Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lariam 250mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg mefloquine (as 274.09 mg mefloquine hydrochloride).
Each tablet contains 50.61 mg of lactose monohydrate

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white cylindrical biplanar tablets, cross-scored and imprinted Roche on one face.

The tablet can be divided into equal halves to facilitate dosing.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Therapy and prophylaxis of malaria.

Therapy: Lariam is especially indicated for therapy of *P. falciparum* malaria in which the pathogen has become resistant to other antimalarial agents.

Following treatment of *P. vivax* malaria with Lariam, relapse prophylaxis with an 8-amino-quinoline derivative, for example primaquine, should be considered in order to eliminate parasites in the hepatic phase.

Prophylaxis: Malaria prophylaxis with Lariam is particularly recommended for travellers to malarious areas in which multiple resistant *P. falciparum* strains occur.

4.2 Posology and method of administration

Posology

When chemoprophylaxis with Lariam fails, physicians should carefully evaluate which antimalarial to use for therapy. Regarding the use of halofantrine, see sections 4.3, 4.4 and 4.5.

Chemoprophylaxis
In order to ensure, before arrival in endemic area, that Lariam administration is well tolerated, it is recommended to start chemoprophylaxis with Lariam 10 days before departure (i.e. first intake 10 days before departure and 2nd intake 3 days before departure). Subsequent doses should be taken once a week (on a fixed day).

The stated dose to be given once weekly, always on the same day for a minimum of six weeks. Further doses at weekly intervals during, and for four weeks after visiting the malarious area.

The following dosage schedule is given as a guide:

	Dosage
Adults and children of more than 45 kg bodyweight	1 tablet
Children and adults weighing less than 45 kg: 5 – 19 kg 20 – 30 kg 31 – 45 kg	 ¼ tablet ½ tablet ¾ tablet

The maximum recommended duration of administration of Lariam is 12 months.

The tablets should be swallowed whole preferably after a meal with plenty of liquid.

Curative treatment
The recommended total therapeutic dose of Lariam for non-immune patients is 20 – 25 mg/kg. A lower total dose of 15 mg/kg may suffice for partially immune individuals.

The recommended total therapeutic dosages of Lariam tablets relative to body weight and immune status are presented in the following table:

	Non-immune patients	Partially immune patients
< 20 kg *	¼ tablet / 2.5 – 3 kg 1 tablet / 10 – 12 kg	¼ tablet / 4 kg 1 tablet / 16 kg
20 - 30 kg	2 – 3 tablets	1¼ - 2 tablets
> 30 - 45 kg	3 – 4 tablets	2 – 3 tablets
> 45 – 60 kg	4 – 5 tablets	3 – 4 tablets
> 60 kg **	6 tablets	4 – 6 tablets

* 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.

In order to limit the occurrence and severity of adverse reactions, the total therapeutic dose may be split into 2 – 3 doses (e.g. 3 + 1, 3 + 2 or 3 + 2 + 1 tablets) taken 6 – 8 hours apart.

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 with Lariam does not lead to improvement within 48 - 72 hours, alternative treatments should be considered.

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 (see section 4.5).

In areas with multi-resistant malaria, initial treatment with artemisinin or a derivative, if available, followed by Lariam is also an option.

Elderly
No specific adaptation of the usual adult dosage is required for elderly patients.

4.3 Contraindications

- known hypersensitivity to mefloquine or related compounds (e.g. quinine, quinidine), or to any of the excipients contained in the formulation.

- chemoprophylaxis in patients with active depression, a history of depression, generalised anxiety disorder, psychosis, suicide attempts, suicidal ideations and self-endangering behaviour, schizophrenia or other psychiatric disorders, or with a history of convulsions of any origin (see sections 4.4 and 4.5).

- 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 and 4.5).

- 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 and 4.8).

Prophylactic use in patients with severe impairment of liver function should be regarded for the time being as a contraindication as no experience has been gained in such patients.

4.4 Special warnings and precautions for use

Neuropsychiatric Adverse Reactions

Mefloquine may induce psychiatric symptoms such as anxiety disorders, paranoia, depression, hallucinations and psychosis. Psychiatric symptoms such as abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event (see section 4.8). Cases of suicide, suicidal thoughts and self-endangering behaviour such as attempted suicide (see section 4.8) have been reported.

Patients on malaria chemoprophylaxis with mefloquine should be informed that if these reactions or changes to their mental state occur during mefloquine use, to stop taking mefloquine and seek medical advice immediately so that mefloquine can be replaced by alternative malaria prevention medication.

Adverse reactions may also occur after discontinuation of the drug. In a small number of patients it has been reported that neuropsychiatric reactions (e.g. depression, dizziness or vertigo and loss of balance) may persist for months or even longer, even after discontinuation of the drug.

To minimise the risk for these adverse reactions, mefloquine must not be used <u>for chemoprophylaxis</u> in patients with active or a history of psychiatric disturbances such as depression, anxiety disorders, schizophrenia or other psychiatric disorders (see section 4.3).

Hypersensitivity:
Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis may occur (see section 4.8).

Cardiac toxicity:
Mefloquine should be taken with caution in patients suffering from cardiac conduction disorders, since transient cardiac conduction alterations have been observed during curative and preventative use. Caution is particularly recommended in patients at risk of QT prolongation, including those with organic heart disease (myocardial infarction, congestive heart failure), electrolyte disturbances (e.g. hypokalaemia, hypocalcaemia) and liver disease.

Concomitant administration of mefloquine and other related compounds (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities.

Due to the risk of a potentially fatal prolongation of the QTc interval, halofantrine must not be used during mefloquine chemoprophylaxis or treatment of malaria or within 15 weeks after the last dose of mefloquine.

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 mefloquine chemoprophylaxis or treatment of malaria or within 15 weeks after the last dose of mefloquine (see sections 4.5 and 5.2).

Patients should be advised to consult a doctor, if signs of arrhythmia or palpitations occur during chemoprophylaxis with mefloquine. These symptoms might, in rare cases, precede severe cardiologic side effects.

Seizure disorders:
In patients with epilepsy, mefloquine may increase the risk of convulsions. Therefore in such cases, mefloquine should be used only for curative treatment (i.e. not for stand-by therapy) and only if compelling reasons exist (see sections 4.3 and 4.5).

Concomitant administration of mefloquine and anticonvulsants (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin) may reduce seizure control by lowering the plasma levels of anticonvulsant. Therefore, patients concurrently taking anti-seizure medication, including valproic acid, carbamazepine, phenobarbital and phenytoin, and mefloquine should have the blood level of their anti-seizure medication monitored and the dosage adjusted as necessary.

Concomitant administration of mefloquine and drugs known to lower the epileptogenic threshold (antidepressants such as tricyclic or selective serotonin reuptake inhibitors (SSRIs); bupropion; antipsychotics; tramadol; chloroquine or some antibiotics) may increase the risk of convulsions (see section 4.5).

Neuropathy:
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving mefloquine.
Mefloquine should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Eye disorders:
Any patient presenting with a visual disorder should be referred to a physician as certain conditions (such as retinal disorders or optic neuropathy) may require stopping treatment with mefloquine.

Impaired liver function:
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.

Renal impairment:
Due to limited data, mefloquine should be administered with caution in patients with renal impairment.

Pneumonitis:
Pneumonitis of possible allergic etiology has been reported in patients receiving mefloquine (see section 4.8). Patients who develop signs of dyspnoea, dry cough or fever etc. while receiving mefloquine should be advised to contact a doctor to undergo medical evaluation.

Blood and lymphatic system disorders
Cases of agranulocytosis and aplastic anaemia have been reported during mefloquine therapy (see section 4.8).

Inhibitors and Inducers of CYP3A4:
Inhibitors and Inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase or decrease in mefloquine plasma concentrations (see section 4.5).

Interaction with vaccines:
When mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunisation cannot be excluded. Vaccinations with oral attenuated live bacteria should therefore be completed at least 3 days before the first dose of mefloquine (see section 4.5).

Long term use:
During clinical trials, this drug was not administered for longer than one year. If the drug is to be administered for a prolonged period, periodic evaluations including liver function tests and periodic ophthalmic examinations should be performed.

Galactose intolerance:
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Geographical 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 mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed in some regions. For current advice on geographical resistance patterns competent national expert centres should be consulted.

Hypoglycaemia:
The possibility of hypoglycaemia in patients with congenital hyperinsulinemic hypoglycaemia should be considered.

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

Patients should not disregard the possibility that re-infection or recrudescence may occur after effective antimalarial therapy.

4.5 Interaction with other medicinal products 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.

Halofantrine:
There is evidence that the use of halofantrine during mefloquine chemoprophylaxis or treatment of malaria, or within 15 weeks after the last dose of mefloquine, causes a significant lengthening of the QTc interval (see sections 4.3 and 4.4). Clinically significant QTc prolongation has not been found with mefloquine alone.

Other drugs that prolong the QTc interval:
Concomitant administration of other drugs known to alter cardiac conduction (e.g. anti-arrhythmic or beta-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.

Anticonvulsants and drugs lowering the epileptogenic threshold:
Patients taking mefloquine while on concomitant treatment with anticonvulsants (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin) had loss of seizure control and lower than expected anticonvulsants blood level. Therefore dosage adjustments of anti-seizure medication may be necessary in some cases.
Concomitant administration of mefloquine and drugs known to lower the epileptogenic threshold (antidepressants such as tricyclic or selective serotonin reuptake inhibitors (SSRIs); bupropion; antipsychotics; tramadol; chloroquine or some antibiotics) may increase the risk of convulsions (see sections 4.3 and 4.4).

Other Interactions/ Inhibitors and Inducers of CYP3A4:
Mefloquine does not inhibit or induce the cytochrome P450 enzyme system. It is therefore not expected that the metabolism of drugs given concomitantly with mefloquine is affected. However, inducers (rifampicin, carbamazepine, phenytoin, efavirenz) or inhibitors of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase or decrease in mefloquine plasma concentration. The clinical consequences of these effects are unknown and a close clinical surveillance is warranted (see section 4.4).

Substrates and inhibitors of P-glycoprotein:
It has been shown *in vitro* that mefloquine is a substrate and an inhibitor of P-glycoprotein. Although the clinical relevance of this is not known to date, there is a theoretical risk that drug-drug interactions could occur with drugs that are substrates, or are known to modify the expression of this transporter.

Interaction with vaccines:
When mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunisation cannot be excluded. Vaccinations with oral attenuated live bacteria should therefore be completed at least 3 days before the first dose of mefloquine (see section 4.4).

No other drug interactions are known. Nevertheless, the effects of mefloquine on travellers receiving co-medication, particularly those on anticoagulants or antidiabetics, should be checked before departure.

4.6 Fertility, pregnancy and lactation

Pregnancy
Mefloquine was teratogenic in mice and rats and embryotoxic in rabbits; however, large clinical experience with Lariam as prophylactic treatment has not revealed an embryotoxic or teratogenic effect.

Therefore:

- due to the seriousness of malaria during pregnancy, pregnant women or women who wish to become pregnant should be discouraged from travelling in endemic areas. Prophylactic treatment with mefloquine may be considered regardless the term of pregnancy but in the strict respect of the indications.

- use of mefloquine as curative treatment in pregnant women is limited to the treatment of acute uncomplicated malaria when quinine is contra-indicated or in case of Plasmodium falciparum resistance to quinine.

In case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered as an indication for pregnancy termination. For the use of mefloquine during pregnancy, current national and international guidelines should be consulted.

Breast-feeding
Mefloquine is secreted into the breast milk in small amounts, the activity of which is unknown. As a precautionary measure, melfoquine should be avoided in breast-feeding women. For use of mefloquine in nursing mothers current national and international guidelines should be consulted.

4.7 Effects on ability to drive and use machines

Caution should be exercised with regard to activities requiring alertness and fine motor coordination such as driving, piloting aircraft, operating machinery and deep-sea diving, as dizziness, vertigo or a loss of balance, or other disorders of the central or peripheral nervous system and psychiatric disorders have been reported during and following the use of mefloquine. These effects may occur after therapy is discontinued. In a small number of patients, it has been reported that dizziness or vertigo and loss of balance may persist for months or longer, even after discontinuation of the drug (see section 4.8).

4.8 Undesirable effects

a) Summary of safety profile
At the doses given for acute malaria, adverse reactions to mefloquine may not be distinguishable from symptoms of the disease itself.
In chemoprophylaxis the safety profile of mefloquine is characterised by a predominance of neuropsychiatric adverse reactions.

Adverse reactions may also occur after discontinuation of the drug. The most common adverse reactions to mefloquine chemoprophylaxis are nausea, vomiting and dizziness. Nausea and vomiting are generally mild and may decrease with prolonged use, in spite of increasing plasma drug levels. In a small number of patients it has been reported that neuropsychiatric reactions (e.g. depression, dizziness or vertigo and loss of balance) may persist for months or longer, even after discontinuation of the drug.

b) Tabulated list of adverse reactions
In the table below, an overview of adverse reactions is presented, based on post-marketing data and a double-blind, randomised study including 483 patients on mefloquine (Overbosch et al, 2001). The frequencies presented in this table are based on the double-blind randomised study.

Adverse reactions are listed according to MedRA 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 the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.	
Blood and Lymphatic System Disorders [c)]	
Not known	Agranulocytosis, aplastic anaemia, leukopenia, leukocytosis, thrombocytopenia
Immune system disorders [c)]	
Not known	Hypersensitivity from mild cutaneous events to anaphylaxis
Metabolism and nutrition disorders	
Not known	Decreased appetite
Psychiatric disorders [a),b c))]	
Very common	Abnormal dreams, insomnia
Common	Depression, anxiety
Not known	Suicide, attempted suicide, suicidal ideation and self-endangering behavior, bipolar disprder, psychotic disorder including e.g delusionl disorder, depersonalization, mania and schizophrenia/schizophreniform disorder, paranoia, panic attacks, confusional state, hallucinations, aggression, agitation, restlessness, mood swings, disturbance in attention
Nervous system disorders [a),b, c)]	
Common	Dizziness, headache
Not known	Encepalpathy, cranial nerve paralysis, convulsions, amnesia (sometimes long lasting for more than 3 months), syncope, speech disorder, memory impairment, balance disorder, gait disturbance, peripheral motor neuropathy (including paraesthesia, tremor and ataxia), peripheral sensory neuropathy, somnolence

Eye disorders [c)]	
Common	Visual impairment
Not known	Cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment, vision blurred
Ear and labyrinth disorders	
Common	Vertigo
Not known	Vestibular disorders including tinnitus, partial deafness (sometimes prolonged), hearing impaired, hyperacusis
Cardiac disorders [c)]	
Not known	AV block, tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient conduction disorder
Vascular disorders	
Not known	Cardiovascular disorders (hypotension, hypertension, flushing)
Respiratory, thoracic and mediastinal disorders [c)]	
Not known	Pneumonia, pneumonitis of possible allergic etiology, dyspnoea
Gastrointestinal disorders	
Common	Nausea, diarrhoea, abdominal pain, vomiting
Not known	Pancreatitis, dyspepsia
Hepatobiliary disorders [c)]	
Not known	Hepatic failure, hepatitis, jaundice, asymptomatic transient transaminase (ALT, AST, GGT) increased
Skin and subcutaneous tissue disorders	
Common	Pruritus
Not known	Stevens-Johnson syndrome, erythema multiforme, rash, erythema, urticaria, alopecia, hyperhidrosis
Musculoskeletal and Connective Tissue Disorders	
Not known	Muscular weakness, muscle spasms, myalgia, arthralgia
General disorders and administration site disorders	
Not known	Oedema, chest pain, asthenia, malaise, fatigue, chills, pyrexia
Renal and urinary disorder	
Not known	Renal failure acute, nephritis, blood creatinine increased

a) Occasionally it has been reported that these symptoms persist for a long time after mefloquine is discontinued.
b) See section 4.8
c) See section 4.4

c) Description of selected adverse reactions
Neuropsychiatric adverse reactions:
If neuropsychiatric reactions or changes to the mental state occur during mefloquine chemoprophylaxis, the patient should be advised to stop taking mefloquine and seek medical advice immediately so that mefloquine can be replaced by alternative malaria prevention medication (see section 4.4).

Abnormal dreams/nightmares
Abnormal dreams are a very common adverse reaction with mefloquine, therefore their significance should be considered in the overall evaluation of patients reporting reactions or changes to their mental state with mefloquine (see boxed warning section 4.4).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and signs
In cases of overdosage with mefloquine, the symptoms mentioned under section 4.8 may be more pronounced.

Treatment
Patients should be managed by symptomatic and supportive care following mefloquine overdose. There are no specific antidotes. The use of oral activated charcoal to limit mefloquine absorption may be considered within one hour of ingestion of an overdose. 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 disorders. Elimination of mefloquine and its metabolites is limited by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Methanolquinolines, ATC code: P01BC02

The effectiveness of Lariam in the therapy and prophylaxis of malaria is due essentially to destruction of the asexual forms of the malarial pathogens that affect humans (*Plasmodium falciparum, P. vivax, P. malariae, P. ovale*).

Lariam is also effective against malarial parasites resistant to other antimalarials such as chloroquine and other 4-aminoquinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulphonamide combinations.
In a randomized, double-blind study, non-immune travelers received malaria prophylaxis with mefloquine (483 subjects) and atovaquoine-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 traveled to Africa. 1013 subjects were initially randomized to receive mefloquine (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 mefloquine and atovaquone-proguanil was 100%). Overall, there were no cases of confirmed malaria in this study (maximum efficacy for both mefloquine and atovaquone-proguanil was 100%). Results indicated that mefloquine and atovaquone-proguanil are similarly effective for malaria prophylaxis in non-immune travellers (see Table 3).

Table 3 Estimates of minimum and maximum efficacy for malaria prophylaxis

	Subjects who received	
Variable	**Atovaquone-proguanil**	**Mefloquine**
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)]

In vitro and *in vivo* studies with mefloquine showed no haemolysis associated with glucose-6-phosphate dehydrogenase deficiency.

5.2 Pharmacokinetic properties

Absorption: The maximum plasma concentration is reached within 6 to 24 hours after a single oral dose of Lariam. The level in micrograms per litre is roughly equivalent to the dose in milligrams (for example approximately 1000 micrograms/l after a single dose of 1000 mg). The presence of food significantly enhances the rate and extent of absorption.

At a dose of 250 mg once weekly, maximum steady state plasma concentrations of 1000-2000 micrograms/l are reached after 7-10 weeks. The RBC concentration is almost twice as high as the plasma level. Plasma protein binding is about 98%. Clinical experience suggests a minimal suppressive plasma concentration of mefloquine in the order of 600 micrograms/l.

Biotransformation: Mefloquine is extensively metabolised in the liver by the cytochrome P450 system. *In vitro* and *in vivo* studies strongly suggest that CYP3A4 is the major isoform involved.

Elimination: The average half-life of mefloquine in Europeans is 21 days. 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.

Special clinical situations: The pharmacokinetics of mefloquine may be altered in acute malaria. Pharmacokinetic differences have been observed between various ethnic populations. In practice however, these are of minor importance compared with the host immune status and sensitivity of the parasite.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal.

5.3 Preclinical safety data

Mefloquine crosses the placenta and is teratogenic when administered to rats and mice in early gestation. (See section *4.6*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poloxamer
Microcrystalline cellulose
Lactose monohydrate
Maize starch
Crospovidone
Ammonium calcium alginate
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC, store in the original package. Sensitive to moisture.

6.5 Nature and contents of container

Aluminium foil packs containing 8 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0050/073/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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