

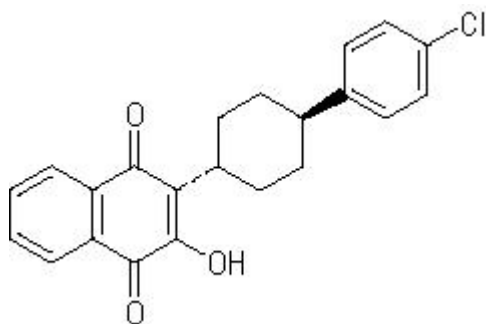
1 **PRESCRIBING INFORMATION**

2 **MALARONE<sup>®</sup>**  
3 **(atovaquone and proguanil hydrochloride)**  
4 **Tablets**

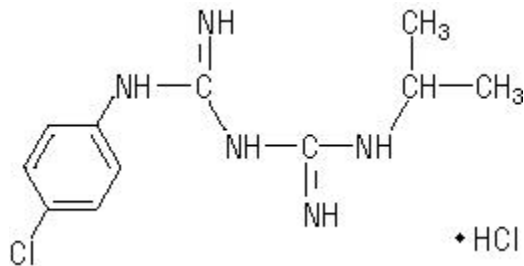
5 **MALARONE<sup>®</sup>**  
6 **(atovaquone and proguanil hydrochloride)**  
7 **Pediatric Tablets**

8 **DESCRIPTION**

9 MALARONE (atovaquone and proguanil hydrochloride) is a fixed-dose combination of the  
10 antimalarial agents atovaquone and proguanil hydrochloride. The chemical name of atovaquone  
11 is *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione. Atovaquone is a  
12 yellow crystalline solid that is practically insoluble in water. It has a molecular weight of 366.84  
13 and the molecular formula C<sub>22</sub>H<sub>19</sub>ClO<sub>3</sub>. The compound has the following structural formula:  
14



15  
16  
17 The chemical name of proguanil hydrochloride is 1-(4-chlorophenyl)-5-isopropyl-biguanide  
18 hydrochloride. Proguanil hydrochloride is a white crystalline solid that is sparingly soluble in  
19 water. It has a molecular weight of 290.22 and the molecular formula C<sub>11</sub>H<sub>16</sub>ClN<sub>5</sub>•HCl. The  
20 compound has the following structural formula:  
21



22  
23  
24 MALARONE Tablets and MALARONE Pediatric Tablets are for oral administration. Each  
25 MALARONE Tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride and  
26 each MALARONE Pediatric Tablet contains 62.5 mg of atovaquone and 25 mg of proguanil

27 hydrochloride. The inactive ingredients in both tablets are low-substituted hydroxypropyl  
28 cellulose, magnesium stearate, microcrystalline cellulose, poloxamer 188, povidone K30, and  
29 sodium starch glycolate. The tablet coating contains hypromellose, polyethylene glycol 400,  
30 polyethylene glycol 8000, red iron oxide, and titanium dioxide.

## 31 **CLINICAL PHARMACOLOGY**

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

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

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

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

50 Dietary fat taken with atovaquone increases the rate and extent of absorption, increasing AUC  
51 2 to 3 times and  $C_{max}$  5 times over fasting. The absolute bioavailability of the tablet formulation  
52 of atovaquone when taken with food is 23%. MALARONE Tablets should be taken with food or  
53 a milky drink.

54 Proguanil hydrochloride is extensively absorbed regardless of food intake.

55 **Distribution:** Atovaquone is highly protein bound (>99%) over the concentration range of 1  
56 to 90 mcg/mL. A population pharmacokinetic analysis demonstrated that the apparent volume of  
57 distribution of atovaquone (V/F) in adult and pediatric patients after oral administration is  
58 approximately 8.8 L/kg.

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

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

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

72 **Elimination:** The elimination half-life of atovaquone is about 2 to 3 days in adult patients.  
 73 The elimination half-life of proguanil is 12 to 21 hours in both adult patients and pediatric  
 74 patients, but may be longer in individuals who are slow metabolizers.

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

79  
 80 **Table 1. Apparent Clearance for Atovaquone and Proguanil in Patients as a Function of**  
 81 **Body Weight**

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

82 \*SD = standard deviation.

83  
 84 The pharmacokinetics of atovaquone and proguanil in patients with body weight below 11 kg  
 85 have not been adequately characterized.

86 **Special Populations: Pediatrics:** The pharmacokinetics of proguanil and cycloguanil are  
 87 similar in adult patients and pediatric patients. However, the elimination half-life of atovaquone  
 88 is shorter in pediatric patients (1 to 2 days) than in adult patients (2 to 3 days). In clinical trials,  
 89 plasma trough levels of atovaquone and proguanil in pediatric patients weighing 5 to 40 kg were  
 90 within the range observed in adults after dosing by body weight.

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

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

98 **Hepatic Impairment:** In a single-dose study, the pharmacokinetics of atovaquone,  
 99 proguanil, and cycloguanil were compared in 13 subjects with hepatic impairment (9 mild,  
 100 4 moderate, as indicated by the Child-Pugh method) to 13 subjects with normal hepatic function.  
 101 In subjects with mild or moderate hepatic impairment as compared to healthy subjects, there  
 102 were no marked differences (<50%) in the rate or extent of systemic exposure of atovaquone.  
 103 However, in subjects with moderate hepatic impairment, the elimination half-life of atovaquone  
 104 was increased (point estimate = 1.28, 90% CI = 1.00 to 1.63). Proguanil AUC,  $C_{max}$ , and its  $t_{1/2}$   
 105 increased in subjects with mild hepatic impairment when compared to healthy subjects (Table 2).  
 106 Also, the proguanil AUC and its  $t_{1/2}$  increased in subjects with moderate hepatic impairment  
 107 when compared to healthy subjects. Consistent with the increase in proguanil AUC, there were  
 108 marked decreases in the systemic exposure of cycloguanil ( $C_{max}$  and AUC) and an increase in its  
 109 elimination half-life in subjects with mild hepatic impairment when compared to healthy  
 110 volunteers (Table 2). There were few measurable cycloguanil concentrations in subjects with  
 111 moderate hepatic impairment (see DOSAGE AND ADMINISTRATION). The pharmacokinetics  
 112 of atovaquone, proguanil, and cycloguanil after administration of MALARONE have not been  
 113 studied in patients with severe hepatic impairment.

114

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

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

117 ND = not determined due to lack of quantifiable data.

118 \*Ratio of geometric means.

119 †Mean difference.

120

121 **Renal Impairment:** In patients with mild renal impairment (creatinine clearance 50 to  
 122 80 mL/min), oral clearance and/or AUC data for atovaquone, proguanil, and cycloguanil are  
 123 within the range of values observed in patients with normal renal function (creatinine clearance  
 124 >80 mL/min). In patients with moderate renal impairment (creatinine clearance 30 to  
 125 50 mL/min), mean oral clearance for proguanil was reduced by approximately 35% compared  
 126 with patients with normal renal function (creatinine clearance >80 mL/min) and the oral

127 clearance of atovaquone was comparable between patients with normal renal function and mild  
128 renal impairment. No data exist on the use of MALARONE for long-term prophylaxis (over  
129 2 months) in individuals with moderate renal failure. In patients with severe renal impairment  
130 (creatinine clearance <30 mL/min), atovaquone C<sub>max</sub> and AUC are reduced but the elimination  
131 half-lives for proguanil and cycloguanil are prolonged, with corresponding increases in AUC,  
132 resulting in the potential of drug accumulation and toxicity with repeated dosing (see  
133 CONTRAINDICATIONS).

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

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

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

140 Concomitant administration of **rifampin** or **rifabutin** is known to reduce atovaquone levels  
141 by approximately 50% and 34%, respectively (see PRECAUTIONS: Drug Interactions). The  
142 mechanisms of these interactions are unknown.

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

## 147 **INDICATIONS AND USAGE**

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

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

## 155 **CONTRAINDICATIONS**

156 MALARONE is contraindicated in individuals with known hypersensitivity to atovaquone or  
157 proguanil hydrochloride or any component of the formulation. Rare cases of anaphylaxis  
158 following treatment with atovaquone/proguanil have been reported.

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

162 **PRECAUTIONS**

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

166 Elevated liver function tests and rare cases of hepatitis have been reported with prophylactic  
167 use of MALARONE. A single case of hepatic failure requiring liver transplantation has also  
168 been reported with prophylactic use.

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

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

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

182 **Information for Patients:** Patients should be instructed:

- 183 • to take MALARONE tablets at the same time each day with food or a milky drink.
- 184 • to take a repeat dose of MALARONE if vomiting occurs within 1 hour after dosing.
- 185 • to take a dose as soon as possible if a dose is missed, then return to their normal dosing  
186 schedule. However, if a dose is skipped, the patient should not double the next dose.
- 187 • that rare serious adverse events such as hepatitis, severe skin reactions, neurological, and  
188 hematological events have been reported when MALARONE was used for the prophylaxis or  
189 treatment of malaria.
- 190 • to consult a healthcare professional regarding alternative forms of prophylaxis if prophylaxis  
191 with MALARONE is prematurely discontinued for any reason.
- 192 • that protective clothing, insect repellents, and bednets are important components of malaria  
193 prophylaxis.
- 194 • that no chemoprophylactic regimen is 100% effective; therefore, patients should seek  
195 medical attention for any febrile illness that occurs during or after return from a  
196 malaria-endemic area and inform their healthcare professional that they may have been  
197 exposed to malaria.
- 198 • that falciparum malaria carries a higher risk of death and serious complications in pregnant  
199 women than in the general population. Pregnant women anticipating travel to malarious areas  
200 should discuss the risks and benefits of such travel with their physicians (see Pregnancy  
201 section).

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

207 Concomitant administration of **rifampin** or **rifabutin** is known to reduce atovaquone levels  
208 by approximately 50% and 34%, respectively. The concomitant administration of MALARONE  
209 and rifampin or rifabutin is not recommended.

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

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

#### 214 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

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

222 **Proguanil:** No evidence of a carcinogenic effect was observed in 24-month studies  
223 conducted in CD-1 mice (doses up to 1.5 times the average systemic human exposure based on  
224 AUC) and in Wistar Hannover rats (doses up to 1.1 times the average systemic human exposure).

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

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

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

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

239 Atovaquone was not teratogenic and did not cause reproductive toxicity in rats at maternal  
240 plasma concentrations up to 5 to 6.5 times the estimated human exposure during treatment of  
241 malaria. Following single-dose administration of <sup>14</sup>C-labeled atovaquone to pregnant rats,

242 concentrations of radiolabel in rat fetuses were 18% (mid-gestation) and 60% (late gestation) of  
243 concurrent maternal plasma concentrations. In rabbits, atovaquone caused maternal toxicity at  
244 plasma concentrations that were approximately 0.6 to 1.3 times the estimated human exposure  
245 during treatment of malaria. Adverse fetal effects in rabbits, including decreased fetal body  
246 lengths and increased early resorptions and post-implantation losses, were observed only in the  
247 presence of maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of  
248 the concurrent maternal plasma concentrations.

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

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

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

265 Proguanil is excreted into human milk in small quantities.

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

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

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

275 **Geriatric Use:** Clinical studies of MALARONE did not include sufficient numbers of subjects  
276 aged 65 and over to determine whether they respond differently from younger subjects. In  
277 general, dose selection for an elderly patient should be cautious, reflecting the greater frequency  
278 of decreased hepatic, renal, or cardiac function, the higher systemic exposure to cycloguanil (see  
279 CLINICAL PHARMACOLOGY: Special Populations: Geriatrics), and the greater frequency of  
280 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  $\geq 5\%$  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  $\geq 5\%$  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  $\geq 5\%$  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

320 was discontinued prematurely due to a treatment-related adverse experience in 3 of 381 adults  
 321 and 0 of 125 pediatric patients.

322

323 **Table 3. Adverse Experiences in Placebo-Controlled Clinical Trials of MALARONE for**  
 324 **Prophylaxis of Malaria**

| Adverse Experience          | Percent of Subjects With Adverse Experiences<br>(Percent of Subjects With Adverse Experiences Attributable to Therapy) |                      |                      |                          |                     |
|-----------------------------|--|----------------------|----------------------|--------------------------|---------------------|
|                             | Adults   |                      |                      | Children and Adolescents |                     |
|                             | Placebo<br>n = 206   | MALARONE*<br>n = 206 | MALARONE†<br>n = 381 | Placebo<br>n = 140       | MALARONE<br>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)             |

325 \* Subjects receiving the recommended dose of atovaquone and proguanil hydrochloride in  
 326 placebo-controlled trials.

327 † Subjects receiving the recommended dose of atovaquone and proguanil hydrochloride in any  
 328 trial.

329

330 In an additional placebo-controlled study of malaria prophylaxis with MALARONE involving  
 331 330 pediatric patients in a malaria-endemic area (see CLINICAL STUDIES), the safety profile  
 332 of MALARONE was consistent with that described above. The most common  
 333 treatment-emergent adverse events with MALARONE were abdominal pain (13%), headache  
 334 (13%), and cough (10%). Abdominal pain (13% vs. 8%) and vomiting (5% vs. 3%) were  
 335 reported more often with MALARONE than with placebo, while fever (5% vs. 12%) and  
 336 diarrhea (1% vs. 5%) were more common with placebo. No patient withdrew from the study due  
 337 to an adverse experience with MALARONE. No routine laboratory data were obtained during  
 338 this study.

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

351

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

| Adverse Experience     | Percent of Subjects With Adverse Experiences*<br>(Percent of Subjects With Adverse Experiences Attributable to Therapy) |                       |                     |  |
|------------------------|---|-----------------------|---------------------|--|
|                        | Study 1   |                       | Study 2             |  |
|                        | MALARONE<br>n = 493   | Mefloquine<br>n = 483 | MALARONE<br>n = 511 | Chloroquine plus<br>Proguanil<br>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                    | 20 (14)   | 37 (29)               | 16 (10)             | 20 (10)                                  |

|                        |         |         |         |         |
|------------------------|---------|---------|---------|---------|
| neuropsychiatric event |         |         |         |         |
| Any GI event           | 49 (16) | 50 (19) | 43 (12) | 54 (20) |

354 \* Adverse experiences that started while receiving active study drug.

355

356 In a third active-controlled study, MALARONE (n = 110) was compared with  
 357 chloroquine/proguanil (n = 111) for the prophylaxis of malaria in 221 non-immune pediatric  
 358 patients (see CLINICAL STUDIES). The mean duration of exposure was 23 days for  
 359 MALARONE, 46 days for chloroquine, and 43 days for proguanil, reflecting the different  
 360 recommended dosage regimens for these products. Fewer patients treated with MALARONE  
 361 reported abdominal pain (2% vs. 7%) or nausea (<1% vs. 7%) than children who received  
 362 chloroquine/proguanil. Oral ulceration (2% vs. 2%), vivid dreams (2% vs. <1%), and blurred  
 363 vision (0% vs. 2%) occurred in similar proportions of patients receiving either MALARONE or  
 364 chloroquine/proguanil, respectively. Two patients discontinued prophylaxis with  
 365 chloroquine/proguanil due to adverse events, while none of those receiving MALARONE  
 366 discontinued due to adverse events.

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

373 **Blood and Lymphatic System Disorders:** Neutropenia and rarely anemia. Pancytopenia  
 374 in patients with severe renal impairment treated with proguanil.

375 **Immune System Disorders:** Allergic reactions including angioedema, urticaria, and rare  
 376 cases of anaphylaxis.

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

379 **Hepatobiliary Disorders:** Elevated liver function tests and rare cases of hepatitis; a single  
 380 case of hepatic failure requiring transplant have been reported.

381 **Skin and Subcutaneous Tissue Disorders:** Photosensitivity, rash, and rare cases of  
 382 erythema multiforme and Stevens-Johnson syndrome.

383 **OVERDOSAGE**

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

386 There is no known antidote for atovaquone, and it is currently unknown if atovaquone is  
 387 dialyzable. The median lethal dose is higher than the maximum oral dose tested in mice and rats  
 388 (1,825 mg/kg/day). Overdoses up to 31,500 mg of atovaquone have been reported. In one such

389 patient who also took an unspecified dose of dapson, methemoglobinemia occurred. Rash has  
390 also been reported after overdose.

391 Overdoses of proguanil hydrochloride as large as 1,500 mg have been followed by complete  
392 recovery, and doses as high as 700 mg twice daily have been taken for over 2 weeks without  
393 serious toxicity. Adverse experiences occasionally associated with proguanil hydrochloride doses  
394 of 100 to 200 mg/day, such as epigastric discomfort and vomiting, would be likely to occur with  
395 overdose. There are also reports of reversible hair loss and scaling of the skin on the palms  
396 and/or soles, reversible aphthous ulceration, and hematologic side effects.

## 397 **DOSAGE AND ADMINISTRATION**

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

400 **Prevention of Malaria:** Prophylactic treatment with MALARONE should be started 1 or  
401 2 days before entering a malaria-endemic area and continued daily during the stay and for 7 days  
402 after return.

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

405 **Pediatric Patients:** The dosage for prevention of malaria in pediatric patients is based upon  
406 body weight (Table 5).

407

408 **Table 5. Dosage for Prevention of Malaria in Pediatric Patients**

| Weight (kg) | Atovaquone/<br>Proguanil HCl<br>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 |

409

410 **Treatment of Acute Malaria: Adults:** Four MALARONE Tablets (adult strength; total daily  
411 dose 1 g atovaquone/400 mg proguanil hydrochloride) as a single dose daily for 3 consecutive  
412 days.

413 **Pediatric Patients:** The dosage for treatment of acute malaria in pediatric patients is based  
414 upon body weight (Table 6).

415

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

| Weight (kg) | Atovaquone/<br>Proguanil HCl<br>Total Daily<br>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 |

417  
 418 MALARONE Tablets may be crushed and mixed with condensed milk just prior to  
 419 administration for children who may have difficulty swallowing tablets.

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

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

432 **HOW SUPPLIED**

433 MALARONE Tablets, containing 250 mg atovaquone and 100 mg proguanil hydrochloride,  
 434 are pink, film-coated, round, biconvex tablets engraved with “GX CM3” on one side.

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

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

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

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

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

### 443 **ANIMAL TOXICOLOGY**

444 Fibrovascular proliferation in the right atrium, pyelonephritis, bone marrow hypocellularity,  
445 lymphoid atrophy, and gastritis/enteritis were observed in dogs treated with proguanil  
446 hydrochloride for 6 months at a dose of 12 mg/kg/day (approximately 3.9 times the  
447 recommended daily human dose for malaria prophylaxis on a mg/m<sup>2</sup> basis). Bile duct  
448 hyperplasia, gall bladder mucosal atrophy, and interstitial pneumonia were observed in dogs  
449 treated with proguanil hydrochloride for 6 months at a dose of 4 mg/kg/day (approximately  
450 1.3 times the recommended daily human dose for malaria prophylaxis on a mg/m<sup>2</sup> basis).  
451 Mucosal hyperplasia of the cecum and renal tubular basophilia were observed in rats treated with  
452 proguanil hydrochloride for 6 months at a dose of 20 mg/kg/day (approximately 1.6 times the  
453 recommended daily human dose for malaria prophylaxis on a mg/m<sup>2</sup> basis). Adverse heart, lung,  
454 liver, and gall bladder effects observed in dogs and kidney effects observed in rats were not  
455 shown to be reversible.

### 456 **CLINICAL STUDIES**

457 **Treatment of Acute Malarial Infections:** In 3 phase II clinical trials, atovaquone alone,  
458 proguanil hydrochloride alone, and the combination of atovaquone and proguanil hydrochloride  
459 were evaluated for the treatment of acute, uncomplicated malaria caused by *P. falciparum*.  
460 Among 156 evaluable patients, the parasitological cure rate was 59/89 (66%) with atovaquone  
461 alone, 1/17 (6%) with proguanil hydrochloride alone, and 50/50 (100%) with the combination of  
462 atovaquone and proguanil hydrochloride.

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

471 The overall efficacy in 521 evaluable patients was 98.7% (Table 7).  
472

473 **Table 7. Parasitological Response in Clinical Trials of MALARONE for Treatment of**  
 474 ***P. falciparum* Malaria**

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

475 \* MALARONE = 1,000 mg atovaquone and 400 mg proguanil hydrochloride (or equivalent  
 476 based on body weight for patients weighing ≤40 kg) once daily for 3 days.

477 † Elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days.

478 ‡ Patients hospitalized only for acute care. Follow-up conducted in outpatients.

479 § Study in pediatric patients 3 to 12 years of age.

480

481 Eighteen of 521 (3.5%) evaluable patients with acute falciparum malaria presented with a  
 482 pretreatment serum creatinine greater than 2.0 mg/dL (range 2.1 to 4.3 mg/dL). All were  
 483 successfully treated with MALARONE and 17 of 18 (94.4%) had normal serum creatinine levels  
 484 by day 7.

485 Data from a phase II trial of atovaquone conducted in Zambia suggested that approximately  
 486 40% of the study population in this country were HIV-infected patients. The enrollment criteria  
 487 were similar for the phase III trial of MALARONE conducted in Zambia and the results are  
 488 presented in Table 7. Efficacy rates for MALARONE in this study population were high and  
 489 comparable to other populations studied.

490 The efficacy of MALARONE in the treatment of the erythrocytic phase of nonfalciparum  
 491 malaria was assessed in a small number of patients. Of the 23 patients in Thailand infected with  
 492 *P. vivax* and treated with atovaquone/proguanil hydrochloride 1,000 mg/400 mg daily for 3 days,  
 493 parasitemia cleared in 21 (91.3%) at 7 days. Parasite relapse occurred commonly when *P. vivax*  
 494 malaria was treated with MALARONE alone. Seven patients in Gabon with malaria due to  
 495 *P. ovale* or *P. malariae* were treated with atovaquone/proguanil hydrochloride 1,000 mg/400 mg  
 496 daily for 3 days. All 6 evaluable patients (3 with *P. malariae*, 2 with *P. ovale*, and 1 with mixed



497 *P. falciparum* and *P. ovale*) were cured at 28 days. Relapsing malarias including *P. vivax* and  
498 *P. ovale* require additional treatment to prevent relapse.

499 The efficacy of MALARONE in treating acute uncomplicated *P. falciparum* malaria in  
500 children weighing  $\geq 5$  and  $< 11$  kg was examined in an open-label, randomized trial conducted in  
501 Gabon. Patients received either MALARONE (2 or 3 MALARONE Pediatric Tablets once daily  
502 depending upon body weight) for 3 days ( $n = 100$ ) or amodiaquine (10 mg/kg/day) for 3 days  
503 ( $n = 100$ ). In this study, the MALARONE Tablets were crushed and mixed with condensed milk  
504 just prior to administration. In the per-protocol population, adequate clinical response was  
505 obtained in 95% (87/92) of the pediatric patients who received MALARONE and in 53% (41/78)  
506 of those who received amodiaquine. A response of RI resistance (elimination of parasitemia but  
507 with recurrent parasitemia between 7 and 28 days after starting treatment) was noted in 3% and  
508 40% of the patients, respectively. Two cases of RIII resistance (rising parasite count despite  
509 therapy) were reported in the patients receiving MALARONE. There were 4 cases of RIII in the  
510 amodiaquine arm.

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

514 Three placebo-controlled studies of 10 to 12 weeks' duration were conducted among residents  
515 of malaria-endemic areas in Kenya, Zambia, and Gabon. Of a total of 669 randomized patients  
516 (including 264 pediatric patients 5 to 16 years of age), 103 were withdrawn for reasons other  
517 than falciparum malaria or drug-related adverse events. (Fifty-five percent of these were lost to  
518 follow-up and 45% were withdrawn for protocol violations.) The results are listed in Table 8.

519

520 **Table 8. Prevention of Parasitemia in Placebo-Controlled Clinical Trials of MALARONE**  
521 **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 ( <i>P. falciparum</i> ) | 2        | 92      |

522

523 In another study, 330 Gabonese pediatric patients (weighing 13 to 40 kg, and aged 4 to  
524 14 years) who had received successful open-label radical cure treatment with artesunate, were  
525 randomized to receive either MALARONE (dosage based on body weight) or placebo in a  
526 double-blind fashion for 12 weeks. Blood smears were obtained weekly and any time malaria  
527 was suspected. Nineteen of the 165 children given MALARONE and 18 of 165 patients given  
528 placebo withdrew from the study for reasons other than parasitemia (primary reason was lost to  
529 follow-up). In the per-protocol population, 1 out of 150 patients ( $< 1\%$ ) who received  
530 MALARONE developed *P. falciparum* parasitemia while receiving prophylaxis with  
531 MALARONE compared with 31 (22%) of the 144 placebo recipients.

532 In a 10-week study in 175 South African subjects who moved into malaria-endemic areas and  
 533 were given prophylaxis with 1 MALARONE Tablet daily, parasitemia developed in 1 subject  
 534 who missed several doses of medication. Since no placebo control was included, the incidence of  
 535 malaria in this study was not known.

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

544

545 **Table 9. Prevention of Parasitemia in Active-Controlled Clinical Trials of MALARONE for**  
 546 **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 ( <i>P. falciparum</i> )              | 0        | 0          | 3                          |

547

548 A third randomized, open-label study was conducted which included 221 otherwise healthy  
 549 pediatric patients (weighing  $\geq 11$  kg and 2 to 17 years of age) who were at risk of contracting  
 550 malaria by traveling to an endemic area. The mean duration of travel was 15 days (range 1 to  
 551 30 days). Prophylaxis with MALARONE (n = 110, dosage based on body weight) began 1 or  
 552 2 days before entering the endemic area and lasted until 7 days after leaving the area. A control  
 553 group (n = 111) received prophylaxis with chloroquine/proguanil dosed according to WHO  
 554 guidelines. No cases of malaria occurred in either group of children. However, the study was not  
 555 large enough to allow for statements of comparative efficacy. In addition, the true exposure rate  
 556 to *P. falciparum* malaria in this study is unknown.

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

559 **Causal Prophylaxis:** In separate studies with small numbers of volunteers, atovaquone and  
 560 proguanil hydrochloride were independently shown to have causal prophylactic activity directed  
 561 against liver-stage parasites of *P. falciparum*. Six patients given a single dose of atovaquone  
 562 250 mg 24 hours prior to malaria challenge were protected from developing malaria, whereas all  
 563 4 placebo-treated patients developed malaria.

564 During the 4 weeks following cessation of prophylaxis in clinical trial participants who  
 565 remained in malaria-endemic areas and were available for evaluation, malaria developed in 24 of

566 211 (11.4%) subjects who took placebo and 9 of 328 (2.7%) who took MALARONE. While new  
567 infections could not be distinguished from recrudescent infections, all but 1 of the infections in  
568 patients treated with MALARONE occurred more than 15 days after stopping therapy, probably  
569 representing new infections. The single case occurring on day 8 following cessation of therapy  
570 with MALARONE probably represents a failure of prophylaxis with MALARONE.

571 The possibility that delayed cases of *P. falciparum* malaria may occur some time after  
572 stopping prophylaxis with MALARONE cannot be ruled out. Hence, returning travelers  
573 developing febrile illnesses should be investigated for malaria.  
574



575  
576 GlaxoSmithKline  
577 Research Triangle Park, NC 27709  
578

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581 Month Year

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