

NEW ZEALAND DATA SHEET

LARIAM[®] 250 mg tablets Mefloquine hydrochloride

1 PRODUCT NAME

Lariam 250 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 274.09 mg racemic mefloquine hydrochloride, equivalent to 250 mg mefloquine base.

Excipient(s) with known effect: Lactose

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

3 PHARMACEUTICAL FORM

Lariam 250 mg tablets are white, cross-scored cylindrical and biplane, marked "RO", "C", "HE" and an imprinted hexagon on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Chemoprophylaxis, therapy and stand-by treatment of malaria.

Chemoprophylaxis

Chemoprophylaxis with Lariam is recommended for travellers to malarious areas, particularly those travelling to areas where there is a high risk of infection with strains of *P. falciparum* resistant to other antimalarials.

Therapy

Lariam is indicated for the oral treatment of malaria, particularly when caused by strains of *P. falciparum* resistant to other antimalarials. It may also be used for the treatment of *P. vivax* and mixed malaria (see Section 4.2).

Stand-by treatment

Lariam is also prescribed as a stand-by medication, to be carried by the traveller and self-administered as an emergency measure for suspected malaria when prompt medical attention is unavailable within 24 hours.

4.2 Dosage and Administration

Mefloquine has a bitter and slightly burning taste. Lariam tablets should be swallowed whole, with at least one glass of liquid. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

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Chemoprophylaxis standard dosage

The recommended chemoprophylactic dose of Lariam is approximately 5 mg/kg bodyweight once weekly:

Bodyweight (kg)	Dose
5 – 20 kg	¼ tablet
> 20 – 30 kg	½ tablet
> 30 – 45 kg	¾ tablet
> 45 kg	1 tablet

Weekly doses should be taken regularly, always on the same day of each week, preferably after the main meal. The first dose should be taken at least one week before arrival in an endemic area.

Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited. The dosage for children has been extrapolated from the recommended adult dose (see Section 5.2).

Therapy standard dosage

The recommended total therapeutic dose of mefloquine is 20 – 25 mg/kg bodyweight:

Bodyweight (kg)	Total dose	Split dose (*)
5 – 10 kg	½ – 1 tablet	–
>10 – 20 kg	1 – 2 tablets	–
>20 – 30 kg	2 – 3 tablets	2 + 1
>30 – 45 kg	3 – 4 tablets	2 + 2
>45 – 60 kg	5 tablets	3 + 2
> 60 kg	6 tablets	3 + 2 + 1

* Splitting the total therapeutic dosage into 2–3 doses taken 6–8 hours apart may reduce the occurrence or severity of adverse effects.

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

There is no specific experience with total dosages of more than 6 tablets in very heavy patients.

Special dosage instructions

Chemoprophylaxis

For last-minute travellers to high-risk areas, if the start of chemoprophylaxis one week before arrival in the endemic area is not possible, a "loading dose" administration, consisting of the weekly dosage administered daily for three consecutive days followed, thereafter, by standard weekly dosing, is recommended:

Day 1	1 st dose
Day 2	2 nd dose
Day 3	3 rd dose
Thereafter	Regular weekly doses

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The use of a loading dose may be associated with an increased incidence of adverse events.

In certain cases, e.g. when a traveller is taking other medication, it may be desirable to start chemoprophylaxis 2 to 3 weeks prior to departure, in order to ensure that the combination of medicines is well tolerated (see Section 4.5).

To reduce the risk of malaria after leaving an endemic area, chemoprophylaxis must be continued for 4 additional weeks to ensure suppressive blood levels of the medicine when merozoites emerge from the liver.

When chemoprophylaxis with Lariam fails, physicians should carefully evaluate which antimalarial to use for therapy. Regarding the use of halofantrine, see Section 4.4 and Section 4.5.

Therapy

For partially immune individuals, i.e. for inhabitants of malarious endemic areas, a full standard dose should be used.

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

After treatment of *P. vivax* malaria, relapse chemoprophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate liver forms.

If a full treatment course with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. When breakthrough malaria occurs during Lariam chemoprophylaxis, physicians should carefully evaluate which antimalarial to use for therapy. Regarding the use of halofantrine, see Section 4.4 and Section 4.5.

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.

Stand-by treatment

Lariam may be prescribed for use as stand-by medication when prompt medical attention is unavailable within 24 hours of onset of symptoms. Self-treatment should be started with a dose of about 15 mg/kg; for patients weighing 45 kg or more the initial dose would thus be 3 Lariam tablets. If it will not be possible to obtain professional medical care within 24 hours, and no severe side-effects occur, a second fraction of the total therapeutic dosage should be taken 6 – 8 hours later (2 tablets in patients weighing 45 kg or more). Patients weighing more than 60 kg should take an additional tablet 6 – 8 hours after the second dose. (See dosage recommendations for therapy above.)

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Patients should be advised to consult a physician as soon as possible after self-treatment, even if they feel they have fully recovered to confirm or reject the presumptive diagnosis.

4.3 Contraindications

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

Lariam should not be prescribed for chemoprophylaxis in persons with active depression or with a history of major psychiatric disorders or convulsions.

4.4 Special Warnings and Precautions for use

General

As with most medications, hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted.

Lariam contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

In patients with epilepsy, Lariam may increase the risk of convulsions. Lariam should therefore be prescribed only for curative treatment in such patients and only if there are compelling medical reasons for its use (see Section 4.5).

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.

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). 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 and Section 5.2).

In chemoprophylaxis the safety profile of Lariam is characterized by a predominance of neuropsychiatric adverse reactions such as acute anxiety, depression, restlessness or confusion. If such adverse reactions occur during chemoprophylactic use, Lariam should be discontinued and an alternative chemoprophylactic agent should be recommended. 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 dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

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.

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

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Lariam 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 in some regions. For current advice on geographical resistance patterns competent national expert centres should be consulted.

Cases of agranulocytosis and aplastic anaemia have been reported during Lariam therapy (see Section 4.8).

Children and the elderly

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

Renal impairment

No pharmacokinetic studies have been performed in patients with renal insufficiency since only a small proportion of the medicine is eliminated renally. 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 persons.

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 machinery, deep-sea diving, or other activities requiring alertness and fine motor coordination. 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 Lariam (see *Undesirable Effects*).

4.5 Interactions with other medicines and other forms of interaction

Concomitant administration of Lariam and other related compounds (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions (see Section 4.2). 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 4.4). 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 5.2).

Clinically significant QTc prolongation has not been found with mefloquine alone. This appears to be the only clinically relevant interaction of this kind with Lariam, although theoretically co-administration of other medicines known to alter cardiac conduction (e.g. anti-arrhythmic or β -adrenergic blocking agents, calcium channel blockers, antihistamines or H1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval. There are no data that conclusively establish whether the concomitant administration of mefloquine and the above-listed agents has an effect on cardiac function.

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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 antiseizure medication may be necessary in some cases.

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

No other medicine interactions are known. Nevertheless, the effects of Lariam on travellers receiving concomitant medication, particularly diabetics or patients using anticoagulants, should be checked before departure.

Other potential interactions

Mefloquine does not inhibit or induce the cytochrome P450 enzyme system. It is therefore not expected that the metabolism of medicines given concomitantly with mefloquine is affected. However, 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, mefloquine 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.

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 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, a known strong inhibitor of P-gp and CYP3A4 was found to have no effect on the pharmacokinetics of mefloquine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy category B3.

Administered at 5 to 20 times the therapeutic dose in man, mefloquine 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

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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.

Breastfeeding

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 machinery, deep-sea diving, or other activities requiring alertness and fine motor coordination. 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 Lariam (see Section 4.8).

4.8 Undesirable Effects

At the doses given for acute malaria, adverse reactions to Lariam may not be distinguishable from symptoms of the disease itself. Of the most common adverse reactions to Lariam chemoprophylaxis, nausea, vomiting and dizziness are generally mild and may decrease with prolonged use, in spite of increasing plasma mefloquine levels.

In chemoprophylaxis the safety profile of Lariam is characterised by a predominance of neuropsychiatric adverse reactions (see Section 4.4).

Studies in vitro and in vivo showed no haemolysis associated with G6PD deficiency.

Clinical trials

See Post marketing section below.

Laboratory abnormalities

See Post marketing section below.

Post marketing

In the table below, an overview of adverse reactions is presented, based on post marketing data and a double-blind, randomized study including 976 patients (483 patients on mefloquine, 493 patients on atovaquone/proguanil). Treatment-related neuropsychiatric adverse events occurred in 139/483 (28.8%) patients receiving mefloquine compared to 69/493 (14%) patients receiving atovaquone-proguanil. No drug-attributable serious adverse events occurred in either group.

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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 ($\geq 1/100$ to < 1/10), uncommon ($\geq 1/1,000$ to < 1/100), rare ($\geq 1/10,000$ to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

	Very Common (>1/10)	Common (1/100 to <1/10)	Not known
Blood and lymphatic system disorders			Agranulocytosis, aplastic anaemia, leukopenia, leukocytosis, thrombocytopenia
Metabolism and nutrition disorders			Decreased appetite
Psychiatric disorders	Abnormal dreams, insomnia	Anxiety, depression	Agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation disorder and mania, paranoia
Nervous system disorders		Dizziness, headache	Balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy
Eye disorders		Visual impairment	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment
Ear and labyrinth disorders		Vertigo	Vestibular disorders including tinnitus and hearing impaired
Cardiac disorders			Tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient conduction disorder, AV block

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	Very Common (>1/10)	Common (1/100 to <1/10)	Not known
Vascular disorders			Cardiovascular disorders (hypotension, hypertension, flushing)
Respiratory, thoracic and mediastinal disorders			Dyspnoea, pneumonitis of possible allergic etiology
Gastrointestinal disorders		Nausea, diarrhoea, abdominal pain, vomiting	Dyspepsia
Hepatobiliary disorders			Drug-related hepatic disorders from asymptomatic transient transaminase increase to hepatic failure
Skin and subcutaneous tissue disorders		Pruritus	Rash, erythema, urticaria, alopecia, hyperhidrosis, erythema multiforme, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			Muscular weakness, muscle spasms, myalgia, arthralgia
General disorders and administration site disorders			Oedema, chest pain, asthenia, malaise, fatigue, chills, pyrexia

There have been rare reports of suicidal ideations. No relationship to drug administration has been established.

4.9 Overdose

Symptoms and signs

In cases of overdosage with Lariam, the symptoms mentioned under 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antiprotozoals, Antimalarials

ATC code: P01BC02

Mechanism of Action

Lariam acts on the asexual intraerythrocytic forms of the human malaria parasites: *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*.

Lariam is effective against malaria parasites resistant to other antimalarials such as chloroquine, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations.

Clinical/Efficacy Studies

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 1).

Table 1. Estimates of minimum and maximum efficacy for malaria chemoprophylaxis

Variable	Subjects who received	
	Atovaquone-proguanil	Lariam
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% CI) ^a	100 (48-100)	100 (48-100)
Maximum efficacy, % (95% CI) ^b	100 (99-100)	100 (99-100)

^a Minimum efficacy = $100 \times [1 - (\text{no. of subjects with confirmed malaria}/\text{no. with circumsporozoite antibodies})]$

^b Maximum efficacy = $100 \times [1 - (\text{no. of subjects with confirmed malaria}/\text{no. with 60-day efficacy data})]$

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

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solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability. Plasma concentrations peak 6 – 24 hours (median, about 17 hours) after a single dose of Lariam. Maximum plasma concentrations in $\mu\text{g/L}$ are roughly equivalent to the dose in milligrams (for example, a single 1000 mg dose produces a maximum concentration of about 1000 $\mu\text{g/L}$). At a dose of 250 mg once weekly, maximum steady state plasma concentrations of 1000 – 2000 $\mu\text{g/L}$ are reached after 7 – 10 weeks.

Distribution

In healthy adults, the apparent volume of distribution is approximately 20 L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitized erythrocytes at an erythrocyte-to-plasma concentration ratio of about 2. Protein binding is about 98%. Mefloquine blood concentrations of 620 ng/mL are considered necessary to achieve 95% chemoprophylactic efficacy. Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see Section 4.6).

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 compound. The other metabolite, an alcohol, was present in minute quantities only.

Elimination

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

Pharmacokinetics in special populations

Pregnancy

Pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

Acute malaria

The pharmacokinetics of mefloquine may be altered in acute malaria.

Ethnic populations

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

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Long term chemoprophylaxis

During long-term chemoprophylaxis, the elimination half-life of mefloquine remains unchanged.

5.3 Preclinical safety data

See Section 4.6

6 Pharmaceutical Particulars

6.1 List of excipients

Poloxamer 3800

Microcrystalline cellulose

Lactose

Maize starch

Crospovidone

Ammonium calcium alginate

Talc

Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from date of manufacture.

6.4 Special precautions for storage

The tablets are sensitive to moisture and should remain in the original container until taken. Store below 30 °C.

This medicine should not be used after the expiry date shown on the pack.

6.5 Nature and contents of container

Lariam tablets (cross-scored) 250 mg: Blister packs containing 8 tablets.

6.6 Special precautions for disposal

No special precautions for disposal. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 Medicine Classification

Prescription medicine

8 Sponsor

Pharmaco (NZ) Ltd

4 Fisher Crescent

Mt Wellington

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Auckland 1060
Telephone: 0800 804 079

9 DATE OF FIRST APPROVAL

06 Aug 1990

10 DATE OF REVISION OF THE TEXT

04 October 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted to new SPC format
Section 2 & 4.4	Addition of excipients with known effect and associated warnings as per SPC requirements
Section 8	Details updated to reflect change in sponsorship