Commonwealth Department of
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Applic No: 97.400.2
Clin: 97/14530

The Managing Director
Roche Products Pty Ltd
P O Box 255
DEE WHY NSW 2099

Attention: [redacted]

Dear Sir/Madam

Thank you for your letter of 15 July 1998 concerning the Product Information for Lariam (mefloquine hydrochloride).

Evaluation of your application **(Application No 97.400.2)** has been completed.

In accordance with Section 28 of the *Therapeutic Goods Act 1989*, the amended text of the Product Information is approved. A copy of the document is provided as Attachment 1. The attached document must be the document supplied from three months from the date of this letter in connection with Lariam tablet 250mg (as mefloquine hydrochloride), Australian Registration No 43321.

The CMI enclosed with your letter of 4 September 1998 is considered to meet the format as required in Schedule 12 of the Therapeutic Goods Regulations and not to contain any statement contrary to the approved Product Information. You are reminded that there is a continuing obligation to ensure that at all times the patient information document (Consumer Medicine Information - CMI) complies with the statutory requirements. Following amendment of the Product Information, any changes needed to the CMI to ensure consistency with the Product Information must be made within three months of the approval or notification of the change to the Product Information. In the case of changes relating to the safety or safe use of the product, more rapid change of the CMI may be warranted.

Two copies of the final printed version of the Product Information quoting the date of this letter are to be supplied in due course. Please note that if any safety related

changes are made to this Product Information by notification in the future, you should retain the date of this approval but also cite the date of notification of the safety related change made.

This decision is an "initial decision" within the meaning of Section 60 of the Therapeutic Goods Act 1989 ("the Act"). This means that if your interests are affected by the decision, you may seek review of this decision by the Minister. Any appeal should be made in writing within 90 days after this decision first comes to your notice or to the notice of your company, and should be sent to the following address:

The Parliamentary Secretary to the Minister
for Health and Family Services
Parliament House
CANBERRA ACT 2600

The letter should be headed "APPEAL UNDER SECTION 60 OF THE THERAPEUTIC GOODS ACT 1989".

Before embarking upon this course of action you are invited to contact the initial decision maker to see whether the matter can be resolved informally.

The Parliamentary Secretary may either deal with the appeal personally, or send it to be dealt with by one of the Minister's delegates within the Department. Should you be dissatisfied with the result of your appeal then, subject to the Administrative Appeals Tribunal Act 1975, you may appeal to the Tribunal for review of the Minister's/Delegate's decision.

Yours faithfully

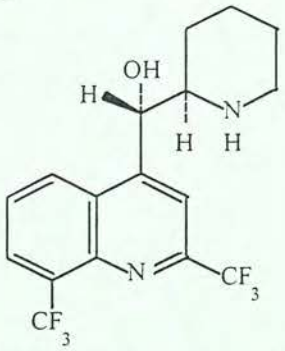
[redacted]

ARTG 30/9/98 BW.

[redacted]
DELEGATE OF THE SECRETARY
11/9/98

LARIAM
(mefloquine hydrochloride)

LARIAM contains DL - erythro - alpha - 2 - piperidyl - 2,8 - bis (trifluoromethyl)- 4 - quinoline methanol (mefloquine) which has the following formula:



Mefloquine is an odourless, bitter-tasting, white crystalline powder of molecular weight 414.78. It is soluble in methanol and ethanol but practically insoluble in water. A 1% aqueous suspension has a pH of 5.6.

LARIAM tablets contain the active substance 250 mg mefloquine in the form of mefloquine hydrochloride (274.09 mg). Lariam tablets also contain the excipients poloxamer 3800, microcrystalline cellulose, lactose, maize starch, crospovidone, ammonium calcium alginate, talc and magnesium stearate.

PHARMACOLOGY

Actions

Mefloquine is an antimalarial belonging to the quinoline-methanol group of drugs and is structurally related to quinine. Its effectiveness in the treatment of malaria is due essentially to destruction of the asexual erythrocytic forms of the malarial pathogens. It is also effective against *Plasmodium 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. Cross-resistance can be shown between mefloquine and quinine.

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

Mode of Action: The basic mode of action of mefloquine has not yet 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.

Pharmacokinetics

Absorption: Following oral doses of 250 mg mean peak plasma levels of approximately 300 ng/mL were observed. They were reached approximately 14 hours after administration.

Bioavailability: The absolute bioavailability of mefloquine is not known. However, relative to an oral solution the bioavailability of mefloquine from LARIAM tablets was determined to be 87 ± 11%.

Distribution: Mefloquine is taken up largely in the liver but also into the lungs, muscles, brain and retina. The concentration in erythrocytes is approximately twice that in the plasma. The apparent volume of distribution has been calculated as approximately 19 litres/kg body weight. 98.2% of mefloquine is bound to plasma proteins.

Metabolism: Animal studies have demonstrated that several metabolites of mefloquine are formed, the major metabolite being the cinchonic acid derivative. In addition to the acid, other known metabolites are the corresponding alcohol, a mefloquine derivative with a hydroxy group in the piperidine moiety and the mefloquine lactam (6-keto-piperidine derivative).

In human beings the cinchonic acid metabolite appeared in the plasma 4 hours after administration of LARIAM and reached its maximum concentration after 2 weeks. During the first 12 weeks the mean concentration of the acid metabolite was 2 to 5 times greater than that of mefloquine. The metabolite has a longer half-life than mefloquine and is not active against the malarial parasite.

Elimination: 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.

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/P.vivax* malaria with LARIAM relapse prophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate liver forms of *P.vivax*.

Malaria Prophylaxis: For travellers to countries with documented chloroquine and antifolate combination (FANSIDAR/Maloprim) 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.

CONTRAINDICATIONS

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 psychiatric disturbances or convulsions should not be prescribed LARIAM prophylactically.

PRECAUTIONS

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.

Animal studies indicate that mefloquine can induce retinopathy. There are no data on the ophthalmological effects of mefloquine in human beings.

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine must not be given simultaneously with or subsequent to LARIAM. No data are available on the use of LARIAM after halofantrine.

Caution should be exercised with regard to driving, piloting aircraft and operating machines, since dizziness. disturbed sense of balance on neuropsychiatric reactions have been reported during and up to 3 weeks after use of LARIAM.

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.

In patients with epilepsy, mefloquine, 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 Interactions with Other Drugs).

Use in 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.

Prophylaxis 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 mefloquine.

Use in Lactation

Mefloquine is excreted into breast milk. Since no data on drug levels in breast milk after high dosage (curative treatment) or prolonged administration (prophylaxis) is available, LARIAM should not be used by nursing mothers or breast feeding should be discontinued.

Paediatric Use

At present data are inadequate to establish the safety of mefloquine in children below the age of 14 years.

Interactions with Other Drugs

Drug-drug interactions with LARIAM have not been explored in detail.

Concomitant administration of LARIAM and other related compounds (e.g. quinine, quinidine or chloroquine) may produce electrocardiographic abnormalities and could increase the risk of convulsions (see Dosage and Administration, Treatment).

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 (see Precautions).

Concomitant administration of LARIAM and quinine, quinidine or drugs producing beta-adrenergic blockade may produce electrocardiographic abnormalities or cardiac arrest.

Theoretically, co-administration of other drugs 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.

There is evidence that the use of halofantrine after mefloquine causes a significant lengthening of the QTc interval.

Although no cardiovascular action of mefloquine hydrochloride, 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 mefloquine hydrochloride on the compromised cardiovascular system has not been evaluated. The benefits of LARIAM therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

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 prophylaxis should be started one week before arrival in a malarious area.

No other drug interactions are known. Since interactions with oral antidiabetics and oral anticoagulants have not been tested, the relevant parameters should be checked when LARIAM is taken for malaria prophylaxis.

ADVERSE REACTIONS

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 mefloquine 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 mefloquine is published to be similar to that with other antimalarial prophylactic medications.

Events listed below are classified within body system categories and enumerated in order of decreasing frequency using the following definitions.

Common = ≥1/100 (≥1%)
Uncommon = ≥1/1000 and < 1/100 patients (≥0.1% and <1%)
Rarely = <1/100 patients (<0.1%)

Psychiatric disorders: Common: somnolence, sleep disorders (insomnia, abnormal dreams); Uncommon: anxiety, depressive mood, confusion, restlessness, forgetfulness, hallucinations and psychotic or paranoid reactions.

Central and peripheral nervous system disorders:
Common: dizziness is generally mild and may decrease with prolonged use, in spite of increasing plasma drug levels, vertigo, loss of balance, headache Uncommon: sensory and motor neuropathies (including paraesthesia), convulsions Rarely: encephalopathy.

Severe neuropsychiatric events with mefloquine use are rare.

Gastrointestinal system disorders:
Common: nausea and vomiting are generally mild and may decrease with prolonged use, in spite of increasing plasma drug levels, loose stools, diarrhoea and abdominal pain.

Body as a whole, general disorders: Uncommon: asthenia, malaise, fatigue, fever, chills, loss of appetite.

Skin and appendages disorders: Uncommon: rash, exanthema, erythema, urticaria, pruritus, hair loss Rarely: erythema multiforme, Stevens-Johnson syndrome.

Visual disorders: Uncommon: visual disturbances.

Musculo-skeletal system disorders: Uncommon: muscle weakness, muscle cramps, myalgia, arthralgia.

Hearing disorders: Uncommon: Tinnitus and vestibular disorders may be accompanied by transitory hearing disorders.

Cardiovascular disorders, general: Uncommon: circulatory disturbances (hypotension, hypertension, flushing, syncope).

Heart rate and rhythm disorders: Uncommon: tachycardia or palpitation, irregular pulse, bradycardia, extrasystoles and other transient cardiac conduction alterations Rarely: AV-block

Liver and biliary disorders: Uncommon: transient elevation of transaminases.

Platelet and bleeding disorders: Uncommon: thrombocytopenia.

White blood cell disorders: Uncommon: leucopenia, leucocytosis.

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

DOSAGE AND ADMINISTRATION

Malaria Treatment: Adults and children of more than 45 kg bodyweight:

(i) Non-immune patients recently arrived from endemic areas.
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).

ii) Semi-immune patients
For patients in malaria endemic areas, a smaller total dosage of LARIAM - 750 to 1,000 mg - is sufficient since they have usually developed partial immunity. Adults weighing 60 kg receive an initial dose of 3 tablets, followed by 1 tablet 6 to 8 hours later.

If a full treatment course has been administered without clinical cure, alternative treatments should be given. Similarly if previous prophylaxis with mefloquine has failed, LARIAM should not be used for curative treatment.

Malaria Prophylaxis: Prophylaxis 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 prophylaxis of malaria.

	Dosage	Course of Prophylaxis
Adults and children of more than 45kg 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.

OVERDOSAGE

Symptoms: In cases of overdosage with LARIAM, the symptoms mentioned under ADVERSE REACTIONS may be more pronounced.

Treatment: The following procedure is recommended: Induce vomiting or perform gastric lavage as appropriate. 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.

PRESENTATION

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

DISTRIBUTOR

ROCHE PRODUCTS PTY LTD
ACN 000 132 865
4 - 10 Inman Road
Dee Why NSW 2099

TGA Approval date: