AUSTRALIAN PRODUCT INFORMATION – LARIAM (MEFLOQUINE HYDROCHLORIDE) TABLETS

1 NAME OF THE MEDICINE

Mefloquine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lariam tablets contain 250 mg mefloquine in the form of mefloquine hydrochloride (274.09 mg). Lariam (mefloquine) is an antimalarial belonging to the quinoline methanol group of medicines and is structurally related to quinine.

Excipients with known effect:
Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablets.

Lariam tablets are cylindrical biplanar, white to off-white, cross-scored with break bars on both faces and marked with "LA", "RI", "AM" and “CP” in each quadrant of one face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Malaria treatment
Lariam is indicated for the treatment of acute attacks of malaria due to *P. falciparum* infection resistant to conventional antimalarial drugs.

Following therapy of mixed *P. falciparum* and *P. vivax* malaria with Lariam, relapse chemoprophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate hepatic forms of *P. vivax*.

Malaria chemoprophylaxis
For travellers to countries with documented chloroquine and antifolate combination ([sulfadoxine/pyrimethamine] / [dapsone/pyrimethamine]) resistant *P. falciparum* malaria, who are considered to be at high risk for malaria in view of their residence or travel (of up to 3 months duration) through rural areas (between the dusk to dawn period).

For travellers hypersensitive to sulphonamides and sulphones, who are considered to be at high risk for malaria in view of their residence or travel (of up to 3 months duration) through rural areas, (between the dusk to dawn period) in countries with high level chloroquine-resistant *P. falciparum* malaria.

4.2 DOSE AND METHOD OF ADMINISTRATION

Malaria Treatment

Adults and children of more than 45 kg bodyweight:
The recommended total dosage of Lariam, 1,250 mg according to bodyweight, should be administered as follows:

A loading dose of 3 tablets (750 mg), followed 6 to 8 hours later by 2 tablets (500 mg).

For partially immune patients (i.e. for inhabitants of malaria endemic areas), a full standard dosage of Lariam should also be used.

A second full dose should be given to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30-60 minutes after a dose, an additional half dose should be given.

If a full treatment course has been administered without clinical cure, alternative treatments should be given. Similarly, if previous chemoprophylaxis with Lariam has failed, Lariam should not be used for curative treatment and physicians should carefully evaluate which antimalarial to use for therapy. See Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions regarding the use of halofantrine.

Lariam can be given for severe acute malaria after an initial course of intravenous quinine lasting at least 2–3 days. Interactions leading to adverse events can largely be prevented by allowing an interval of at least 12 hours after the last dose of quinine.

Artemisinin combination therapy (ACT) is recommended as the standard of care for treatment of *P. falciparum* malaria, regardless of region of acquisition. Mefloquine is a recommended partner molecule for inclusion in ACT. As parasite sensitivity can vary geographically and over time, it is recommended that treatment be guided by national and international guidelines.

Malaria Chemoprophylaxis
Chemoprophylaxis of malaria with Lariam should be initiated 1 week before arrival in a malarious area.

The following dosage schedule is given as a guide:

Lariam can be used for up to 3 months in the chemoprophylaxis of malaria.

	Dosage	**Course of Chemoprophylaxis**
Adults and children of more than 45 kg bodyweight	1 tablet	Stated dose to be given once weekly, always on the same day. First dose one week before departure. Further doses at weekly intervals during travel in malarious areas and for 2 weeks after leaving the area.

The tablets should be swallowed whole with plenty of liquid.

4.3 CONTRAINDICATIONS

Lariam is contraindicated in patients with known hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine) or any of the excipients in Lariam.

The use of Lariam is presently contraindicated in patients with renal insufficiency or severe impairment of liver function as no experience has been gained in such patients.

Patients with a past history of active depression, a recent history of depression, generalised anxiety disorder, psychosis, suicide attempts, suicidal ideations and self-endangering behaviour, or schizophrenia or other major psychiatric disorders or convulsions should not be prescribed Lariam prophylactically.

The use of Lariam is contraindicated:

- in patients with a history of Blackwater fever, a complication of falciparum malaria with massive intravascular haemolysis causing haemoglobinuria.
- in patients with severe hepatic impairment (see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).

Halofantrine must not be used during mefloquine chemoprophylaxis or treatment of malaria or within 15 weeks after the last dose of mefloquine, due to the risk of a potentially fatal prolongation of the QTc interval (see sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Circumstances where special attention is required

Due to the risk of a potentially fatal prolongation of the QTc interval, halofantrine must not be given during Lariam therapy for chemoprophylaxis or treatment of malaria or within 15 weeks after the last dose of Lariam (see Section 5.2 Pharmacokinetic properties, Excretion; 4.5 Interactions with other medicines and other forms of interactions).

Due to increased plasma concentrations and elimination half-life of mefloquine following co-administration with ketoconazole, the risk of QTc prolongation may also be expected if ketoconazole is taken during Lariam therapy for chemoprophylaxis or treatment of malaria, or within 15 weeks after the last dose of Lariam (see Section 4.5 Interactions with other medicines and other forms of interactions).

Concomitant administration of Lariam and quinine or quinidine may produce electrocardiographic abnormalities (see Section 4.4 Special warnings and precautions for use, Cardiac Effects and Section 4.5 Interactions with other medicines and other forms of interactions).

Concomitant administration of Lariam and quinine or chloroquine may increase the risk of convulsions (see Section 4.5 Interactions with other medicines and other forms of interactions).

In patients with epilepsy, Lariam, especially when used in high doses may increase the risk of convulsions. Therefore in such patients Lariam should be used only for curative treatment and only if there are compelling medical reasons (see Section 4.5 Interactions with other medicines and other forms of interactions).

Hypersensitivity Reactions

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

Cardiac Effects

As mefloquine is related structurally to quinine, its use in patients with cardiac disease should be avoided as data on the cardiac effects of mefloquine are at present inadequate to establish safety.

Although no cardiovascular action of Lariam, a myocardial suppressant has been observed during clinical trials, parenteral studies in animals show that it possesses 20% of the antifibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. The effect of Lariam on the compromised cardiovascular system has not been evaluated. However transitory and clinically silent ECG alterations have been reported during the use of Lariam. Alterations included sinus bradycardia, sinus arrhythmia, first degree AV-block, prolongation of the QTc interval and abnormal T waves (see Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse effects (Undesirable effects)). The benefits of Lariam therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Ocular Effects

Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with Lariam.

Neuropsychiatric Effects

Lariam may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behaviour. On occasions, these symptoms have been reported to continue long after Lariam has been stopped. Lariam should not be prescribed in patients with a history of psychiatric symptoms (see Section 4.3 Contraindications) and should be used with caution in patients with a previous history of depression.

In chemoprophylaxis the safety profile of mefloquine is characterised by a predominance of neuropsychiatric adverse reactions. During prophylactic use, if signs of unexplained acute anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued. Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist after discontinuation of the drug. In a small number of patients, it has been reported that some neuropsychiatric events (including depression, dizziness or vertigo and loss of balance) may continue for months or longer after discontinuation of the drug. Therapy should be initiated one week before travel commences (see Section 4.2 Dose and method of administration), as acute psychiatric effects are more likely to manifest at the start of treatment.

Blood and Lymphatic System Disorders

Cases of agranulocytosis and aplastic anaemia have been reported during Lariam therapy.

Drug Resistance

Geographical drug resistance patterns of *P. falciparum* occur and preferred choice of malaria chemoprophylaxis might be different from one area to another. Resistance of *P. falciparum* to mefloquine has been reported, predominantly in areas of multi-drug resistance in South-East Asia. Cross-resistance between Lariam and halofantrine and cross-resistance between Lariam and quinine have been observed. For current advice on geographical resistance patterns competent national expert centres should be consulted.

The basic mode of action of mefloquine has not been elucidated.

Use in hepatic impairment

In patients with impaired liver function, the elimination of mefloquine may be prolonged; leading to higher plasma levels and a higher risk of adverse reactions (see Section 4.3 Contraindications).

Use in the elderly

No data available.

Paediatric use

Data are inadequate to establish the safety of Lariam in children below the age of 14 years.

Effects on laboratory tests

Refer to Section 4.5 Interactions with other medicines and other forms of interactions, Effects on Laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicine interactions with Lariam have not been explored in detail.

Beta blockers, quinine, quinidine or chloroquine:
Concomitant administration of Lariam and quinine, quinidine or medicines producing β-adrenergic blockade may produce electrocardiographic abnormalities or cardiac arrest.

Although no cardiovascular action of Lariam, a myocardial suppressant has been observed during clinical trials, parenteral studies in animals show that it possesses 20% of the antifibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. The effect of Lariam on the compromised cardiovascular system has not been evaluated. However transitory and clinically silent ECG alterations have been reported during the use of Lariam. Alterations included sinus bradycardia, sinus arrhythmia, first degree AV-block, prolongation of the QTc interval and abnormal T waves. The benefits of Lariam therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Theoretically, co-administration of other medicines known to prolong cardiac conduction (e.g. anti-arrhythmic or β-adrenergic blocking agents, calcium channel blockers, antihistamines or H_1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval.

Concurrent administration of Lariam and the same related compounds (i.e. quinine, quinidine or chloroquine) could also increase the risk of convulsions.

Halofantrine:
There is evidence that the use of halofantrine during Lariam therapy for chemoprophylaxis or treatment of malaria or within 15 weeks of the last dose of Lariam causes a significant lengthening of the QTc interval (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

Ketoconazole:
Due to increased plasma concentrations and elimination half-life of Lariam following co-administration with ketoconazole, the risk of QTc prolongation may also be expected if ketoconazole is taken during Lariam therapy for chemoprophylaxis or treatment of malaria, or within 15 weeks after the last dose of Lariam.

Anticonvulsants:
In patients taking an anticonvulsant (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of Lariam may reduce seizure control by lowering the plasma levels of the anticonvulsant. Dosage adjustments of anticonvulsant medication may be necessary in some cases.

Vaccines:
When Lariam is taken at the same time or shortly before oral live typhoid vaccines, attenuation of the immunisation induced by such vaccines cannot be excluded. Vaccinations with attenuated live bacteria should be completed at least three days before the first dose of Lariam, keeping in mind that Lariam chemoprophylaxis should be started one week before arrival in a malarious area.

Effects on Laboratory tests:
The most frequently observed laboratory alterations which could be possibly attributable to drug administration were decreased haematocrit, transient elevation of transaminases, leukopenia and thrombocytopenia. These alterations were observed in patients with acute malaria who received treatment doses of the drug and were attributed to the disease itself.

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

Other Potential Interactions
Mefloquine does not inhibit the cytochrome P450 isoenzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 at prophylactic concentrations. Mefloquine does not induce CYP3A4. Although no information is available with regard to induction of other cytochrome P450 enzymes, mefloquine is not expected to alter the metabolism of concomitantly-administered medicines.

Inhibitors of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase in mefloquine plasma concentrations and potential risk of adverse reactions. Therefore, Lariam should be used with caution when administered concomitantly with CYP3A4 inhibitors. Similarly, inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine leading to a decrease in mefloquine plasma concentrations.

Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist up to several weeks after discontinuation of the drug.

No other medicine interactions are known. Since interactions with oral anti-diabetics and oral anticoagulants have not been tested, the relevant parameters should be checked when Lariam is taken for malaria chemoprophylaxis.

Periodic evaluation of hepatic function should be performed during prolonged chemoprophylaxis.

Inhibitors of CYP3A4
One pharmacokinetic study in healthy volunteers showed that the co-administration of ketoconazole, a strong inhibitor of CYP3A4, increased the plasma concentrations and elimination half-life of mefloquine.

Inducers of CYP3A4
The long-term use of rifampicin, a potent inducer of CYP3A4, reduced the plasma concentrations and elimination half-life of mefloquine.

Substrates and inhibitors of P-glycoprotein
Mefloquine is an inhibitor of P-glycoprotein (P-gp) in vitro. Therefore, interactions could potentially also occur with medicines that are substrates of this transporter. The clinical relevance of these interactions is not known to date. In a clinical interaction study in healthy volunteers, ritonavir, caused less than 7% changes with high precision (90% CIs: x12% to 11%) in overall plasma exposure (AUC 0, 168h) and peak concentration (Cmax) of mefloquine, its two enantiomers, and carboxylic acid metabolite, and in the metabolite/mefloquine and enantiomeric AUC ratios. Mefloquine significantly decreased steady state ritonavir plasma AUC 0, 12h by 31%, Cmax by 36% and pre-dose levels by 43%, and did not affect ritonavir binding to plasma proteins.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Epididymal lesions were evident in rats treated with 20 mg/kg/day (5 times the prophylactic dose on a mg/m^2 basis), while a lower number of viable spermatozoa and a lower fertility index were seen in male rats treated with 50 mg/kg/day (13 times the prophylactic dose).

Adverse effects on fertility were also evident in female rats treated with these doses. No adverse effects were observed in either male or female rats at 5 mg/kg/day, approximately equivalent to the prophylactic dose on a mg/m^2 basis.

Administration of 250 mg/week of mefloquine (base) in adult males for 22 weeks failed to reveal any deleterious effects on human spermatozoa.

Use in pregnancy – Pregnancy Category B3

The use of Lariam in the treatment of malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus.

Chemoprophylaxis in high risk situations is also justified.

Women of childbearing potential who are travelling to malaria endemic areas in which multi drug resistant *P. falciparum* is found should use an effective contraceptive throughout the therapy and for at least 3 months after taking the last dose of Lariam.

Mefloquine crosses the placenta and is detectable in the foetal circulation.

Administered at 3 to 12 times the therapeutic dose in humans, Lariam was teratogenic in mice and rats and embryotoxic in rabbits; however, clinical experience with Lariam has not revealed an embryotoxic or teratogenic effect. Nevertheless, Lariam should be used during the first trimester only if the expected benefit justifies the potential risk to the foetus.

Women of childbearing potential should be advised to practice contraception during malaria chemoprophylaxis with Lariam and for up to 3 months thereafter. However, in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered an indication for pregnancy termination. For use of Lariam during pregnancy, current national and international guidelines should be consulted.

Use in lactation

Mefloquine is excreted into breast milk in small amounts, the activity of which is unknown. Circumstantial evidence suggests that adverse effects do not occur in breast-fed infants whose mothers are taking Lariam. For use of Lariam in nursing mothers current national and international guidelines should be consulted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Persons experiencing dizziness and loss of balance or other disorders of the central or peripheral nervous system should be cautious with regard to driving, piloting aircraft, operating machines, deep- sea diving, or other activities requiring alertness and fine motor co-ordination. In a small number of patients, it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

At the doses given for acute malaria, adverse reactions to Lariam may not be distinguishable from symptoms of the disease itself.

Among subjects who received Lariam for treatment, the most frequently observed adverse experiences included: dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhoea, skin rash, abdominal pain, fatigue, loss of appetite and tinnitus. Those side effects occurring less frequently included bradycardia, hair loss, emotional problems, pruritus, asthenia, transient emotional disturbances and telogen effluvium (loss of resting hair). Seizures have also been reported.

The rate of adverse events associated with Lariam is published to be similar to that with other antimalarial prophylactic medications. In chemoprophylaxis the safety profile of Lariam adverse events is characterised by a predominance of neuropsychiatric adverse reactions (see Section 4.4 Special warnings and precautions for use).

Clinical trials

A systematic review published in 2009 identified a double-blind, randomized study including 976 patients (483 patients on Lariam, 493 patients on atovaquone/proguanil), where treatment-related neuropsychiatric adverse events occurred in 139/483 (28.8%) patients receiving Lariam compared to 69/493 (14%) patients receiving atovaquone-proguanil (Tables 1 and 2). No drug-attributable serious adverse events occurred in either group.

Table 1 Adverse Events Attributed to the Study Drug[#]

	Lariam (n = 483)		**atovaquone-proguanil (n = 493)**	
Event	**Number**	**(%)**	**Number**	**(%)**
Any adverse event	204	(42.2)	149	(30.2)
Any neuropsychiatric event	139	(28.8)	69	(14)
Strange or vivid dreams	66	(13.7)	33	(6.7)
Insomnia	65	(13.5)	15	(3)
Dizziness or vertigo	43	(8.9)	11	(2.2)

Visual difficulties	16	(3.3)	8	(1.6)
Anxiety	18	(3.7)	3	(0.6)
Depression	17	(3.5)	3	(0.6)
Any gastrointestinal event	94	(19. 5)	77	(15.6)
Diarrhoea	34	(7)	37	(7.5)
Nausea	40	(8.3)	15	(3)
Abdominal pain	23	(4.8)	26	(5.3)
Mouth ulcers	17	(3.5)	29	(5.9)
Vomiting	9	(1.9)	7	(1.4)
Headache	32	(6.6)	19	(3.9)
Itching	15	(3.1)	12	(2.4)

[#]Mean duration of treatment ± SD was 28 ± 8 days for atovaquone-proguanil and 53 ± 16 days for Lariam.

Post-Marketing

In the table below, an overview of adverse reactions is presented, based on post marketing data.

Table 2 Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from available data).	
Blood and lymphatic system disorders	
Not known	Agranulocytosis, aplastic anaemia, leukopenia, leukocytosis, thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity from mild cutaneous events to anaphylaxis
Metabolism and nutrition disorders	
Not known	Decreased appetite
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Common	Anxiety, depression
Uncommon	Agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania, paranoia, suicidal ideation
Nervous system disorders	

Common	Dizziness, headache
Uncommon	Balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy
Eye disorders	
Common	Visual impairment
Not known	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Vestibular disorders (long term) including tinnitus and hearing impaired
Cardiac disorders	
Not known	Chest pain, Tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient conduction disorder, AV block
Vascular disorders	
Not known	Cardiovascular disorders (hypotension, hypertension, flushing)
Respiratory, thoracic and mediastinal disorders	
Not known	Dyspnoea, pneumonitis of possible allergic etiology
Gastrointestinal disorders	
Common	Nausea, diarrhoea, abdominal pain, vomiting
Not known	Dyspepsia
Hepatobiliary disorders	
Not known	Drug-related hepatic disorders from asymptomatic transient transaminase increase to hepatic failure
Skin and subcutaneous tissue disorders	
Common	Pruritus
Not known	Rash, erythema, urticaria, alopecia, hyperhidrosis, erythema multiforme, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	
Not known	Muscular weakness, muscle spasms, myalgia, arthralgia
Renal and urinary disorders	
Not known	Renal failure acute, nephritis, blood creatinine increased

General disorders and administration site disorders	
Not known	Oedema, asthenia, malaise, fatigue, chills, pyrexia, hyperhidrosis

Due to the long half-life of Lariam, adverse reactions to Lariam may occur or persist up to several weeks after the last dose. In a small number of patients, it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine. There have been rare reports of suicidal ideations. No relationship to drug administration has been established.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms
In cases of overdosage with Lariam, the symptoms mentioned under Section 4.8 Adverse effects (Undesirable effects) may be more pronounced.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The effectiveness in the treatment of malaria is due essentially to destruction of the asexual intraerythrocytic forms of the human malarial parasites: *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. However data concerning the treatment of *P. malariae* and *P. ovale* were limited.

It is also effective against *P. falciparum* infections resistant to other antimalarials such as chloroquine and other 4-amino-quinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations.

Laboratory animal studies have shown that resistance to mefloquine can be readily induced in the malarial parasite and that this resistance is stable during passage through the insect vector. Mefloquine resistance has also been seen in a few clinical isolates from patients receiving mefloquine.

Resistance of *P. falciparum* to mefloquine has been reported, mainly in parts of South-East Asia. Cross-resistance between mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed.

The basic mode of action of mefloquine has not been elucidated. However, a number of studies of its actions in biochemical systems have been made.

Like quinine, mefloquine is able to form complexes with haemin. The ability to co-ordinate with haemin seems to correlate with the antimalarial activity of the compound. But, unlike chloroquine, quinacrine and quinine, mefloquine does not intercalate with DNA. Thus, interaction with DNA does not seem to be involved in the antimalarial action of mefloquine.

Mefloquine does not exert antifolic activity and its antimalarial action is not antagonised by p-aminobenzoic acid.

Clinical trials

In a randomised, double-blind study, non-immune travellers received malaria chemoprophylaxis with Lariam (483 subjects) and atovaquone-proguanil (493 subjects) who visited a malaria-endemic area. Efficacy of chemoprophylaxis was evaluated as a secondary end point. The average duration of travel was ~2.5 weeks, and 79% of subjects travelled to Africa. 1013 subjects were initially randomised to receive Lariam (n=505) or atovaquone-proguanil (n=508). Thirty-seven subjects withdrew due to a variety of reasons. Of the 976 subjects who received ≥1 dose of study drug, 966 (99%) completed the trial and 963 completed the 60-day follow-up period and had efficacy information recorded. Although 10 subjects (5 in each study arm) were identified with circumsporozoite antibodies, none of them developed malaria (minimum efficacy for both Lariam and atovaquone-proguanil was 100%). Overall, there were no cases of confirmed malaria in this study (maximum efficacy for both Lariam and atovaquone-proguanil was 100%). Results indicated that Lariam and atovaquone-proguanil are similarly effective for malaria chemoprophylaxis in non-immune travellers (see Table 3).

Table 3 Estimates of minimum and maximum efficacy for malaria chemoprophylaxis

	Subjects who received	
Variable	Atovaquone-proguanil[c]	Lariam[c]
Subjects with 60-day efficacy data available, no.	486	477
Subjects who developed circumsporozoite antibodies, no.	5	5
Subjects with confirmed malaria, no.	0	0
Minimum efficacy, % (95% Cl)[a]	100 (48-100)	100 (48-100)
Maximum efficacy, % (95% Cl)[b]	100 (99-100)	100 (99-100)

[a] Minimum efficacy = 100 x [1 – (no. of subjects with confirmed malaria/no. with circumsporozoite antibodies)]
[b] Maximum efficacy = 100 x [1 – (no. of subjects with confirmed malaria/no. with 60-day efficacy data)]
[c] Atovaquone/proguanil administered daily (250/25 mg tabs.) in pat. > 40 kg BW, mefloquine weekly (250 mg tabs.) in pat. > 35 kg BW.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formulation 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 patients, the absorption half-life of mefloquine was 5 to 6 hours with plasma concentrations peaking 12 to 23 hours (mean about 16.6 hours). Maximum blood concentrations appear to be 2 to 3 times higher in Asian compared with

non-Asian volunteers. Reasons for this ethnic difference are unclear. Also, plasma C_{max} were higher in patients with acute uncomplicated *P. falciparum* malaria.

In healthy volunteers a dose of 250 mg once weekly produces maximum steady state plasma concentrations of 1,000 to 2,000 µg/L, which are reached after 7 to 10 weeks.

Distribution

In healthy adults, the apparent volume of distribution is approximately 20 L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitised erythrocytes. Experiments conducted in vitro with human blood using concentrations between 50 and 1,000 mg/mL showed a relatively constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 minutes was found to be reversible. Mefloquine is approximately 98.2% protein bound.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see Section 4.6 Fertility, pregnancy and lactation, Use in lactation).

Metabolism

Mefloquine is extensively metabolised in the liver by the cytochrome P450 system. *In vitro* and *in vivo* studies strongly suggested that CYP3A4 is the major isoform involved. Two metabolites of mefloquine have been identified in humans. The main metabolite 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *P. falciparum*.

In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma concentrations of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug.

In addition to the acid, other known metabolite is a mefloquine derivative with a hydroxy group in the piperidine moiety.

Excretion

The average half-life of mefloquine in Caucasians is 21 days. Clinical studies carried out to date have shown that only a minute proportion of the active ingredient is excreted unchanged in the urine. Animal studies suggest that mefloquine is primarily excreted via the bile and faeces as unchanged drug and metabolites.

Pharmacokinetics in Special Populations

Renal Impairment

As only a small proportion of mefloquine is eliminated renally, no pharmacokinetic studies have been performed in patients with renal insufficiency. Mefloquine and its main metabolite are not appreciably removed by haemodialysis. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy subjects.

Hepatic Impairment

Mefloquine is extensively metabolised in the liver by the CYP P450 system with CYP3A4 likely to be the major isoform. There have been no formal clinical studies in patients with hepatic impairment, so that the magnitude of effect of hepatic impairment on mefloquine pharmacokinetics is not known. However, it is considered likely that patients with impaired liver function will be exposed to higher plasma mefloquine levels due to reduced clearance and will be at higher risk of adverse effects (see

Section 4.3 Contraindications).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of mefloquine was assessed in bacterial, yeast and mammalian mutagenicity tests, in a host-mediated assay in mice and a mouse micronucleus assay at appropriate concentrations or doses. In vitro tests were performed with and without metabolic activation. All assays returned negative results for mefloquine.

Carcinogenicity

The carcinogenic potential of mefloquine was investigated in 2 year feeding studies in mice and rats at doses up to 30 mg/kg/day, equivalent to 4 and 8 times the prophylactic dose on a mg/m^2 basis. There were no treatment-related increases in tumour incidence in either species.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lariam tablets also contain the following excipients: poloxamer, microcrystalline cellulose, lactose monohydrate, maize starch, crospovidone, ammonium calcium alginate, purified talc and magnesium stearate.

Refer to Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in original container. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Packs of 8 tablets (cross-scored) each containing 250 mg mefloquine.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

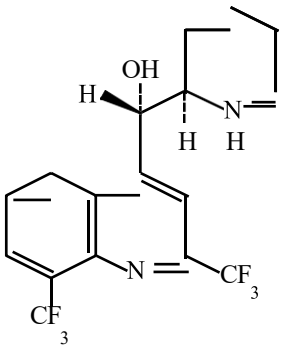
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: *dl-erythro-alpha-2-piperidy-2,8-bis(trifluoromethyl)-4-quinoline methanol*
MW: 414.78

Mefloquine is an odourless, bitter tasting, white crystalline powder. It is soluble in methanol and ethanol but practically insoluble in water. A 1% aqueous suspension has a pH of 5.6.

Chemical structure



CAS number

51773-92-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Pharmaco (Australia) Ltd
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Zenith Towers
821 Pacific Highway
Chatswood, NSW 2067
Australia

Phone: 1800 201 564

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9 DATE OF FIRST APPROVAL

27 January 1993

10 DATE OF REVISION

30 May 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Addition of suicide attempts, suicidal ideations and self-endangering behaviour. Addition of information related to Blackwater fever. Addition of information from sections 4.4 and 4.8 relating to patients with severe hepatic impairment. Addition of information from section 4.4 and 4.5 relating to halofantrine.
4.5	Reference to section 4.3 added to Halofantrine use.

4.8	Update to Table 2 to add information relating to Immune system disorders from section 4.4. Update to Table 2 to add information relating to Renal and urinary disorders.