FINAL CSP

4.2 Posology and method of administration

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

….
When chemoprophylaxis with mefloquine 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 mefloquine administration is well tolerated, it is recommended to start chemoprophylaxis with mefloquine 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).

Curative treatment
(…)
In order to limit the occurrence and severity of adverse reactions, the total therapeutic dose may be split into 2 – 3 doses taken 6 – 8 hours apart.

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, generalized 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 section 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 patient with severe hepatic impairment (see section 4.4 and 4.8).

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 longer, even after discontinuation of the drug.

To minimise the risk for these adverse reactions, mefloquine must not be used for chemoprophylaxis 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:
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 be 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 aniticonvulsant. Therefore, patients concurrently taking antiseizure medication, including valproic acid, carbamazepine, phenobarbital, and phenytoin, and mefloquine should have the blood level of their antiseizure 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 disorders 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 centers should be consulted.

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

Only for France:

Only for indication limited to uncomplicated malaria!
An increased risk of neuropsychiatric syndrome occurring after recovery from severe acute malaria has been evidenced in Southeast Asia in patients whose parenteral anti-malaria treatment was switched to oral mefloquine. Cases of convulsions, mental confusion, psychosis, tremors in extremity have been reported. Patients recovered without sequelea within 10 days. Consequently, as far as possible, mefloquine use as oral switch in case of severe acute malaria should be avoided."

4.5 Interaction with other medicinal products and other forms of interaction

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 section 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 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.

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 antiseizure 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 section 4.4).

Other Interactions/ Inhibitors and Inducer 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 (rifampicine, carbamazepine, phenytoin, efavirenz) or inhibitor 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).

***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 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.

Lactation
Mefloquine is secreted into the breast milk in small amounts, the activity of which is unknown. As a precautionary measure, mefloquine 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 disorder 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, randomized study including 483 patients on mefloquine (Overbosch et al, 2001). The frequencies presented in this table are based on the double-blind randomized 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	Anxiety, depression
Not known	Agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including e.g. delusional disorder, depersonalization, mania, and schizophrenia/schizophreniform disorder, paranoia, disturbance in attention, suicide, attempted suicide, suicidal ideation and self-endangering behavior

Nervous system disorders [a),b, c)]	
Common	Dizziness, headache
Not known	Balance disorder, gait disturbance somnolence, syncope, convulsions, memory impairment, amnesia (sometimes long lasting for more than 3 months), peripheral sensory neuropathy, peripheral motor neuropathy, (including paraesthesia, tremor and ataxia), encephalopathy, speech disorder, cranial nerve paralysis
Eye disorders [c)]	
Common	Visual impairment
Not known	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment
Ear and labyrinth disorders	
Common	Vertigo
Not known	Vestibular disorders including tinnitus, partial deafness (sometimes prolonged), hearing impaired, hyperacusis
Cardiac disorders [c)]	
Not known	Tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient conduction disorder, AV block
Vascular disorders	
Not known	Cardiovascular disorders (hypotension, hypertension, flushing)
Respiratory, thoracic and mediastinal disorders [c)]	
Not known	Dyspnoea, pneumonia, pneumonitis of possible allergic etiology
Gastrointestinal disorders	
Common	Nausea, diarrhoea, abdominal pain, vomiting
Not known	Dyspepsia, pancreatitis
Hepatobiliary disorders [c)]	
Not known	Asymptomatic transient transaminase (ALT, AST, GGT) increased, hepatitis, hepatic failure, jaundice
Skin and subcutaneous tissue disorders	
Common	Pruritus
Not known	Rash, erythema, urticaria, alopecia, hyperhidrosis, erythema multiforme, Stevens-Johnson syndrome
Musculoskeletal and Connective Tissue Disorders	
Not known	Muscular weakness, muscle spasms, myalgia, arthralgia
General disorders and administration site disorders	
Not known	Oedema, chest pain, asthenia, malaise, fatigue, chills, pyrexia
Renal and urinary disorder	
Not known	Blood creatinine increased, nephritis, renal failure acute

[a)] *Occasionally it has been reported that these symptoms persist for a long time after mefloquine is discontinued.*

[b] *See section 4.8 c)*
[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.

4.9 Overdose

Symptoms and signs:
In cases of overdosage with mefloquine, the symptoms mentioned under section 4.8 (Undesirable effects) 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.