

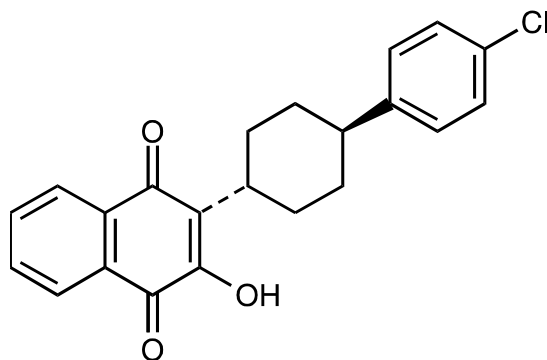
1 PRESCRIBING INFORMATION

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

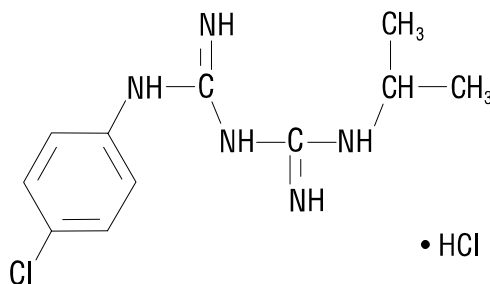
5 **MALARONE[®]**
6 **(atovaquone and proguanil hydrochloride)**
7 **Pediatric Tablets**

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 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 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 to moderate renal impairment, oral clearance
 122 and/or AUC data for atovaquone, proguanil, and cycloguanil are within the range of values
 123 observed in patients with normal renal function. In patients with severe renal impairment
 124 (creatinine clearance <30 mL/min), atovaquone C_{max} and AUC are reduced but the elimination
 125 half-lives for proguanil and cycloguanil are prolonged, with corresponding increases in AUC,

126 resulting in the potential of drug accumulation with repeated dosing (see
127 CONTRAINDICATIONS).

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

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

132 Concomitant treatment with **metoclopramide** has also been associated with decreased
133 bioavailability of atovaquone.

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

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

141 **INDICATIONS AND USAGE**

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

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

149 **CONTRAINDICATIONS**

150 MALARONE is contraindicated in individuals with known hypersensitivity to atovaquone or
151 proguanil hydrochloride or any component of the formulation. During clinical trials, 1 case of
152 anaphylaxis following treatment with atovaquone/proguanil was observed.

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

156 **PRECAUTIONS**

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

160 Absorption of atovaquone may be reduced in patients with diarrhea or vomiting. If
161 MALARONE is used in patients who are vomiting (see DOSAGE AND ADMINISTRATION),
162 parasitemia should be closely monitored and the use of an antiemetic considered. Vomiting
163 occurred in up to 19% of pediatric patients given treatment doses of MALARONE. In the

164 controlled clinical trials of MALARONE, 15.3% of adults who were treated with
165 atovaquone/proguanil received an antiemetic drug during that part of the trial when they received
166 atovaquone/proguanil. Of these patients, 98.3% were successfully treated. In patients with severe
167 or persistent diarrhea or vomiting, alternative antimalarial therapy may be required.

168 Parasite relapse occurred commonly when *P. vivax* malaria was treated with MALARONE
169 alone.

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

173 In patients with severe renal impairment (creatinine clearance <30 mL/min) alternatives to
174 MALARONE should be recommended for treatment of acute *P. falciparum* malaria whenever
175 possible (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY: Special
176 Populations: Renal Impairment). The concomitant administration of MALARONE and any other
177 medication containing proguanil hydrochloride should be avoided.

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

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

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

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

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

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

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

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

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

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

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

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

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

231 Atovaquone was not teratogenic and did not cause reproductive toxicity in rats at maternal
232 plasma concentrations up to 5 to 6.5 times the estimated human exposure during treatment of
233 malaria. Following single-dose administration of ¹⁴C-labeled atovaquone to pregnant rats,
234 concentrations of radiolabel in rat fetuses were 18% (mid-gestation) and 60% (late gestation) of
235 concurrent maternal plasma concentrations. In rabbits, atovaquone caused maternal toxicity at
236 plasma concentrations that were approximately 0.6 to 1.3 times the estimated human exposure
237 during treatment of malaria. Adverse fetal effects in rabbits, including decreased fetal body
238 lengths and increased early resorptions and post-implantation losses, were observed only in the
239 presence of maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of
240 the concurrent maternal plasma concentrations.

241 The combination of atovaquone and proguanil hydrochloride was not teratogenic in rats at
242 plasma concentrations up to 1.7 and 0.10 times, respectively, the estimated human exposure
243 during treatment of malaria. In rabbits, the combination of atovaquone and proguanil

244 hydrochloride was not teratogenic or embryotoxic to rabbit fetuses at plasma concentrations up
245 to 0.34 and 0.82 times, respectively, the estimated human exposure during treatment of malaria.

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

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

257 Proguanil is excreted into human milk in small quantities.

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

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

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

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

273 **ADVERSE REACTIONS**

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

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

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

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

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

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

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

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

314

315 **Table 3. Adverse Experiences in Placebo-Controlled Clinical Trials of MALARONE for**
 316 **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)

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

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

321
 322 In an additional placebo-controlled study of malaria prophylaxis with MALARONE involving
 323 330 pediatric patients in a malaria-endemic area (see CLINICAL STUDIES), the safety profile
 324 of MALARONE was consistent with that described above. The most common
 325 treatment-emergent adverse events with MALARONE were abdominal pain (13%), headache
 326 (13%), and cough (10%). Abdominal pain (13% vs. 8%) and vomiting (5% vs. 3%) were
 327 reported more often with MALARONE than with placebo, while fever (5% vs. 12%) and
 328 diarrhea (1% vs. 5%) were more common with placebo. No patient withdrew from the study due
 329 to an adverse experience with MALARONE. No routine laboratory data were obtained during
 330 this study.

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

344 **Table 4. Adverse Experiences in Active–Controlled Clinical Trials of MALARONE for**
 345 **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)

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

347
 348 In a third active-controlled study, MALARONE (n = 110) was compared with
 349 chloroquine/proguanil (n = 111) for the prophylaxis of malaria in 221 non-immune pediatric
 350 patients (see CLINICAL STUDIES). The mean duration of exposure was 23 days for
 351 MALARONE, 46 days for chloroquine, and 43 days for proguanil, reflecting the different
 352 recommended dosage regimens for these products. Fewer patients treated with MALARONE
 353 reported abdominal pain (2% vs. 7%) or nausea (<1% vs. 7%) than children who received
 354 chloroquine/proguanil. Oral ulceration (2% vs. 2%), vivid dreams (2% vs. <1%), and blurred
 355 vision (0% vs. 2%) occurred in similar proportions of patients receiving either MALARONE or

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

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

365 **Skin:** Cutaneous reactions ranging from rash, photosensitivity, and urticaria to rare cases of
366 erythema multiforme and Stevens-Johnson syndrome.

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

369 **OVERDOSAGE**

370 There is limited information regarding overdosage from the administration of MALARONE.

371 There is no known antidote for atovaquone, and it is currently unknown if atovaquone is
372 dialyzable. The median lethal dose is higher than the maximum oral dose tested in mice and rats
373 (1,825 mg/kg/day). Overdoses up to 31,500 mg of atovaquone have been reported. In one such
374 patient who also took an unspecified dose of dapson, methemoglobinemia occurred. Rash has
375 also been reported after overdose.

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

382 **DOSAGE AND ADMINISTRATION**

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

385 **Prevention of Malaria:** Prophylactic treatment with MALARONE should be started 1 or
386 2 days before entering a malaria-endemic area and continued daily during the stay and for 7 days
387 after return.

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

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

392

393 **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

394
 395 **Treatment of Acute Malaria: Adults:** Four MALARONE Tablets (adult strength; total daily
 396 dose 1 g atovaquone/400 mg proguanil hydrochloride) as a single dose daily for 3 consecutive
 397 days.

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

400
 401 **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

402
 403 MALARONE Tablets may be crushed and mixed with condensed milk just prior to
 404 administration for children who may have difficulty swallowing tablets.

405 **Patients with Renal Impairment:** MALARONE should not be used for malaria prophylaxis
 406 in patients with severe renal impairment (creatinine clearance <30 mL/min), and alternatives to
 407 MALARONE should be recommended for treatment of acute *P. falciparum* malaria whenever
 408 possible (see CONTRAINDICATIONS, PRECAUTIONS: General, and CLINICAL
 409 PHARMACOLOGY: Special Populations). No dosage adjustments are needed in patients with
 410 mild to moderate renal impairment.

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

414 **HOW SUPPLIED**

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

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

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

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

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

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

425 **ANIMAL TOXICOLOGY**

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

438 **CLINICAL STUDIES**

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

445 MALARONE was evaluated for treatment of acute, uncomplicated malaria caused by
446 *P. falciparum* in 8 phase III controlled clinical trials. Among 471 evaluable patients treated with
447 the equivalent of 4 MALARONE Tablets once daily for 3 days, 464 had a sensitive response
448 (elimination of parasitemia with no recurrent parasitemia during follow-up for 28 days) (see

449 Table 7). Seven patients had a response of RI resistance (elimination of parasitemia but with
 450 recurrent parasitemia between 7 and 28 days after starting treatment). In these trials, the response
 451 to treatment with MALARONE was similar to treatment with the comparator drug in 4 trials, and
 452 better than the response to treatment with the comparator drug in the other 4 trials.

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

454

455 **Table 7. Parasitological Response in Clinical Trials of MALARONE for Treatment of**
 456 ***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%

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

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

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

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

462

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

467 Data from a phase II trial of atovaquone conducted in Zambia suggested that approximately
 468 40% of the study population in this country were HIV-infected patients. The enrollment criteria
 469 were similar for the phase III trial of MALARONE conducted in Zambia and the results are
 470 presented in Table 6. Efficacy rates for MALARONE in this study population were high and
 471 comparable to other populations studied.

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

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

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

496 Three placebo-controlled studies of 10 to 12 weeks' duration were conducted among residents
 497 of malaria-endemic areas in Kenya, Zambia, and Gabon. Of a total of 669 randomized patients
 498 (including 264 pediatric patients 5 to 16 years of age), 103 were withdrawn for reasons other
 499 than falciparum malaria or drug-related adverse events. (Fifty-five percent of these were lost to
 500 follow-up and 45% were withdrawn for protocol violations.) The results are listed in Table 8.
 501

502 **Table 8. Prevention of Parasitemia in Placebo-Controlled Clinical Trials of MALARONE**
 503 **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

504
 505 In another study, 330 Gabonese pediatric patients (weighing 13 to 40 kg, and aged 4 to
 506 14 years) who had received successful open-label radical cure treatment with artesunate, were
 507 randomized to receive either MALARONE (dosage based on body weight) or placebo in a

508 double-blind fashion for 12 weeks. Blood smears were obtained weekly and any time malaria
 509 was suspected. Nineteen of the 165 children given MALARONE and 18 of 165 patients given
 510 placebo withdrew from the study for reasons other than parasitemia (primary reason was lost to
 511 follow-up). In the per-protocol population, 1 out of 150 patients (<1%) who received
 512 MALARONE developed *P. falciparum* parasitemia while receiving prophylaxis with
 513 MALARONE compared with 31 (22%) of the 144 placebo recipients.

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

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

526

527 **Table 9. Prevention of Parasitemia in Active-Controlled Clinical Trials of MALARONE for**
 528 **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

529

530 A third randomized, open-label study was conducted which included 221 otherwise healthy
 531 pediatric patients (weighing ≥ 11 kg and 2 to 17 years of age) who were at risk of contracting
 532 malaria by traveling to an endemic area. The mean duration of travel was 15 days (range 1 to
 533 30 days). Prophylaxis with MALARONE (n = 110, dosage based on body weight) began 1 or
 534 2 days before entering the endemic area and lasted until 7 days after leaving the area. A control
 535 group (n = 111) received prophylaxis with chloroquine/proguanil dosed according to WHO
 536 guidelines. No cases of malaria occurred in either group of children. However, the study was not
 537 large enough to allow for statements of comparative efficacy. In addition, the true exposure rate
 538 to *P. falciparum* malaria in this study is unknown.

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

541 **Causal Prophylaxis:** In separate studies with small numbers of volunteers, atovaquone and
542 proguanil hydrochloride were independently shown to have causal prophylactic activity directed
543 against liver-stage parasites of *P. falciparum*. Six patients given a single dose of atovaquone
544 250 mg 24 hours prior to malaria challenge were protected from developing malaria, whereas all
545 4 placebo-treated patients developed malaria.

546 During the 4 weeks following cessation of prophylaxis in clinical trial participants who
547 remained in malaria-endemic areas and were available for evaluation, malaria developed in 24 of
548 211 (11.4%) subjects who took placebo and 9 of 328 (2.7%) who took MALARONE. While new
549 infections could not be distinguished from recrudescent infections, all but 1 of the infections in
550 patients treated with MALARONE occurred more than 15 days after stopping therapy, probably
551 representing new infections. The single case occurring on day 8 following cessation of therapy
552 with MALARONE probably represents a failure of prophylaxis with MALARONE.

553 The possibility that delayed cases of *P. falciparum* malaria may occur some time after
554 stopping prophylaxis with MALARONE cannot be ruled out. Hence, returning travelers
555 developing febrile illnesses should be investigated for malaria.
556
557



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