Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Lariam (mefloquine hydrochloride)

This is a summary of the risk management plan (RMP) for Lariam. The RMP details important risks of Lariam, how these risks can be minimised, and how more information will be obtained about Lariam's risks and uncertainties (missing information).

Lariam's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lariam should be used.

I. The medicine and what it is used for

Lariam is authorised for chemoprophylaxis, therapy and stand-by treatment of malaria, particularly when caused by strains of *P. falciparum* resistant to other antimalarials (see SmPC for the full indication). It contains mefloquine hydrochloride as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lariam, together with measures to minimise such risks and the proposed studies for learning more about Lariam's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Lariam, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Lariam is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Lariam are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lariam. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Neuropsychiatric adverse reactions Visual disorders Hepatic toxicity Pulmonary toxicity Anaphylaxis and hypersensitivity Cardiovascular disorders / Drug interaction with halofantrine Blackwater fever
Important potential risks	None
Missing information	Treatment in patients with severe hepatic impairment

II.B Summary of important risks

Important Identified Risks

Risk 1: Neuropsychiatric adverse reactions	
Evidence for linking the risk to the medicine	The reported incidence of serious neuropsychiatric effects during chemoprophylactic use of mefloquine varies in different studies. For instance, six studies (Weinke et al 1991; Phillips-Howard 1995; Potasman et al 2000; Schlagenhauf and Steffen 2000; Steffen et al 1990; Barrett et al 1996 have reported different incidences (in the range of 1 in 200 to 1 in 13,000 mefloquine users), presumably reflecting differences in sample populations, trial duration and also possibly trial methodology, efficiency of initial screening for contraindications, definition and assessment of serious events, and adequacy of distinguishing neuropsychiatric adverse reactions caused by mefloquine intake from neuropsychiatric adverse reactions caused by other factors (e.g., alcohol or drug consumption). In some studies, the sample size may have been too small to detect rare events (Ohrt et al 1997). **Psychiatric disorders:** In a large observational study using the UK-based General Practice Research Database (GPRD) the incidence rate of developing first time anxiety, stress disorders/ psychosis, depression, epilepsy or peripheral neuropathies [Schneider, 2013] in patients exposed to mefloquine was estimated. The incidence rates per 1000 person years of anxiety related disorders (*n*=99), depression (*n*=66), epilepsy (*n*=14), neuropathy (*n*=8) among mefloquine users was 6.2 (95% CI: 5.1-7.5), 4.2 (95% CI: 3.3-5.4), 0.8 (95% CI: 0.5-1.4) and 0.5 (95% CI: 0.2-0.9), respectively (Schneider et al 2013).

Risk 1: Neuropsychiatric adverse reactions	
Risk factors and risk groups	In a cohort of 11,725 active duty US military personnel, 9.6% of the cohort had evidence of a contraindication to mefloquine. Females were more than twice as likely as males to have a contraindication (OR, 2.48, $p < 0.001$). A total of 558 subjects (4.8%) had one or more psychiatric or neurological diagnoses prior to deployment consistent with a contraindication to mefloquine use. A total of 837 (7.1%) subjects had one or more prescriptions filled prior to deployment for medications consistent with a contraindication to mefloquine use. A total of 1,127 (9.6%) had either or both (i.e. at least one or more such diagnosis or at least one or more prescription). Of the 837 subjects with one or more prescriptions, 78 (9.4%) had a prescription for an attention-deficit hyperactivity disorder (ADHD) treatment; 93 (11.1%) for an anticonvulsant; 315 (37.6%) for an antidepressant; two (0.2%) for an antiparkinsonian treatment; 24 (2.9%) for an antipsychotic; and 446 (53.3%) for a sedative-anxiolytic. A total of 100 subjects (11.9%) had prescriptions for two or more classes of drug. Diagnoses from inpatient and outpatient visits occurring within the 365 days prior to the date of deployment, consistent with psychiatric and neurological contraindications to mefloquine use included depression, generalised anxiety disorder, psychosis, schizophrenia, and other major psychiatric disorders. Specifically excluded were drug and alcohol-related disorders; transient, acute or poorly-defined conditions; non-specific phobic disorders; and non-depressive personality disorders, sexual and gender identity disorders, and somatoform diagnoses. Specific neurological diagnoses consistent with a history of convulsions were included (Nevin 2008). **Psychiatric disorders:** At-risk groups for psychiatric disorders include patients with a past history of active depression, a recent history of depression, generalised anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders. **Nervous disorders:** At risk groups for nervous disorders include patients with a past history of convulsions.

Risk 1: Neuropsychiatric adverse reactions	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> CDS section 4.3: *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* CDS section 4.4: *In chemoprophylaxis, the safety profile of mefloquine is characterised 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 some neuropsychiatric events (including depression, dizziness or vertigo and loss of balance) may continue for months or longer after discontinuation of the drug.* <u>Additional risk minimisation measures:</u> Educational material for HCP Patient Card Prescriber checklist

Risk 2: Visual disorders	
Evidence for linking the risk to the medicine	A study conducted between 2001 and 2009 aimed to evaluate the risk associated with mefloquine use of developing an eye disorder using data obtained from the UK General Practice Research Database (GPRD). The study population included 83,148 patients; of these, 10,169 received mefloquine, 28,502 received atovaquoneproguanil, and 2,904 received chloroquine and/or proguanil [Schneider 2013]. A total of 652 patients received an incident ocular disorder diagnosis throughout the follow-up period. The incidence rates for all ocular disorders, per 1,000 person-years, were 5.3 (95% [confidence interval [CI] 4.3–6.5) for mefloquine users, 6.3 (95% CI 6.5–7.2) for atovaquone-proguanil users, 7.1 (95% CI 5.0–9.9) for chloroquine and/or proguanil users, and 5.1 (95% CI 4.6–5.7) for patients who did not receive antimalarials. The most frequently occurring ocular disorder was cataract, followed by retinal disorders [Schneider 2013].
Risk factors and risk groups	The follow-up study using data from the UK-based GPRD found that mefloquine users who were overweight or obese had the highest incidence rate of eye disorders. The incidence rate for those with a body mass index (BMI) of 25.0–29.9 kg/m^2 was 6.8

	(95% CI 4.5–10.4), and for those with a BMI of ≥30 kg/m^2 was 14.6 (95% CI 9.8–21.9), compared with 6.2 (95% CI 3.7–10.4) for those with a BMI of 20.0–21.9 kg/m^2. However, the authors indicate that the association between obesity and diabetes and hypertension, which are both associated with ocular disorders, may account for part of the observed incidence rates in these populations (Schneider 2014). In the study population, 25.5% of antimalarial users were aged over 50 years; this population accounted for 68.8% of patients in the nested case-control analysis. As the study authors indicate, the incidence of cataract and glaucoma is increased in those aged greater than 50 years in the general population (Schneider 2013).
Risk minimisation measures	Routine risk minimisation measures: CDS section 4.4: *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 (such as retinal disorders or optic neuropathy) may require stopping treatment with Lariam.* Additional risk minimisation measures: Educational material for HCP

Risk 3: Hepatic toxicity	
Evidence for linking the risk to the medicine	Not available.
Risk factors and risk groups	No particular subgroups of patients at risk or specific risk factors are known.

Risk 3: Hepatic toxicity	
Risk minimisation measures	Routine risk minimisation measures: CDS section 4.3: *Use of Lariam is contraindicated:* • *in patients with severe hepatic impairment (see sections 4.4 and 4.8).* CDS section 4.4: *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.* CDS section 4.8: *Hepatobiliary disorders: Drug-related hepatic disorders from asymptomatic transient transaminase increase to hepatic failure (frequency not known).* Additional risk minimisation measures: Educational material for HCP Patient Card Prescriber checklist

Risk 4: Pulmonary toxicity	
Evidence for linking the risk to the medicine	Not available.
Risk factors and risk groups	No particular subgroups of patients at risk or specific risk factors are known.
Risk minimisation measures	Routine risk minimisation measures: CDS section 4.8: *Respiratory, thoracic and mediastinal disorders: Dyspnoea, pneumonitis of possible allergic aetiology (frequency not known)* Additional risk minimisation measures: Educational material for HCP

Risk 5: Anaphylaxis and hypersensitivity	
Evidence for linking the risk to the medicine	Not available.
Risk factors and risk groups	Patients with a known hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine) or to any of the excipients contained in the formulation are at risk of hypersensitivity reactions.

Risk 5: Anaphylaxis and hypersensitivity	
Risk minimisation measures	Routine risk minimisation measures: CDS section 4.3: *Use of Lariam is contraindicated:* • *in patients with known hypersensitivity to mefloquine or related compounds (e.g. quinine, quinidine), or to any of the excipients contained in the formulation.* CDS section 4.4: *As with most medications, hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted*. Additional risk minimisation measures: Educational material for HCP Patient Card Prescriber checklist

Risk 6: Cardiovascular disorders / Drug interaction with halofantrine	
Evidence for linking the risk to the medicine	Not available.
Risk factors and risk groups	Risk factors for QT prolongation include many medications (including antimalarial drugs), female gender, hypokalaemia, congenital long QT syndrome and underlying severe cardiac disorders. Risk factors for torsade de pointes include female gender, diuretic use (independent of serum electrolytes), bradycardia, congestive heart failure or cardiac hypertrophy, and baseline QT prolongation or T-wave lability. The occurrence is higher in patients with anorexia nervosa or starvation, and after central nervous system injuries such as subarachnoid haemorrhage and brainstem haemorrhage (Drug Safety Report, 2007).

Risk 6: Cardiovascular disorders / Drug interaction with halofantrine	
Risk minimisation measures	Routine risk minimisation measures: CDS section 4.3: *Use of Lariam is contraindicated:* *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).* CDS section 4.4: *QT prolongation* *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 5.2) [18-20]. 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 4.5 and 5.2).* CDS section 4.5: *Concomitant administration of Lariam and other related compounds (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions* *QTc prolongation* *There is evidence that the use of halofantrine during Lariam therapy for chemoprophylaxis or treatment of malaria or within 15 weeks after the last dose of Lariam causes a significant lengthening of the QTc interval (see 4.4).* Additional risk minimisation measures: Educational material for HCP Patient Card Prescriber checklist

Risk 7: Blackwater fever	
Evidence for linking the risk to the medicine	Not available.
Risk factors and risk groups	Regarding risk factors, from the available data, mefloquine was the presumed trigger for blackwater fever in 12 of the 157 cases, with a possible causality in 7 of the 12; none were re-exposed. In vitro and in vivo studies showed no haemolysis associated with G6PD deficiency with mefloquine (Scientific Expert Statement, 2010).

Risk 7: Blackwater fever	
Risk minimisation measures	Routine risk minimisation measures: CDS section 4.3: *Use of Lariam is contraindicated:* • *in patients with a history of Blackwater fever, a complication of falciparum malaria with massive intravascular haemolysis causing haemoglobinuria.* Additional risk minimisation measures: Educational material for HCP Patient Card Prescriber checklist

Important Potential Risks

None.

Missing Information

Risk 1: Treatment in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures CDS section 4.3: *Use of Lariam is contraindicated:* • *in patients with severe hepatic impairment (see sections 4.4 and 4.8).* CDS section 4.4: *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.* CDS section 4.8: *Hepatobiliary disorders: Drug-related hepatic disorders from asymptomatic transient transaminase increase to hepatic failure (frequency not known).* Additional risk minimisation measures: Educational material for HCP Patient Card Prescriber checklist

II.C Post-Authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lariam.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Lariam.