shanks GD, et al. *Clin Infect Dis* 1998;27:494-499.



# MALARONE™

## *Prevention of Malaria (Zambia)*

- R, DB, PC trial in healthy adult volunteers (16 - 64 yo)
  - MALARONE - 1 tablet (250 mg atovaquone/ 100 mg proguanil) daily
  - Placebo
- Treated with MALARONE (4 tabs daily x 3d) to clear pre-existing malaria
- Administration of drug daily for 10 wks
- Blood films weekly or for symptoms
- 274 enrolled in the study; 213 completed the study

Sukwa TY, et al. *Am J Trop Med Hyg* 1999; 60:521-525.



# MALARONE™

## Prevention of Malaria (Zambia)

	Enrolled	Completed Study	Developed Parasitemia	Efficacy
Placebo	138	111	41	
MALARONE 1 tab/day	136	102	2	95%

Sukwa TY, et al. *Am J Trop Med Hyg* 199;60:521-525.



# MALARONE™

## *Prevention of Malaria (Gabon)*

- R, DB, PC trial in healthy children (4 - 16 yo)
  - Dosage based on body weight and given for up to 12 wks
    - 11 \_20 Kg (ONE *MALARONE* Pediatric Tablet)
    - >20 \_30 Kg (TWO *MALARONE* Pediatric Tablets)
    - >30 \_40 Kg (THREE *MALARONE* Pediatric Tablets)
    - >40 Kg (ONE *MALARONE* Tablet)
  - Placebo
- Initial curative treatment QD x 3d (based on BW)
- Blood films weekly or for symptoms
- 265 enrolled in the study; 247 completed the study

Lell B, et al. *Lancet* 1998;351(9104):709-713.



# MALARONE™

## Prevention of Malaria (Gabon)

	Enrolled	Completed Study	Developed Parasitemia	Efficacy
Placebo	140	134*	25*	
MALARONE	125	113	0	100%

\* Includes 2 patients who developed *P. ovale* or *P. malariae*

Lell et al. *Lancet* 1998;351(9104):709-713



# MALARONE™

## *Summary of Controlled Clinical Trials for Prevention of Malaria*

Country	Completed Study		Developed Parasitemia		MALARONE Efficacy
	Placebo	MALARONE	Placebo	MALARONE	
Kenya	54	54	28	0	100%
Zambia	111	102	41	2	95%
Gabon	134	113	25	0	100%
<b>Total</b>	<b>299</b>	<b>269</b>	<b>94</b>	<b>2</b>	<b>98%</b>

Shanks GD. *J Travel Med* 1999;6:S21-27.



# MALARONE™

## ***Uncontrolled Trial for Prevention (South Africa)***

- Uncontrolled, open-label study in nonimmune military personnel
- 175 subjects received ONE *MALARONE* Tablet daily x 10 wks
- Parasitemia developed in 1 subject
  - subject was noncompliant
- Three subjects discontinued therapy due to adverse effects (headache n=2, nausea/dizziness n=1)
- Chemoprophylaxis success rate of 97%

van der Berg JD. *Clin Ther* 1999;21:741-749.



# MALARONE™

## ***Adverse Experiences in Clinical Trials for Prevention of Malaria***

- Adverse effects similar in groups using placebo and groups using *MALARONE*
- Most commonly reported adverse effects:
  - headache
  - abdominal pain
- Therapy discontinued prematurely in 3/381 adults and 0/125 pediatric patients

Product Information for MALARONE.



# MALARONE™

## Summary of Adverse Experiences Prevention of Malaria

% of Subjects with a Treatment-related  
Adverse Experience in Placebo-controlled Trials

	Adults		Children	
	Placebo n=206	MALARONE n=206	Placebo n=140	MALARONE n=125
Headache	7	3	14	14
Abdominal pain	5	4	29	31
Diarrhea	3	2	1	0
Vomiting	<1	<1	6	7

Product Information for MALARONE.



# MALARONE™

## *Dosage in Prevention of Malaria*

- **One dose daily**
  - Start 1-2 days before entering endemic area, continue daily during stay & for 7 days after return
- **Adults:**
  - One *MALARONE* Tablet (adult strength = 250 mg atovaquone/100 mg proguanil hydrochloride) per day.
- **Pediatric Patients:**
  - Pediatric dosage for prevention based on body weight (see pediatric dosing slide)



# MALARONE™

## *Dosage in Prevention of Malaria*

### Dosage for Prevention of Malaria in Pediatric Patients

Weight (kg)	Total Daily Dose	Dosage Regimen
11-20	62.5 mg/25 mg	1 Pediatric Tablet daily
21-30	125 mg/50 mg	2 Pediatric Tablets daily
31-40	187.5 mg/75 mg	3 Pediatric Tablets daily
>40	250 mg/100 mg	1 Adult Strength Tablet daily



# MALARONE™

## *Clinical Trial Design for Acute Treatment*

- Enrolled patients with uncomplicated malaria caused by *P falciparum*
- Endpoint:  
*Cured*: parasitemia cleared within 7 days & did not recur by day 28

Kremsner PG. *J Travel Med* 1999;6:S18-20.



# MALARONE™

## Treatment of Acute Malaria

Study site	MALARONE		Drug	Comparator	
	Evaluable Patients (n)	Sensitive Response*		Evaluable Patients (n)	Sensitive Response*
Brazil	74	98.6%	Quinine & tetracycline	76	100%
Thailand	79	100%	Mefloquine	79	86.1%
France	21	100%	Halofantrine	18	100%
Kenya†	81	93.8	Halofantrine	83	90.4%

\* Elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days  
 † Study in pediatric patients 3-12 years of age



Product Information for MALARONE.

# MALARONE™

## Treatment of Acute Malaria

Study site	MALARONE		Drug	Comparator	
	Evaluable Patients (n)	Sensitive Response*		Evaluable Patients (n)	Sensitive Response*
Zambia	80	100%	Pyrimethamine/ sulfadoxine (P/S)	80	98.8%
Gabon	63	98.4%		Amodiaquine	63
Phillipines	54	100%	Chloroquine (Cq)	23	30.4%
			Cq & P/S	32	87.5%
Peru	19	100%	Chloroquine	13	7.7%
			P/S	7	100%

\* Elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days  
Product Information for MALARONE.



# MALARONE™

## ***Adverse Experiences in Clinical Trials for Acute Treatment***

Attributable Adverse Experiences  
Occurring in  $\geq 10\%$  of Adult Patients

Abdominal pain	17%
Nausea	12%
Vomiting	12%
Headache	10%

Product Information for MALARONE.



# MALARONE™

## *Adverse Experiences in Clinical Trials for Acute Treatment*

Attributable Adverse Experiences Occurring in  
>5% of Pediatric Patients

- Vomiting 10%
- Pruritus 6%

Product Information for MALARONE.



# MALARONE™

## *Dosage for Treatment of Acute Malaria*

- **Adults:** Four *MALARONE* Tablets (adult strength) as a single dose daily for 3 consecutive days
- **Pediatrics:** Dosage based on body weight (see pediatric dosing slide) administered daily for 3 consecutive days

Product Information for *MALARONE*.



# MALARONE™

## *Dosage for Treatment of Acute Malaria*

### Dosage for Treatment of Acute Malaria in Pediatric Patients

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

Product Information for MALARONE.



## MALARONE™

### ***Dosage and Administration***

*MALARONE* 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.

MALARONE  
(atovaquone and proguanil HCl)  
Tablets

# MALARONE™

## ***Dosage and Administration (cont)***

- *MALARONE* should not be used for malaria prophylaxis in patients with severe renal impairment (creatinine clearance <30 mL/min).
- Alternatives to *MALARONE* should be recommended for treatment of acute *P. falciparum* malaria whenever possible in patients with severe renal impairment.
- No dosage adjustments are needed in patients with mild to moderate renal impairment.



# MALARONE™

## *How Supplied*

- MALARONE™ Tablet:  
atovaquone 250 mg + proguanil HCl 100 mg
- MALARONE™ Pediatric Tablet:  
atovaquone 62.5 mg + proguanil HCl 25 mg

Product Information for MALARONE.

