



LARIAM®

brand of

mefloquine hydrochloride

TABLETS

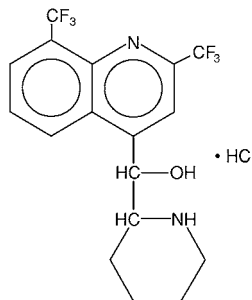
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## DESCRIPTION

Lariam (mefloquine hydrochloride) is an antimalarial agent available as 250-mg tablets of mefloquine hydrochloride (equivalent to 228.0 mg of the free base) for oral administration.

Mefloquine hydrochloride is a 4-quinolinemethanol derivative with the specific chemical name of (R\*, S\*)-(±)-α-2-piperidiny-2,8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride. It is a 2-aryl substituted chemical structural analog of quinine. The drug is a white to almost white crystalline compound, slightly soluble in water.

Mefloquine hydrochloride has a calculated molecular weight of 414.78 and the following structural formula:



18

The inactive ingredients are ammonium-calcium alginate, corn starch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer #331, and talc.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics

#### Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formation compared with an oral solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability. In healthy volunteers, plasma concentrations

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30 peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a  
31 similar group of volunteers, maximum plasma concentrations in  $\mu\text{g/L}$  are  
32 roughly equivalent to the dose in milligrams (for example, a single 1000 mg  
33 dose produces a maximum concentration of about 1000  $\mu\text{g/L}$ ). In healthy  
34 volunteers, a dose of 250 mg once weekly produces maximum steady-state  
35 plasma concentrations of 1000 to 2000  $\mu\text{g/L}$ , which are reached after 7 to 10  
36 weeks.

### 37 Distribution

38 In healthy adults, the apparent volume of distribution is approximately 20  
39 L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in  
40 parasitized erythrocytes. Experiments conducted in vitro with human blood  
41 using concentrations between 50 and 1000 mg/mL showed a relatively  
42 constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The  
43 equilibrium reached in less than 30 minutes was found to be reversible.  
44 Protein binding is about 98%.

45 Mefloquine crosses the placenta. Excretion into breast milk appears to be  
46 minimal (see **PRECAUTIONS: Nursing Mothers**).

### 47 Metabolism

48 Two metabolites have been identified in humans. The main metabolite, 2,8-  
49 *bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *Plasmodium*  
50 *falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite  
51 appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma  
52 concentrations, which were about 50% higher than those of mefloquine, were  
53 reached after 2 weeks. Thereafter, plasma levels of the main metabolite and  
54 mefloquine declined at a similar rate. The area under the plasma  
55 concentration-time curve (AUC) of the main metabolite was 3 to 5 times  
56 larger than that of the parent drug. The other metabolite, an alcohol, was  
57 present in minute quantities only.

### 58 Elimination

59 In several studies in healthy adults, the mean elimination half-life of  
60 mefloquine varied between 2 and 4 weeks, with an average of about 3 weeks.  
61 Total clearance, which is essentially hepatic, is in the order of 30 mL/min.  
62 There is evidence that mefloquine is excreted mainly in the bile and feces. In  
63 volunteers, urinary excretion of unchanged mefloquine and its main  
64 metabolite under steady-state condition accounted for about 9% and 4% of the  
65 dose, respectively. Concentrations of other metabolites could not be measured  
66 in the urine.

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### 67 Pharmacokinetics in Special Clinical Situations

#### 68 *Children and the Elderly*

69 No relevant age-related changes have been observed in the pharmacokinetics  
70 of mefloquine. Therefore, the dosage for children has been extrapolated from  
71 the recommended adult dose.

72 No pharmacokinetic studies have been performed in patients with renal  
73 insufficiency since only a small proportion of the drug is eliminated renally.  
74 Mefloquine and its main metabolite are not appreciably removed by  
75 hemodialysis. No special chemoprophylactic dosage adjustments are indicated  
76 for dialysis patients to achieve concentrations in plasma similar to those in  
77 healthy persons.

78 Although clearance of mefloquine may increase in late pregnancy, in general,  
79 pregnancy has no clinically relevant effect on the pharmacokinetics of  
80 mefloquine.

81 The pharmacokinetics of mefloquine may be altered in acute malaria.

82 Pharmacokinetic differences have been observed between various ethnic  
83 populations. In practice, however, these are of minor importance compared  
84 with host immune status and sensitivity of the parasite.

85 During long-term prophylaxis (>2 years), the trough concentrations and the  
86 elimination half-life of mefloquine were similar to those obtained in the same  
87 population after 6 months of drug use, which is when they reached steady  
88 state.

89 In vitro and in vivo studies showed no hemolysis associated with glucose-6-  
90 phosphate dehydrogenase deficiency (see **ANIMAL TOXICOLOGY**).

### 91 **Microbiology**

#### 92 Mechanism of Action

93 Mefloquine is an antimalarial agent which acts as a blood schizonticide. Its  
94 exact mechanism of action is not known.

#### 95 Activity In Vitro and In Vivo

96 Mefloquine is active against the erythrocytic stages of *Plasmodium* species  
97 (see **INDICATIONS AND USAGE**). However, the drug has no effect against  
98 the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective  
99 against malaria parasites resistant to chloroquine (see **INDICATIONS AND**  
100 **USAGE**).

#### 101 Drug Resistance

102 Strains of *P. falciparum* with decreased susceptibility to mefloquine can be  
103 selected in vitro or in vivo. Resistance of *P. falciparum* to mefloquine has

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104 been reported in areas of multi-drug resistance in South East Asia. Increased  
105 incidences of resistance have also been reported in other parts of the world.

### 106 Cross-Resistance

107 Cross-resistance between mefloquine and halofantrine and cross-resistance  
108 between mefloquine and quinine have been observed in some regions.

## 109 INDICATIONS AND USAGE

### 110 Treatment of Acute Malaria Infections

111 Lariam is indicated for the treatment of mild to moderate acute malaria caused  
112 by mefloquine-susceptible strains of *P. falciparum* (both chloroquine-  
113 susceptible and resistant strains) or by *Plasmodium vivax*. There are  
114 insufficient clinical data to document the effect of mefloquine in malaria  
115 caused by *P. ovale* or *P. malariae*.

116 *Note:* Patients with acute *P. vivax* malaria, treated with Lariam, are at  
117 high risk of relapse because Lariam does not eliminate exoerythrocytic  
118 (hepatic phase) parasites. To avoid relapse, after initial treatment of the  
119 acute infection with Lariam, patients should subsequently be treated  
120 with an 8-aminoquinoline derivative (eg, primaquine).

### 121 Prevention of Malaria

122 Lariam is indicated for the prophylaxis of *P. falciparum* and *P. vivax* malaria  
123 infections, including prophylaxis of chloroquine-resistant strains of *P.*  
124 *falciparum*.

## 125 CONTRAINDICATIONS

126 Use of Lariam is contraindicated in patients with a known hypersensitivity to  
127 mefloquine or related compounds (eg, quinine and quinidine) or to any of the  
128 excipients contained in the formulation. Lariam should not be prescribed for  
129 prophylaxis in patients with active depression, a recent history of depression,  
130 generalized anxiety disorder, psychosis, or schizophrenia or other major  
131 psychiatric disorders, or with a history of convulsions.

## 132 WARNINGS

133 **In case of life-threatening, serious or overwhelming malaria infections**  
134 **due to *P. falciparum*, patients should be treated with an intravenous**  
135 **antimalarial drug. Following completion of intravenous treatment,**  
136 **Lariam may be given to complete the course of therapy.**

137 **Data on the use of halofantrine subsequent to administration of Lariam**  
138 **suggest a significant, potentially fatal prolongation of the QTc interval of**  
139 **the ECG. Therefore, halofantrine must not be given simultaneously with**  
140 **or subsequent to Lariam. No data are available on the use of Lariam after**  
141 **halofantrine (see PRECAUTIONS: Drug Interactions).**

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142 **Mefloquine may cause psychiatric symptoms in a number of patients,**  
143 **ranging from anxiety, paranoia, and depression to hallucinations and**  
144 **psychotic behavior. On occasions, these symptoms have been reported to**  
145 **continue long after mefloquine has been stopped. Rare cases of suicidal**  
146 **ideation and suicide have been reported though no relationship to drug**  
147 **administration has been confirmed. To minimize the chances of these**  
148 **adverse events, mefloquine should not be taken for prophylaxis in**  
149 **patients with active depression or with a recent history of depression,**  
150 **generalized anxiety disorder, psychosis, or schizophrenia or other major**  
151 **psychiatric disorders. Lariam should be used with caution in patients**  
152 **with a previous history of depression.**

153 **During prophylactic use, if psychiatric symptoms such as acute anxiety,**  
154 **depression, restlessness or confusion occur, these may be considered**  
155 **prodromal to a more serious event. In these cases, the drug must be**  
156 **discontinued and an alternative medication should be substituted.**

157 **Concomitant administration of Lariam and quinine or quinidine may**  
158 **produce electrocardiographic abnormalities.**

159 **Concomitant administration of Lariam and quinine or chloroquine may**  
160 **increase the risk of convulsions.**

## 161 **PRECAUTIONS**

### 162 **General**

163 Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis  
164 cannot be predicted.

165 In patients with epilepsy, Lariam may increase the risk of convulsions. The  
166 drug should therefore be prescribed only for curative treatment in such  
167 patients and only if there are compelling medical reasons for its use (see  
168 **PRECAUTIONS: Drug Interactions**).

169 Caution should be exercised with regard to activities requiring alertness and  
170 fine motor coordination such as driving, piloting aircraft, operating  
171 machinery, and deep-sea diving, as dizziness, a loss of balance, or other  
172 disorders of the central or peripheral nervous system have been reported  
173 during and following the use of Lariam. These effects may occur after therapy  
174 is discontinued due to the long half-life of the drug. Lariam should be used  
175 with caution in patients with psychiatric disturbances because mefloquine use  
176 has been associated with emotional disturbances (see **ADVERSE**  
177 **REACTIONS**).

178 In patients with impaired liver function the elimination of mefloquine may be  
179 prolonged, leading to higher plasma levels.

180 This drug has been administered for longer than 1 year. If the drug is to be  
181 administered for a prolonged period, periodic evaluations including liver

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182 function tests should be performed. Although retinal abnormalities seen in  
183 humans with long-term chloroquine use have not been observed with  
184 mefloquine use, long-term feeding of mefloquine to rats resulted in dose-  
185 related ocular lesions (retinal degeneration, retinal edema and lenticular  
186 opacity at 12.5 mg/kg/day and higher) (see **ANIMAL TOXICOLOGY**).  
187 Therefore, periodic ophthalmic examinations are recommended.

188 Parenteral studies in animals show that mefloquine, a myocardial depressant,  
189 possesses 20% of the antifibrillatory action of quinidine and produces 50% of  
190 the increase in the PR interval reported with quinine. The effect of mefloquine  
191 on the compromised cardiovascular system has not been evaluated. However,  
192 transitory and clinically silent ECG alterations have been reported during the  
193 use of mefloquine. Alterations included sinus bradycardia, sinus arrhythmia,  
194 first degree AV-block, prolongation of the QTc interval and abnormal T  
195 waves (see also cardiovascular effects under **PRECAUTIONS: Drug**  
196 **Interactions** and **ADVERSE REACTIONS**). The benefits of Lariam therapy  
197 should be weighed against the possibility of adverse effects in patients with  
198 cardiac disease.

### **199 Laboratory Tests**

200 Periodic evaluation of hepatic function should be performed during prolonged  
201 prophylaxis.

### **202 Information for Patients**

203 Medication Guide: As required by law, a Lariam Medication Guide is  
204 supplied to patients when Lariam is dispensed. An information wallet card is  
205 also supplied to patients when Lariam is dispensed. Patients should be  
206 instructed to read the Medication Guide when Lariam is received and to carry  
207 the information wallet card with them when they are taking Lariam. The  
208 complete texts of the Medication Guide and information wallet card are  
209 reprinted at the end of this document.

210 Patients should be advised:

- 211 • that malaria can be a life-threatening infection in the traveler;
- 212 • that Lariam is being prescribed to help prevent or treat this serious  
213 infection;
- 214 • that in a small percentage of cases, patients are unable to take this  
215 medication because of side effects, and it may be necessary to change  
216 medications;
- 217 • that when used as prophylaxis, the first dose of Lariam should be taken 1  
218 week prior to arrival in an endemic area;
- 219 • that if the patients experience psychiatric symptoms such as acute anxiety,  
220 depression, restlessness or confusion, these may be considered prodromal  
221 to a more serious event. In these cases, the drug must be discontinued and  
222 an alternative medication should be substituted;

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- 223 • that no chemoprophylactic regimen is 100% effective, and protective  
224 clothing, insect repellents, and bednets are important components of  
225 malaria prophylaxis;  
226 • to seek medical attention for any febrile illness that occurs after return  
227 from a malarious area and to inform their physician that they may have  
228 been exposed to malaria.

### 229 Drug Interactions

230 Drug-drug interactions with Lariam have not been explored in detail. There is  
231 one report of cardiopulmonary arrest, with full recovery, in a patient who was  
232 taking a beta blocker (propranolol) (see **PRECAUTIONS: General**). The  
233 effects of mefloquine on the compromised cardiovascular system have not  
234 been evaluated. The benefits of Lariam therapy should be weighed against the  
235 possibility of adverse effects in patients with cardiac disease.

236 Because of the danger of a potentially fatal prolongation of the QTc interval,  
237 halofantrine must not be given simultaneously with or subsequent to Lariam  
238 (see **WARNINGS**).

239 Concomitant administration of Lariam and other related compounds (eg,  
240 quinine, quinidine and chloroquine) may produce electrocardiographic  
241 abnormalities and increase the risk of convulsions (see **WARNINGS**). If  
242 these drugs are to be used in the initial treatment of severe malaria, Lariam  
243 administration should be delayed at least 12 hours after the last dose. There is  
244 evidence that the use of halofantrine after mefloquine causes a significant  
245 lengthening of the QTc interval. Clinically significant QTc prolongation has  
246 not been found with mefloquine alone.

247 This appears to be the only clinically relevant interaction of this kind with  
248 Lariam, although theoretically, coadministration of other drugs known to alter  
249 cardiac conduction (eg, anti-arrhythmic or beta-adrenergic blocking agents,  
250 calcium channel blockers, antihistamines or H<sub>1</sub>-blocking agents, tricyclic  
251 antidepressants and phenothiazines) might also contribute to a prolongation of  
252 the QTc interval. There are no data that conclusively establish whether the  
253 concomitant administration of mefloquine and the above listed agents has an  
254 effect on cardiac function.

255 In patients taking an anticonvulsant (eg, valproic acid, carbamazepine,  
256 phenobarbital or phenytoin), the concomitant use of Lariam may reduce  
257 seizure control by lowering the plasma levels of the anticonvulsant. Therefore,  
258 patients concurrently taking antiseizure medication and Lariam should have  
259 the blood level of their antiseizure medication monitored and the dosage  
260 adjusted appropriately (see **PRECAUTIONS: General**).

261 When Lariam is taken concurrently with oral live typhoid vaccines,  
262 attenuation of immunization cannot be excluded. Vaccinations with attenuated  
263 live bacteria should therefore be completed at least 3 days before the first dose  
264 of Lariam.

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265 No other drug interactions are known. Nevertheless, the effects of Lariam on  
266 travelers receiving comedication, particularly diabetics or patients using  
267 anticoagulants, should be checked before departure.

268 In clinical trials, the concomitant administration of sulfadoxine and  
269 pyrimethamine did not alter the adverse reaction profile.

### **270 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### 271 Carcinogenesis

272 The carcinogenic potential of mefloquine was studied in rats and mice in 2-  
273 year feeding studies at doses of up to 30 mg/kg/day. No treatment-related  
274 increases in tumors of any type were noted.

#### 275 Mutagenesis

276 The mutagenic potential of mefloquine was studied in a variety of assay  
277 systems including: Ames test, a host-mediated assay in mice, fluctuation tests  
278 and a mouse micronucleus assay. Several of these assays were performed with  
279 and without prior metabolic activation. In no instance was evidence obtained  
280 for the mutagenicity of mefloquine.

#### 281 Impairment of Fertility

282 Fertility studies in rats at doses of 5, 20, and 50 mg/kg/day of mefloquine have  
283 demonstrated adverse effects on fertility in the male at the high dose of 50  
284 mg/kg/day, and in the female at doses of 20 and 50 mg/kg/day.  
285 Histopathological lesions were noted in the epididymides from male rats at  
286 doses of 20 and 50 mg/kg/day. Administration of 250 mg/week of mefloquine  
287 (base) in adult males for 22 weeks failed to reveal any deleterious effects on  
288 human spermatozoa.

### **289 Pregnancy**

#### 290 Teratogenic Effects

291 Pregnancy Category C. Mefloquine has been demonstrated to be teratogenic  
292 in rats and mice at a dose of 100 mg/kg/day. In rabbits, a high dose of 160  
293 mg/kg/day was embryotoxic and teratogenic, and a dose of 80 mg/kg/day was  
294 teratogenic but not embryotoxic. There are no adequate and well-controlled  
295 studies in pregnant women. However, clinical experience with Lariam has not  
296 revealed an embryotoxic or teratogenic effect. Mefloquine should be used  
297 during pregnancy only if the potential benefit justifies the potential risk to the  
298 fetus. Women of childbearing potential who are traveling to areas where  
299 malaria is endemic should be warned against becoming pregnant. Women of  
300 childbearing potential should also be advised to practice contraception during  
301 malaria prophylaxis with Lariam and for up to 3 months thereafter. However,  
302 in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is  
303 not considered an indication for pregnancy termination.

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### 304 **Nursing Mothers**

305 Mefloquine is excreted in human milk in small amounts, the activity of which  
306 is unknown. Based on a study in a few subjects, low concentrations (3% to  
307 4%) of mefloquine were excreted in human milk following a dose equivalent  
308 to 250 mg of the free base. Because of the potential for serious adverse  
309 reactions in nursing infants from mefloquine, a decision should be made  
310 whether to discontinue the drug, taking into account the importance of the  
311 drug to the mother.

### 312 **Pediatric Use**

313 Use of Lariam to treat acute, uncomplicated *P. falciparum* malaria in pediatric  
314 patients is supported by evidence from adequate and well-controlled studies of  
315 Lariam in adults with additional data from published open-label and  
316 comparative trials using Lariam to treat malaria caused by *P. falciparum* in  
317 patients younger than 16 years of age. The safety and effectiveness of Lariam  
318 for the treatment of malaria in pediatric patients below the age of 6 months  
319 have not been established.

320 In several studies, the administration of Lariam for the treatment of malaria  
321 was associated with early vomiting in pediatric patients. Early vomiting was  
322 cited in some reports as a possible cause of treatment failure. If a second dose  
323 is not tolerated, the patient should be monitored closely and alternative  
324 malaria treatment considered if improvement is not observed within a  
325 reasonable period of time (see **DOSAGE AND ADMINISTRATION**).

### 326 **Geriatric Use**

327 Clinical studies of Lariam did not include sufficient numbers of subjects aged  
328 65 and over to determine whether they respond differently from younger  
329 subjects. Other reported clinical experience has not identified differences in  
330 responses between the elderly and younger patients. Since  
331 electrocardiographic abnormalities have been observed in individuals treated  
332 with Lariam (see **PRECAUTIONS**) and underlying cardiac disease is more  
333 prevalent in elderly than in younger patients, the benefits of Lariam therapy  
334 should be weighed against the possibility of adverse cardiac effects in elderly  
335 patients.

## 336 **ADVERSE REACTIONS**

### 337 **Clinical**

338 At the doses used for treatment of acute malaria infections, the symptoms  
339 possibly attributable to drug administration cannot be distinguished from  
340 those symptoms usually attributable to the disease itself.

341 Among subjects who received mefloquine for prophylaxis of malaria, the  
342 most frequently observed adverse experience was vomiting (3%). Dizziness,

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343 syncope, extrasystoles and other complaints affecting less than 1% were also  
344 reported.

345 Among subjects who received mefloquine for treatment, the most frequently  
346 observed adverse experiences included: dizziness, myalgia, nausea, fever,  
347 headache, vomiting, chills, diarrhea, skin rash, abdominal pain, fatigue, loss of  
348 appetite, and tinnitus. Those side effects occurring in less than 1% included  
349 bradycardia, hair loss, emotional problems, pruritus, asthenia, transient  
350 emotional disturbances and telogen effluvium (loss of resting hair). Seizures  
351 have also been reported.

352 Two serious adverse reactions were cardiopulmonary arrest in one patient  
353 shortly after ingesting a single prophylactic dose of mefloquine while  
354 concomitantly using propranolol (see **PRECAUTIONS: Drug Interactions**),  
355 and encephalopathy of unknown etiology during prophylactic mefloquine  
356 administration. The relationship of encephalopathy to drug administration  
357 could not be clearly established.

### 358 **Postmarketing**

359 Postmarketing surveillance indicates that the same kind of adverse  
360 experiences are reported during prophylaxis, as well as acute treatment.

361 The most frequently reported adverse events are nausea, vomiting, loose  
362 stools or diarrhea, abdominal pain, dizziness or vertigo, loss of balance, and  
363 neuropsychiatric events such as headache, somnolence, and sleep disorders  
364 (insomnia, abnormal dreams). These are usually mild and may decrease  
365 despite continued use.

366 Occasionally, more severe neuropsychiatric disorders have been reported such  
367 as: sensory and motor neuropathies (including paresthesia, tremor and ataxia),  
368 convulsions, agitation or restlessness, anxiety, depression, mood changes,  
369 panic attacks, forgetfulness, confusion, hallucinations, aggression, psychotic  
370 or paranoid reactions and encephalopathy. Rare cases of suicidal ideation and  
371 suicide have been reported though no relationship to drug administration has  
372 been confirmed.

373 Other infrequent adverse events include:

374 *Cardiovascular Disorders:* circulatory disturbances (hypotension,  
375 hypertension, flushing, syncope), chest pain, tachycardia or palpitation,  
376 bradycardia, irregular pulse, extrasystoles, A-V block, and other transient  
377 cardiac conduction alterations

378 *Skin Disorders:* rash, exanthema, erythema, urticaria, pruritus, edema, hair  
379 loss, erythema multiforme, and Stevens-Johnson syndrome

380 *Musculoskeletal Disorders:* muscle weakness, muscle cramps, myalgia, and  
381 arthralgia

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382 *Respiratory Disorders:* dyspnea, pneumonitis of possible allergic etiology

383 *Other Symptoms:* visual disturbances, vestibular disorders including tinnitus  
384 and hearing impairment, asthenia, malaise, fatigue, fever, sweating, chills,  
385 dyspepsia and loss of appetite

### **386 Laboratory**

387 The most frequently observed laboratory alterations which could be possibly  
388 attributable to drug administration were decreased hematocrit, transient  
389 elevation of transaminases, leukopenia and thrombocytopenia. These  
390 alterations were observed in patients with acute malaria who received  
391 treatment doses of the drug and were attributed to the disease itself.

392 During prophylactic administration of mefloquine to indigenous populations  
393 in malaria-endemic areas, the following occasional alterations in laboratory  
394 values were observed: transient elevation of transaminases, leukocytosis or  
395 thrombocytopenia.

396 Because of the long half-life of mefloquine, adverse reactions to Lariam may  
397 occur or persist up to several weeks after the last dose.

### **398 OVERDOSAGE**

#### **399 Symptoms and Signs**

400 In cases of overdosage with Lariam, the symptoms mentioned under  
401 **ADVERSE REACTIONS** may be more pronounced.

#### **402 Treatment**

403 Patients should be managed by symptomatic and supportive care following  
404 Lariam overdose. There are no specific antidotes. Monitor cardiac function (if  
405 possible by ECG) and neuropsychiatric status for at least 24 hours. Provide  
406 symptomatic and intensive supportive treatment as required, particularly for  
407 cardiovascular disturbances.

### **408 DOSAGE AND ADMINISTRATION (see INDICATIONS AND USAGE)**

#### **409 Adult Patients**

410 Treatment of mild to moderate malaria in adults caused by *P. vivax* or  
411 mefloquine-susceptible strains of *P. falciparum*

412 Five tablets (1250 mg) mefloquine hydrochloride to be given as a single oral  
413 dose. The drug should not be taken on an empty stomach and should be  
414 administered with at least 8 oz (240 mL) of water.

415 If a full-treatment course with Lariam does not lead to improvement within 48  
416 to 72 hours, Lariam should not be used for retreatment. An alternative therapy  
417 should be used. Similarly, if previous prophylaxis with mefloquine has failed,  
418 Lariam should not be used for curative treatment.

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419 *Note:* Patients with acute *P. vivax* malaria, treated with Lariam, are at  
420 high risk of relapse because Lariam does not eliminate exoerythrocytic  
421 (hepatic phase) parasites. To avoid relapse after initial treatment of the  
422 acute infection with Lariam, patients should subsequently be treated  
423 with an 8-aminoquinoline derivative (eg, primaquine).

### 424 Malaria Prophylaxis

425 One 250 mg Lariam tablet once weekly.

426 Prophylactic drug administration should begin 1 week before arrival in an  
427 endemic area. Subsequent weekly doses should be taken regularly, always on  
428 the same day of each week, preferably after the main meal. To reduce the risk  
429 of malaria after leaving an endemic area, prophylaxis must be continued for 4  
430 additional weeks to ensure suppressive blood levels of the drug when  
431 merozoites emerge from the liver. Tablets should not be taken on an empty  
432 stomach and should be administered with at least 8 oz (240 mL) of water.

433 In certain cases, eg, when a traveler is taking other medication, it may be  
434 desirable to start prophylaxis 2 to 3 weeks prior to departure, in order to  
435 ensure that the combination of drugs is well tolerated (see **PRECAUTIONS:**  
436 **Drug Interactions**).

437 When prophylaxis with Lariam fails, physicians should carefully evaluate  
438 which antimalarial to use for therapy.

### 439 Pediatric Patients

440 Treatment of mild to moderate malaria in pediatric patients caused by  
441 mefloquine-susceptible strains of *P. falciparum*

442 Twenty (20) to 25 mg/kg body weight. Splitting the total therapeutic dose into  
443 2 doses taken 6 to 8 hours apart may reduce the occurrence or severity of  
444 adverse effects. Experience with Lariam in infants less than 3 months old or  
445 weighing less than 5 kg is limited. The drug should not be taken on an empty  
446 stomach and should be administered with ample water. The tablets may be  
447 crushed and suspended in a small amount of water, milk or other beverage for  
448 administration to small children and other persons unable to swallow them  
449 whole.

450 If a full-treatment course with Lariam does not lead to improvement within 48  
451 to 72 hours, Lariam should not be used for retreatment. An alternative therapy  
452 should be used. Similarly, if previous prophylaxis with mefloquine has failed,  
453 Lariam should not be used for curative treatment.

454 In pediatric patients, the administration of Lariam for the treatment of malaria  
455 has been associated with early vomiting. In some cases, early vomiting has  
456 been cited as a possible cause of treatment failure (see **PRECAUTIONS**). If a  
457 significant loss of drug product is observed or suspected because of vomiting,  
458 a second full dose of Lariam should be administered to patients who vomit

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459 less than 30 minutes after receiving the drug. If vomiting occurs 30 to 60  
460 minutes after a dose, an additional half-dose should be given. If vomiting  
461 recurs, the patient should be monitored closely and alternative malaria  
462 treatment considered if improvement is not observed within a reasonable  
463 period of time.

464 The safety and effectiveness of Lariam to treat malaria in pediatric patients  
465 below the age of 6 months have not been established.

### 466 Malaria Prophylaxis

467 The following doses have been extrapolated from the recommended adult  
468 dose. Neither the pharmacokinetics, nor the clinical efficacy of these doses  
469 have been determined in children owing to the difficulty of acquiring this  
470 information in pediatric subjects. The recommended prophylactic dose of  
471 Lariam is approximately 5 mg/kg body weight once weekly. One 250 mg  
472 Lariam tablet should be taken once weekly in pediatric patients weighing over  
473 45 kg. In pediatric patients weighing less than 45 kg, the weekly dose  
474 decreases in proportion to body weight:

475	30 to 45 kg:	3/4 tablet
476	20 to 30 kg:	1/2 tablet
477	10 to 20 kg:	1/4 tablet
478	5 to 10 kg:	1/8 tablet*

479 \*Approximate tablet fraction based on a dosage of 5 mg/kg body weight.  
480 Exact doses for children weighing less than 10 kg may best be prepared and  
481 dispensed by pharmacists.

482 Experience with Lariam in infants less than 3 months old or weighing less  
483 than 5 kg is limited.

### 484 HOW SUPPLIED

485 Lariam is available as scored, white, round tablets, containing 250 mg of  
486 mefloquine hydrochloride in unit-dose packages of 25 (NDC 0004-0172-02).  
487 Imprint on tablets: LARIAM 250 ROCHE

488 Tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C  
489 (59° to 86°F).

### 490 ANIMAL TOXICOLOGY

491 Ocular lesions were observed in rats fed mefloquine daily for 2 years. All  
492 surviving rats given 30 mg/kg/day had ocular lesions in both eyes  
493 characterized by retinal degeneration, opacity of the lens, and retinal edema.  
494 Similar but less severe lesions were observed in 80% of female and 22% of  
495 male rats fed 12.5 mg/kg/day for 2 years. At doses of 5 mg/kg/day, only  
496 corneal lesions were observed. They occurred in 9% of rats studied.

## **LARIAM® (mefloquine hydrochloride)**

497 Revised: Month Year

### 498 **MEDICATION GUIDE**

499 **This Medication Guide is intended only for travelers who are taking**  
500 **Lariam to prevent malaria.** The information may not apply to patients who  
501 are sick with malaria and who are taking Lariam to treat malaria.

502 An information wallet card is provided with this Medication Guide. Carry it  
503 with you when you are taking Lariam.

504 This Medication Guide was revised in May 2004. Please read it before you  
505 start taking Lariam and each time you get a refill. There may be new  
506 information. This Medication Guide does not take the place of talking with  
507 your prescriber (doctor or other health care provider) about Lariam and  
508 malaria prevention. Only you and your prescriber can decide if Lariam is right  
509 for you. If you cannot take Lariam, you may be able to take a different  
510 medicine to prevent malaria.

### 511 **What is the most important information I should know about Lariam?**

#### 512 **1. Take Lariam exactly as prescribed to prevent malaria.**

513 Malaria is an infection that can cause death and is spread to humans  
514 through mosquito bites. If you travel to parts of the world where the  
515 mosquitoes carry the malaria parasite, you must take a malaria prevention  
516 medicine. Lariam is one of a small number of medications approved to  
517 prevent and to treat malaria. If taken correctly, Lariam is effective at  
518 preventing malaria but, like all medications, it may produce side effects in  
519 some patients.

#### 520 **2. Lariam can rarely cause serious mental problems in some patients.**

521 The most frequently reported side effects with Lariam, such as nausea,  
522 difficulty sleeping, and bad dreams are usually mild and do not cause  
523 people to stop taking the medicine. However, people taking Lariam  
524 occasionally experience severe anxiety, feelings that people are against  
525 them, hallucinations (seeing or hearing things that are not there, for  
526 example), depression, unusual behavior, or feeling disoriented. There have  
527 been reports that in some patients these side effects continue after Lariam  
528 is stopped. Some patients taking Lariam think about killing themselves,  
529 and there have been rare reports of suicides. It is not known whether  
530 Lariam was responsible for these suicides.

#### 531 **3. You need to take malaria prevention medicine before you travel to a** 532 **malaria area, while you are in a malaria area, and after you return** 533 **from a malaria area.**

534 Medicines approved in the United States for malaria prevention include  
535 Lariam, doxycycline, atovaquone/proguanil, hydroxychloroquine, and  
536 chloroquine. Not all of these drugs work equally as well in all areas of the

## LARIAM® (mefloquine hydrochloride)

537 world where there is malaria. The chloroquines, for example, do not work  
538 in areas where the malaria parasite has developed resistance to  
539 chloroquine. Lariam may be effective against malaria that is resistant to  
540 chloroquine or other drugs. All drugs to treat malaria have side effects that  
541 are different for each one. For example, some may make your skin more  
542 sensitive to sunlight (Lariam does not do this). However, if you use  
543 Lariam to prevent malaria and you develop a sudden onset of anxiety,  
544 depression, restlessness, confusion (possible signs of more serious mental  
545 problems), or you develop other serious side effects, contact a doctor or  
546 other health care provider. It may be necessary to stop taking Lariam and  
547 use another malaria prevention medicine instead. If you can't get another  
548 medicine, leave the malaria area. However, be aware that leaving the  
549 malaria area may not protect you from getting malaria. You still need to  
550 take a malaria prevention medicine.

### 551 **Who should not take Lariam?**

552 Do not take Lariam to **prevent** malaria if you

- 553 • **have depression or had depression recently**
- 554 • **have had recent mental illness or problems**, including anxiety disorder,  
555 schizophrenia (a severe type of mental illness), or psychosis (losing touch  
556 with reality)
- 557 • **have or had seizures (epilepsy or convulsions)**
- 558 • **are allergic to quinine or quinidine (medicines related to Lariam)**

559 **Tell your prescriber about all your medical conditions.** Lariam may not be  
560 right for you if you have certain conditions, especially the ones listed below:

- 561 • **Heart disease.** Lariam may not be right for you.
- 562 • **Pregnancy.** Tell your prescriber if you are pregnant or plan to become  
563 pregnant. It is dangerous for the mother and for the unborn baby (fetus) to  
564 get malaria during pregnancy. Therefore, ask your prescriber if you should  
565 take Lariam or another medicine to prevent malaria while you are  
566 pregnant.
- 567 • **Breast-feeding.** Lariam can pass through your milk and may harm the  
568 baby. Therefore, ask your prescriber whether you will need to stop breast-  
569 feeding or use another medicine.
- 570 • **Liver problems.**

571 **Tell your prescriber about all the medicines you take, including**  
572 **prescription and non-prescription medicines, vitamins, and herbal**  
573 **supplements.** Some medicines may give you a higher chance of having  
574 serious side effects from Lariam.

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### 575 **How should I take Lariam?**

576 **Take Lariam exactly as prescribed. If you are an adult or pediatric**  
577 **patient weighing 45 kg (99 pounds) or less, your prescriber will tell you**  
578 **the correct dose based on your weight.**

579 To prevent malaria

580 • For adults and pediatric patients weighing over 45 kg, take 1 tablet of  
581 Lariam at least 1 week before you travel to a malaria area (or 2 to 3 weeks  
582 before you travel to a malaria area, if instructed by your prescriber). This  
583 starts the prevention and also helps you see how Lariam affects you and  
584 the other medicines you take. **Take 1 Lariam tablet once a week**, on the  
585 same day each week, while in a malaria area.

586 • **Continue taking Lariam for 4 weeks after returning from a malaria**  
587 **area.** If you cannot continue taking Lariam due to side effects or for other  
588 reasons, contact your prescriber.

589 • Take Lariam just after a meal and with at least 1 cup (8 ounces) of water.

590 • For children, Lariam can be given with water or crushed and mixed with  
591 water or sugar water. The prescriber will tell you the correct dose for  
592 children based on the child's weight.

593 • If you are told by a doctor or other health care provider to stop taking  
594 Lariam due to side effects or for other reasons, it will be necessary to take  
595 another malaria medicine. You must take **malaria prevention medicine**  
596 **before you travel to a malaria area, while you are in a malaria area,**  
597 **and after you return from a malaria area. If you don't have access to**  
598 **a doctor or other health care provider or to another medicine besides**  
599 **Lariam and have to stop taking it, leave the malaria area. However, be**  
600 **aware that leaving the malaria area may not protect you from getting**  
601 **malaria. You still need to take a malaria prevention medicine.**

### 602 **What should I avoid while taking Lariam?**

603 • **Halofantrine (marketed under various brand names)**, a medicine used  
604 to treat malaria. Taking both of these medicines together can cause serious  
605 heart problems that can cause death.

606 • **Do not become pregnant.** Women should use effective birth control  
607 while taking Lariam.

608 • **Quinine, quinidine, or chloroquine (other medicines used to treat**  
609 **malaria).** Taking these medicines with Lariam could cause changes in  
610 your heart rate or increase the risk of seizures.

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### 611 In addition:

- 612 • **Be careful driving or in other activities** needing alertness and careful  
613 movements (fine motor coordination). Lariam can cause dizziness or loss  
614 of balance, even after you stop taking it.
- 615 • **Be aware that certain vaccines may not work if given while you are**  
616 **taking Lariam.** Your prescriber may want you to finish taking your  
617 vaccines at least 3 days before starting Lariam.

### 618 What are the possible side effects of Lariam?

619 Lariam, like all medicines, may cause side effects in some patients. The most  
620 frequently reported side effects with Lariam when used for prevention of  
621 malaria include nausea, vomiting, diarrhea, dizziness, difficulty sleeping, and  
622 bad dreams. These are usually mild and do not cause people to stop taking the  
623 medicine.

624 Lariam may cause serious mental problems in some patients (see “What is the  
625 most important information I should know about Lariam?”).

626 Lariam may affect your liver and your eyes if you take it for a long time. Your  
627 prescriber will tell you if you should have your eyes and liver checked while  
628 taking Lariam.

### 629 What else should I know about preventing malaria?

- 630 • **Find out whether you need malaria prevention.** Before you travel, talk  
631 with your prescriber about your travel plans to determine whether you  
632 need to take medicine to prevent malaria. Even in those countries where  
633 malaria is present, there may be areas of the country that are free of  
634 malaria. In general, malaria is more common in rural (country) areas than  
635 in big cities, and it is more common during rainy seasons, when  
636 mosquitoes are most common. You can get information about the areas of  
637 the world where malaria occurs from the Centers for Disease Control and  
638 Prevention (CDC) and from local authorities in the countries you visit. If  
639 possible, plan your travel to reduce the risk of malaria.
- 640 • **Take medicine to prevent malaria infection.** Without malaria prevention  
641 medicine, you have a higher risk of getting malaria. Malaria starts with  
642 flu-like symptoms, such as chills, fever, muscle pains, and headaches.  
643 However, malaria can make you very sick or cause death if you don’t seek  
644 medical help immediately. These symptoms may disappear for a while,  
645 and you may think you are well. But, the symptoms return later and then it  
646 may be too late for successful treatment.

647 Malaria can cause confusion, coma, and seizures. It can cause kidney  
648 failure, breathing problems, and severe damage to red blood cells.  
649 However, malaria can be easily diagnosed with a blood test, and if  
650 caught in time, can be effectively treated.

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651           **If you get flu-like symptoms (chills, fever, muscle pains, or**  
652           **headaches) after you return from a malaria area,** get medical help  
653           right away and tell your prescriber that you may have been exposed to  
654           malaria.

655           People who have lived for many years in areas with malaria may have  
656           some immunity to malaria (they do not get it as easily) and may not  
657           take malaria prevention medicine. This does not mean that you don't  
658           need to take malaria prevention medicine.

- 659           • **Protect against mosquito bites.** Medicines do not always completely  
660           prevent your catching malaria from mosquito bites. So protect yourself  
661           very well against mosquitoes. Cover your skin with long sleeves and long  
662           pants, and use mosquito repellent and bednets while in malaria areas. If  
663           you are out in the bush, you may want to pre-wash your clothes with  
664           permethrin. This is a mosquito repellent that may be effective for weeks  
665           after use. Ask your prescriber for other ways to protect yourself.

### 666           **General information about the safe and effective use of Lariam.**

667           Medicines are sometimes prescribed for conditions not listed in Medication  
668           Guides. If you have any concerns about Lariam, ask your prescriber. This  
669           Medication Guide contains certain important information for travelers visiting  
670           areas with malaria. Your prescriber or pharmacist can give you information  
671           about Lariam that was written for health care professionals. Do not use  
672           Lariam for a condition for which it was not prescribed. Do not share Lariam  
673           with other people.

674           This Medication Guide has been approved by the U.S. Food and Drug  
675           Administration.


676           Medication Guide Revised: May 2004

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678           Reprint of information wallet card:

**LARIAM<sup>®</sup> (mefloquine hydrochloride)**

679

 <b>Lariam<sup>®</sup> (mefloquine hydrochloride) Tablets</b> Carry this information wallet card with you when you are taking Lariam.	
<p>You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area.</p> <p>If taken correctly, Lariam is effective at preventing malaria but, like all medications, it may produce side effects in some patients.</p> <p>If you use Lariam to prevent malaria and you develop a sudden onset of anxiety, depression, restlessness, confusion (possible signs of more serious mental problems), or you develop other serious side effects, contact a doctor or other health care provider. It may be necessary to stop taking Lariam and use another malaria prevention medicine instead.</p>	<p>Other medicines approved in the United States for malaria prevention include: doxycycline, atovaquone/proguanil, hydroxychloroquine, and chloroquine. Not all malaria medicines work equally well in malaria areas. The chloroquines, for example, do not work in many parts of the world. If you can't get another medicine, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.</p> <p>Please read the Medication Guide for additional information on Lariam.</p> <p style="text-align: right;">Card Revised: May 2004</p>

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