

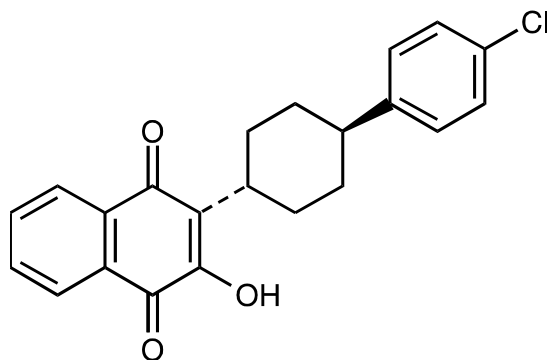
1 **PRESCRIBING INFORMATION**

2 **MALARONE[®]**
3 **(atovaquone and proguanil hydrochloride)**
4 **Tablets**

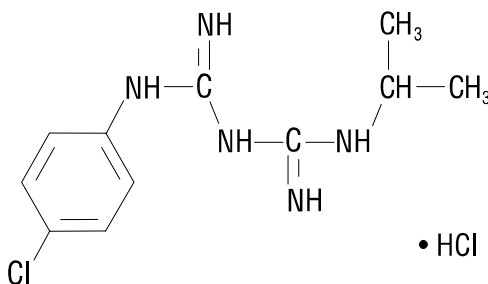
5 **MALARONE[®]**
6 **(atovaquone and proguanil hydrochloride)**
7 **Pediatric Tablets**

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 C₂₂H₁₉ClO₃. 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 C₁₁H₁₆ClN₅•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 recrudescence 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 ¹⁴C-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) Mean ± SD* (range)	N	CL/F (L/hr) Mean ± SD* (range)
11-20 kg	159	1.34 ± 0.63 (0.52-4.26)	146	29.5 ± 6.5 (10.3-48.3)
21-30 kg	117	1.87 ± 0.81 (0.52-5.38)	113	40.0 ± 7.5 (15.9-62.7)
31-40 kg	95	2.76 ± 2.07 (0.97-12.5)	91	49.5 ± 8.30 (25.8-71.5)
>40 kg	368	6.61 ± 3.92 (1.32-20.3)	282	67.9 ± 19.9 (14.0-145)

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

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

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

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

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

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

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

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

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

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

207 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

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

215 **Proguanil:** No evidence of a carcinogenic effect was observed in studies conducted in CD-1
216 mice (doses up to 1.51 times the average systemic human exposure based on AUC) and in Wistar
217 Hannover rats (doses up to 1.12 times the average systemic human exposure).

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

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

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

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

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

240 presence of maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of
241 the concurrent maternal plasma concentrations.

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

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

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

258 Proguanil is excreted into human milk in small quantities.

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

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

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

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

274 **ADVERSE REACTIONS**

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

279 Among adults who received MALARONE for treatment of malaria, attributable adverse
280 experiences that occurred in $\geq 5\%$ of patients were abdominal pain (17%), nausea (12%),
281 vomiting (12%), headache (10%), diarrhea (8%), asthenia (8%), anorexia (5%), and dizziness
282 (5%). Treatment was discontinued prematurely due to an adverse experience in 4 of 436 adults
283 treated with MALARONE.

284 Among pediatric patients (weighing 11 to 40 kg) who received MALARONE for the
285 treatment of malaria, attributable adverse experiences that occurred in $\geq 5\%$ of patients were
286 vomiting (10%) and pruritus (6%). Vomiting occurred in 43 of 319 (13%) pediatric patients who
287 did not have symptomatic malaria but were given treatment doses of MALARONE for 3 days in
288 a clinical trial. The design of this clinical trial required that any patient who vomited be
289 withdrawn from the trial. Among pediatric patients with symptomatic malaria treated with
290 MALARONE, treatment was discontinued prematurely due to an adverse experience in 1 of 116
291 (0.9%).

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

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

300 In one phase III trial of malaria treatment in Thai adults, early elevations of ALT and AST
301 were observed to occur more frequently in patients treated with MALARONE compared to
302 patients treated with an active control drug. Rates for patients who had normal baseline levels of
303 these clinical laboratory parameters were: Day 7: ALT 26.7% vs. 15.6%; AST 16.9% vs. 8.6%.
304 By day 14 of this 28-day study, the frequency of transaminase elevations equalized across the
305 2 groups.

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

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

315

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

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

318 *Subjects receiving the recommended dose of atovaquone and proguanil hydrochloride in
 319 placebo-controlled trials.

320 [†] Subjects receiving the recommended dose of atovaquone and proguanil hydrochloride in any
 321 trial.

322
 323 In an additional placebo-controlled study of malaria prophylaxis with MALARONE involving
 324 330 pediatric patients in a malaria-endemic area (see CLINICAL STUDIES), the safety profile
 325 of MALARONE was consistent with that described above. The most common
 326 treatment-emergent adverse events with MALARONE were abdominal pain (13%), headache
 327 (13%), and cough (10%). Abdominal pain (13% vs. 8%) and vomiting (5% vs. 3%) were
 328 reported more often with MALARONE than with placebo, while fever (5% vs. 12%) and
 329 diarrhea (1% vs. 5%) were more common with placebo. No patient withdrew from the study due
 330 to an adverse experience with MALARONE. No routine laboratory data were obtained during
 331 this study.

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

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

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

347 *Adverse experiences that started while receiving active study drug.

348
 349 In a third active-controlled study, MALARONE (n = 110) was compared with
 350 chloroquine/proguanil (n = 111) for the prophylaxis of malaria in 221 non-immune pediatric
 351 patients (see CLINICAL STUDIES). The mean duration of exposure was 23 days for
 352 MALARONE, 46 days for chloroquine, and 43 days for proguanil, reflecting the different
 353 recommended dosage regimens for these products. Fewer patients treated with MALARONE
 354 reported abdominal pain (2% vs. 7%) or nausea (<1% vs. 7%) than children who received
 355 chloroquine/proguanil. Oral ulceration (2% vs. 2%), vivid dreams (2% vs. <1%), and blurred
 356 vision (0% vs. 2%) occurred in similar proportions of patients receiving either MALARONE or

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

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

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

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

371 **OVERDOSAGE**

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

374 There is no known antidote for atovaquone, and it is currently unknown if atovaquone is
375 dialyzable. The median lethal dose is higher than the maximum oral dose tested in mice and rats
376 (1,825 mg/kg/day). Overdoses up to 31,500 mg of atovaquone have been reported. In one such
377 patient who also took an unspecified dose of dapsone, methemoglobinemia occurred. Rash has
378 also been reported after overdose.

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

385 **DOSAGE AND ADMINISTRATION**

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

388 **Prevention of Malaria:** Prophylactic treatment with MALARONE should be started 1 or
389 2 days before entering a malaria-endemic area and continued daily during the stay and for 7 days
390 after return.

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

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

395

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

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

397
 398 **Treatment of Acute Malaria: Adults:** Four MALARONE Tablets (adult strength; total daily
 399 dose 1 g atovaquone/400 mg proguanil hydrochloride) as a single dose daily for 3 consecutive
 400 days.

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

403
 404 **Table 6. Dosage for Treatment of Acute Malaria in Pediatric Patients**

Weight (kg)	Atovaquone/ Proguanil HCl Total Daily Dose	Dosage Regimen
5-8	125 mg/50 mg	2 MALARONE Pediatric Tablets daily for 3 consecutive days
9-10	187.5 mg/75 mg	3 MALARONE Pediatric Tablets daily for 3 consecutive days
11-20	250 mg/100 mg	1 MALARONE Tablet (adult strength) daily for 3 consecutive days
21-30	500 mg/200 mg	2 MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days
31-40	750 mg/300 mg	3 MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days
>40	1 g/400 mg	4 MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days

405
 406 MALARONE Tablets may be crushed and mixed with condensed milk just prior to
 407 administration for children who may have difficulty swallowing tablets.

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

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

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

420 HOW SUPPLIED

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

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

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

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

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

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

431 ANIMAL TOXICOLOGY

432 Fibrovascular proliferation in the right atrium, pyelonephritis, bone marrow hypocellularity,
433 lymphoid atrophy, and gastritis/enteritis were observed in dogs treated with proguanil
434 hydrochloride for 6 months at a dose of 12 mg/kg/day (approximately 3.9 times the
435 recommended daily human dose for malaria prophylaxis on a mg/m² basis). Bile duct
436 hyperplasia, gall bladder mucosal atrophy, and interstitial pneumonia were observed in dogs
437 treated with proguanil hydrochloride for 6 months at a dose of 4 mg/kg/day (approximately
438 1.3 times the recommended daily human dose for malaria prophylaxis on a mg/m² basis).
439 Mucosal hyperplasia of the cecum and renal tubular basophilia were observed in rats treated with
440 proguanil hydrochloride for 6 months at a dose of 20 mg/kg/day (approximately 1.6 times the
441 recommended daily human dose for malaria prophylaxis on a mg/m² basis). Adverse heart, lung,
442 liver, and gall bladder effects observed in dogs and kidney effects observed in rats were not
443 shown to be reversible.

444 CLINICAL STUDIES

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

451 MALARONE was evaluated for treatment of acute, uncomplicated malaria caused by
452 *P. falciparum* in 8 phase III controlled clinical trials. Among 471 evaluable patients treated with

453 the equivalent of 4 MALARONE Tablets once daily for 3 days, 464 had a sensitive response
 454 (elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days) (see
 455 Table 7). Seven patients had a response of RI resistance (elimination of parasitemia but with
 456 recurrent parasitemia between 7 and 28 days after starting treatment). In these trials, the response
 457 to treatment with MALARONE was similar to treatment with the comparator drug in 4 trials, and
 458 better than the response to treatment with the comparator drug in the other 4 trials.

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

460

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

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

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

465 [†]Elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days.

466 [‡]Patients hospitalized only for acute care. Follow-up conducted in outpatients.

467 [§]Study in pediatric patients 3 to 12 years of age.

468

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

473 Data from a phase II trial of atovaquone conducted in Zambia suggested that approximately
 474 40% of the study population in this country were HIV-infected patients. The enrollment criteria
 475 were similar for the phase III trial of MALARONE conducted in Zambia and the results are

476 presented in Table 7. Efficacy rates for MALARONE in this study population were high and
477 comparable to other populations studied.

478 The efficacy of MALARONE in the treatment of the erythrocytic phase of nonfalciparum
479 malaria was assessed in a small number of patients. Of the 23 patients in Thailand infected with
480 *P. vivax* and treated with atovaquone/proguanil hydrochloride 1,000 mg/400 mg daily for 3 days,
481 parasitemia cleared in 21 (91.3%) at 7 days. Parasite relapse occurred commonly when *P. vivax*
482 malaria was treated with MALARONE alone. Seven patients in Gabon with malaria due to
483 *P. ovale* or *P. malariae* were treated with atovaquone/proguanil hydrochloride 1,000 mg/400 mg
484 daily for 3 days. All 6 evaluable patients (3 with *P. malariae*, 2 with *P. ovale*, and 1 with mixed
485 *P. falciparum* and *P. ovale*) were cured at 28 days. Relapsing malarias including *P. vivax* and
486 *P. ovale* require additional treatment to prevent relapse.

487 The efficacy of MALARONE in treating acute uncomplicated *P. falciparum* malaria in
488 children weighing ≥ 5 and < 11 kg was examined in an open-label, randomized trial conducted in
489 Gabon. Patients received either MALARONE (2 or 3 MALARONE Pediatric Tablets once daily
490 depending upon body weight) for 3 days ($n = 100$) or amodiaquine (10 mg/kg/day) for 3 days
491 ($n = 100$). In this study, the MALARONE Tablets were crushed and mixed with condensed milk
492 just prior to administration. In the per-protocol population, adequate clinical response was
493 obtained in 95% (87/92) of the pediatric patients who received MALARONE and in 53% (41/78)
494 of those who received amodiaquine. A response of RI resistance (elimination of parasitemia but
495 with recurrent parasitemia between 7 and 28 days after starting treatment) was noted in 3% and
496 40% of the patients, respectively. Two cases of RIII resistance (rising parasite count despite
497 therapy) were reported in the patients receiving MALARONE. There were 4 cases of RIII in the
498 amodiaquine arm.

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

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

507
508 **Table 8. Prevention of Parasitemia in Placebo-Controlled Clinical Trials of MALARONE**
509 **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

510

511 In another study, 330 Gabonese pediatric patients (weighing 13 to 40 kg, and aged 4 to
 512 14 years) who had received successful open-label radical cure treatment with artesunate, were
 513 randomized to receive either MALARONE (dosage based on body weight) or placebo in a
 514 double-blind fashion for 12 weeks. Blood smears were obtained weekly and any time malaria
 515 was suspected. Nineteen of the 165 children given MALARONE and 18 of 165 patients given
 516 placebo withdrew from the study for reasons other than parasitemia (primary reason was lost to
 517 follow-up). In the per-protocol population, 1 out of 150 patients (<1%) who received
 518 MALARONE developed *P. falciparum* parasitemia while receiving prophylaxis with
 519 MALARONE compared with 31 (22%) of the 144 placebo recipients.

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

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

532

533 **Table 9. Prevention of Parasitemia in Active-Controlled Clinical Trials of MALARONE for**
 534 **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

535

536 A third randomized, open-label study was conducted which included 221 otherwise healthy
 537 pediatric patients (weighing ≥ 11 kg and 2 to 17 years of age) who were at risk of contracting
 538 malaria by traveling to an endemic area. The mean duration of travel was 15 days (range 1 to
 539 30 days). Prophylaxis with MALARONE (n = 110, dosage based on body weight) began 1 or
 540 2 days before entering the endemic area and lasted until 7 days after leaving the area. A control
 541 group (n = 111) received prophylaxis with chloroquine/proguanil dosed according to WHO
 542 guidelines. No cases of malaria occurred in either group of children. However, the study was not
 543 large enough to allow for statements of comparative efficacy. In addition, the true exposure rate
 544 to *P. falciparum* malaria in this study is unknown.

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

547 **Causal Prophylaxis:** In separate studies with small numbers of volunteers, atovaquone and
548 proguanil hydrochloride were independently shown to have causal prophylactic activity directed
549 against liver-stage parasites of *P. falciparum*. Six patients given a single dose of atovaquone
550 250 mg 24 hours prior to malaria challenge were protected from developing malaria, whereas all
551 4 placebo-treated patients developed malaria.

552 During the 4 weeks following cessation of prophylaxis in clinical trial participants who
553 remained in malaria-endemic areas and were available for evaluation, malaria developed in 24 of
554 211 (11.4%) subjects who took placebo and 9 of 328 (2.7%) who took MALARONE. While new
555 infections could not be distinguished from recrudescent infections, all but 1 of the infections in
556 patients treated with MALARONE occurred more than 15 days after stopping therapy, probably
557 representing new infections. The single case occurring on day 8 following cessation of therapy
558 with MALARONE probably represents a failure of prophylaxis with MALARONE.

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

562
563



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