

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Updated PRAC rapporteur assessment report on the signal of permanent neurologic (vestibular) disorders with mefloquine

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1. Administrative information

Active substance (INN) or class name(s) <i>[Plus invented name, where applicable.]</i>	Mefloquine
Signal and signal status	

From <i>[Rapporteur for this signal]</i>	DE-BfArM
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Assessor(s)	
Scientific administrator	

1.1. Timetable

Date of report (preliminary PRAC Rapp. AR)	07/01/2014
PRAC comments on AR	
Date of report (Updated PRAC Rapp. AR)	28/01/2014
PRAC discussion/adoption	
Date of report (PRAC Rapp. AR on response to RSI)	
PRAC discussion/adoption	

1.2. Product/class details

Strength(s)	250 mg
Pharmaceutical form(s)	film-coated tablet
Route(s) of administration	oral
Indication	Therapy and prophylaxis of malaria
ATC code	P01BC02
Marketing-authorisation holder(s)	Roche
Route of marketing authorisation(s)	
	Centrally authorised (or applied for) product(s) (CAPs)
	Mutual-recognition or decentralised procedure (MRP/DCP)
X	Purely nationally authorised product(s) (NAPs)
	Other (compassionate use, traditional herbal use, etc.):

Background

Mefloquine is a 4-quinoline methanol derivative and is structurally related to quinine. Mefloquine is indicated for the prophylaxis, therapy and stand-by treatment of malaria. Mefloquine acts on the asexual intraerythrocytic forms of the human malaria parasites: *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Mefloquine is effective against malaria parasites resistant to other anti-malarials such as chloroquine, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations.

A signal regarding permanent neurologic (vestibular) disorders was identified by FDA in July 2013 and the FDA-AR was analysed by DE. Subsequently DE introduced the signal to the PRAC. During the meeting on 07 -10 October 2013 PRAC recommended that the MAH of Lariam®, innovator product for mefloquine, be requested to submit a cumulative review of neurologic (vestibular) disorders including a proposal for an update to the product Information.

2. Scientific discussion

2.1. PRAC initial analysis and prioritisation

PRAC Recommendations/Advice

During its meeting of 7-10 October 2013, in accordance with Article 107h of Directive 2001/83/EC and Article 21 of Commission Implementing Regulation (EU) No 520/2012 the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has analysed and prioritised a signal of possibly permanent neurologic (vestibular) side effects with mefloquine (see PRAC Agenda under item 4.2.1.

https://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid-WCOb01ac05805a21cf).

Having considered the available evidence from the FDA communication the PRAC concluded that the current sections 4.4 and 4.8 of SmPC (PL accordingly) of mefloquine-containing medicinal products are not considered appropriate to inform about the possibility of persistent or permanent neurologic (vestibular) disorders.

Recommendation:

Therefore, the PRAC recommended that the Marketing Authorisation Holder (MAH) of Lariam®, innovator product for mefloquine, be requested to submit a cumulative review of neurologic (vestibular) disorders including a proposal for an update to the product Information taking into consideration the

FDA Drug Safety Communication, based on the requirements provided in Article 23(4) of Directive 2001/83/EC. The cumulative review should be submitted by 6 December 2013.

2.2. Marketing-authorisation holder's responses

Following PRAC's request, considering FDA's communication and the signal sent by BfArM to PRAC related to the possible permanent character of these events, the MAH is *submitting* two Drug Safety Reports (DSRs) which need to be reviewed in conjunction:

- Drug Safety Report (DSR) 1040001 (please refer to module 5.3.6); cumulative analysis till 06 May 2010, to analyse all medically confirmed SAEs of psychiatric disorders and nervous system disorders persisting for more than 90 days.
- Addendum DSR 1058255 (please refer to module 5.3.6), which is an addendum to the DSR 1040001, and provides*:

a) An analysis of all medically confirmed SAEs of psychiatric disorders and nervous system disorders persisting for more than 90 days reported between 07 May 2010 and 27 October 2013.

b) A cumulative review (till 27 October 2013) of all vestibular disorders persisting for more than 90 days.

- Based on the assessment in DSR 1040001, the MAH amended the Lariam Company Core Data Sheet (CDS, refer to module 5.4 for the current CDS V. 4.0) regarding the duration of neuropsychiatric disorders in the "Warnings and Precautions" section. The information that adverse reactions to Lariam may occur or persist up to several weeks after discontinuation of the drug and that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug was added. The analysis within the current addendum DSR 1058255 confirmed this outcome for most of the cases; however the persistence of events in a small proportion of patients may be possible.

- Based on the review provided in the addendum DSR 1058255, including case reports from the Roche Global Drug Safety Database ARISg, the MAH will amend the "Warnings and Precautions" section of the current Lariam CDS V. 4.0 (refer to module 5.4 for the current CDS v4) to include information on the persistence of certain neuropsychiatric events after discontinuation of the product.

Search strategy

Since the current DSR is an addendum to the DSR 1040001, prepared in 2010 (cut-off date of 06 May 2010), the same search criteria were applied (see Section 5, page 9 of DSR 1040001). Therefore, a multiaxial search in ARISg was conducted for cases with events in the SOC "Psychiatric Disorders" and SOC "Nervous System Disorders" reported between 07 May 2010 and 27 October 2013 (latest report coding completed). Due to multiaxiality, this search includes relevant terms from the SOC "Ear and Labyrinth Disorders".

However, a second search (cumulative, cut-off date of 27 October 2013) was carried out for the broad SMQ "Vestibular Disorders" (see Appendix 1 for a complete list of MedDRA PTs used in the search) and, for comprehensive reasons to search within the primary SOC, the PT "Tinnitus", reported in individuals who received mefloquine for malaria chemoprophylaxis, malaria treatment, stand-by treatment, or for an unknown indication.

These searches were carried out under the MedDRA version 16.0.

The following cases were excluded:

- Non-substantive follow-up cases
- Inactive cases
- Case reports including only non-serious events

The aim of the searches was to identify the cases conforming to any of the following event criteria groups:

- Group I

Based on the difference between AE Onset Date and AE Cessation Date, event duration was greater than or equal to 90 days.

- **Group II**

For events where AE Cessation Date is missing, based on the difference between AE Onset Date and AER Company Received Date, event duration was greater than or equal to 90 days, and the event outcome was one of the following:

- Fatal
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Recovering/resolving

- **Group III**

For events where the AE Cessation Date is missing, event duration was greater than or equal to 90 days (based on the difference between AE Onset Date and AER Received Date), and the event outcome was:

- Recovered/resolved

The selected events under SOC "Psychiatric Disorders" are presented in Section 6.1.1, and the events under SOC "Nervous System Disorders" in Section 6.2.1. Case reports with both types of SAEs are cross-referenced. The events under the SMQ "Vestibular Disorders" and the PT "Tinnitus", if not covered previously, are discussed in Section 6.3, and Section 6.4, respectively.

The SAEs from groups I, II, and III were analysed in the same way as for the DSR 1040001:

a) In the first step, all cases retrieved from ARISg were individually reviewed in order to determine whether mefloquine was used as treatment or chemoprophylaxis:

- Indication: Malaria chemoprophylaxis
- Indication: Malaria treatment
- Indication: Unknown

This distinction is important, considering that subjects taking mefloquine for malaria chemoprophylaxis are generally healthy, while patients with malaria may develop complications of the disease (e.g. coma, convulsions, liver impairment) or use co- medications (e.g. quinine) that often provide an alternative explanation in the case assessment.

b) In the second step, duration of the SAEs was manually reviewed, as the case selection was based on auto coding, which may not reflect case updates included in the narratives only. The following classification was applied:

- 1: SAE duration <90 days, or pre-existing to mefloquine exposure
- 2: SAE duration 90 days to 1 year
- 3: SAE duration 1 year to 2 years
- 4: SAE duration 2 to 3 years
- 5: SAE duration >3 years

- 6: SAE duration unknown

If the individual relevant SAEs in one case have a differing duration, the longest duration is taken for classification.

c) In the third step, all cases were individually reviewed and classified according to the following assessment criteria:

- Category A: Insufficient information for assessment, or controversial data
- Category B: Relevant medical history and/or confounding factors including e.g. co-medication present
- Category C: The relevant SAE occurred more than 6 months after mefloquine discontinuation
- Category D: No alternative Explanation found
- Category E: Case is out of scope of the review (mainly because of a duration of the relevant SAE of <90 days, or another drug clearly caused the SAE)
- Category F: Overdose

It should be noted that "disability" is marked as a seriousness criterion at the time the event is reported and does not necessarily reflect the final outcome of the event. All case narratives were manually reviewed to determine if there was any evidence of disability outcome reported.

Based on the various cornerstones for defining SAE duration and the different outcomes in a single patient with more than one SAE, a patient may be included in more than one group.

Below the drug safety reports by Roche, have been summarized.

N=whole number of case reports in the category

D=number of case reports under category D with a known duration

Category D = No alternative Explanation found

Summary of Drug Safety report 104001 part of the PSUR-Worksharing for mefloquine 001 (cumulative search: cut- off date May 2010)

(Only case reports from category D with a known duration are mentioned in the summaries)

A) SOC Psychiatric Disorder

Group I

1) Indication: Malaria Prophylaxis (N=37; D=8)

There were 37 patients in this group: of those patients one was out of the scope of this report as the duration of the relevant SAE was less than 90 days (██████████). In addition 12 patients with a relevant SAE duration of 90 days – 1 year from the 37 reports had only very limited information which did not allow for a causality assessment of the report, and 8 patients with a relevant history and/or other alternative explanations confounding their report will be excluded from discussion, while 6 patients are presented below as they had no explanation other than mefloquine for the occurrence of the relevant event. Likewise two further patients from group/category D with a SAE duration of 1 – 2 years are presented below, while a patient with insufficient information from category 3 is also excluded from the review.

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6
Category A	0	12	1	2	0	0
Category B	0	8	0	2	2	0
Category C	0	0	0	0	0	0
Category D	0	6	2	0	0	1
Category E	1	0	0	0	0	0
Category F	0	0	0	0	0	0

Result of case review: Category **A**: insuff/controversial data, **B**: alternative explanation, **C**: SAE occurred > 6 months after mefloquine discontinuation, **D**: no alternative explanation, **E**: out of scope of the review, **F**: overdose. Event persistence: Duration **1**: SAE < 90 d, **2**: SAE 90 d to 1 yr, **3**: SAE 1 yr to 2 yrs, **4**: SAE 2 to 3 yrs, **5**: SAE > 3 yrs, **6**: SAE duration unknown

██████████ (2D): An 18-year-old female patient with a BMI of 19.4, no relevant medical history, and no comedication took 250mg/day mefloquine malaria prophylaxis for three days, when she experienced hyperventilation, dizziness and anxiety with panic attacks, and then continued mefloquine once a week for another two weeks. She was treated with paroxetine and improved subsequently; the psychiatric events were reported to be resolved within 117 days.

██████████ (2D): a 27-year-old male patient with no relevant medical history nor on comedications, and with a BMI of 25.81 took 1x250mg/week mefloquine for 8 days. After the first day he experienced hypomania, then after the next mefloquine dose he became psychotic with mania and paranoia for which he was hospitalized and treated with haloperidol. After repatriation he had a recurrence of the symptoms and was rehospitalized and received depakote and venlafaxine. He recovered after a total duration of 265 days.

██████████ (2D): A 67-year-old female patient with no history of psychosis nor on

comedications received mefloquine 250mg/week (exact dates unknown) which was discontinued prior to her leaving for abroad. Some days later, she became very confused, and manifested psychotic features, and was hospitalized. She initially recovered within a few days, but psychosis and confusion recurred approximately 5 months later, and she was re-hospitalized, and recovered subsequently. Neurologic examinations were carried out which did not reveal dementia. This report is also included in Group I malaria prophylaxis: nervous system disorder events: SAE confusion, classified as 2D.

██████████ (2D): A 30-year-old male patient with no psychiatric history, taking a single dose of ibuprofen and of ketoprofen, respectively while on 1x250mg mefloquine/week for malaria prophylaxis experienced intermittent dyspnea, anxiety attacks, suicidal ideation, psychosis, palpitations, numbness of the head, confusion and muscle cramps for which he was hospitalized after taking 7 doses. After discontinuation of mefloquine the SAE: suicidal ideations resolved slowly over 6 months. This report is also included in Group II malaria prophylaxis: psychiatric system disorder events: SAE psychotic disorder, classified as 1E (Appendix 2), and Group II malaria prophylaxis: nervous system disorders, classified as 2A (Appendix 10).

██████████ (3D): A 23-year-old female patient with no psychiatric history was taking 1x250mg /week mefloquine for malaria prophylaxis for 9 months when she experienced psychosis, and depression. Comedication was a contraceptive. She was prescribed diazepam, mefloquine was maintained. Some eight months later she was repatriated, and discontinued mefloquine. Again three months later she was started on sertraline, she also took several antidepressants. Some weeks later, the symptoms had resolved, and sertraline was finally discontinued.

██████████ (2D): A 26-year-old female patient with no psychiatric history, and no comedication took 1x250mg mefloquine/week for malaria prophylaxis and experienced hypomania. She was treated with haloperidol. Some weeks later, mefloquine was discontinued, and she recovered six weeks later.

██████████ (2D): A 25-year-old male patient with a BMI of 22.9, no psychiatric nor abuse history and was not on any comedication took 1x250mg mefloquine/week for malaria prophylaxis. After completion the course of mefloquine (total dose: 1750mg) he slowly experienced increasing anxiety, persecutory delusions, and became overtly psychotic, he was hospitalized with paranoid psychosis, and he was treated with haloperidol and lorazepam which resulted in improvement of his symptoms. As he presented subsequently with extrapyramidal symptoms his medications was switched to risperidone. Some two weeks later the dose of risperidone was reduced, and he experienced euphoria. Risperidone dose was again increased and biperiden was added for treatment of the extrapyramidal symptoms. Eventually risperidone was replaced with olanzapine, and he presented with major depression for which he was treated with mirtazapine on an out-patient basis. Mefloquine level in serum was at that time below 20ng/ml. Seven months after start of psychosis the patient had completely recovered from all neuropsychiatric SAEs.

██████████ (3D): A 23-year-old male patient with no relevant history and no comedications was taking 1x250mg mefloquine/week for malaria prophylaxis. He experienced amnesia, but he consulted his general practitioner only after discontinuation of mefloquine about this problem. A CT scan, 24hr blood pressure monitoring, and blood tests were all normal. Some months later, he was treated with Ubidecarone which remained ongoing, and he slowly recovered. This report is also included in Group I malaria prophylaxis: nervous system disorder events: SAE amnesia, classified as 3D.

Comments: While all described psychiatric events are listed in the CDS. Following review of the narrative it is questionable whether the events are persisting for a period of more than 90 days. Two patients exhibiting psychotic episodes are reported to have

recovered initially after a short period of time, but then had a recurrence of the symptoms after a prolonged period of time (██████████). Likewise MCN (██████████) initially recovered from psychosis within approximately one month, but had later complications of extrapyramidal symptoms and depression, and made a final recovery only 7 months after his symptomatology of neuropsychiatric events had started.

2) Indication: Malaria treatment (N=3; D=0)

3) Indication unknown N=0

Group II

1) Indication: Malaria Prophylaxis (N=250; D=8)

There were 250 patients in this group: of those 57 patients were out of the scope of this report as the duration of the relevant SAE was less than 90 days. In addition 46 patients with a relevant SAE duration of 90 days – 1 year from the 250 reports had only very limited information which did not allow for a causality assessment of the report, and 23 patients with a relevant history and/or other alternative explanations confounding their report will be also excluded from discussion, while 7 patients are presented below as they had no explanation other than mefloquine for the occurrence of the relevant event. Likewise one further patient from group/category D with SAE duration of 2 – 3 years is presented below,....

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6
Category A	0	46	10	5	9	62
Category B	0	23	7	1	8	9
Category C	0	0	0	0	0	2
Category D	0	7	0	1	0	2
Category E	57	0	0	0	0	0
Category F	0	0	1	0	0	0

Result of case review: Category **A**: insuff/controversial data, **B**: alternative explanation, **C**: SAE occurred > 6 months after mefloquine discontinuation, **D**: no alternative explanation, **E**: out of scope of the review, **F**: overdose. Event persistence: Duration **1**: SAE < 90 d, **2**: SAE 90 d to 1 yr, **3**: SAE 1 yr to 2 yrs, **4**: SAE 2 to 3 yrs, **5**: SAE > 3 yrs, **6**: SAE duration unknown

(2D): A 47-year-old female patient with a BMI of 23.6, no relevant medical history (history of vertigo reported for which she received prochlorperazine) was treated with 250mg/week mefloquine for malaria prophylaxis which he had taken twice in the past with no adverse effects. Approximately 8 weeks after mefloquine had been discontinued she experienced severe anxiety for which she was treated with clomipramine, thioridazine, and propranolol. At last follow-up the SAE was persisting.

██████████ (2D): A 24-year-old female patient with a BMI of 18.5 with no relevant medical history nor comedications took 1x250mg mefloquine/week for malaria prophylaxis for a few weeks when she experienced severe panic attacks, dizziness and vertigo, headache, depression and anxiety. Mefloquine was discontinued, and she was treated with psychotherapy, naproxen, sumatriptan, which gave no relief. The patient had been hospitalized for the SAEs, and citalopram and alprazolam were given. Complete blood count and liver function tests were all normal. The mefloquine drug level was 0.31 mg/ml. A MRI brain scan was normal. The treatment with alprazolam was maintained and other unspecified treatment given. Six months later the SAEs were persisting. This report is also included in Group II malaria prophylaxis: nervous system disorder events: SAE vertigo, headache, classified as 2D.

██████████ (2D): A 42-year-old female patient with no relevant medical history and not taking comedications received mefloquine 1x250mg/week for malaria prophylaxis. She took in total two doses of mefloquine and experienced disabling difficulty writing, optic neuritis, blurred vision, a panic reaction, anxiety, nightmares, delusion, memory loss, neurologic symptoms, irrational thinking, depression, demyelination disorder, hemiparesis, dizziness, memory dysfunction, hair loss, nausea, diarrhea, bloating and abdominal cramps. After repatriation she took a third dose of mefloquine, and her condition deteriorated. Brain MRI was normal, and she was treated with cortical steroids, but contracted Herpes zoster in the right C3-C4 thereafter. Her symptoms improved with gabapentin as well as many other medications. At last follow-up her neurological symptoms gradually improved, but dizziness, memory loss and nightmares were persisting. The cause of her symptoms was unclear. This report is also included in Group II malaria prophylaxis: nervous system disorder events: SAE amnesia, classified as 2D.

██████████ (2D): A 47-year-old male patient with no psychiatric history, on atenolol for hypertension took 1x250mg mefloquine/week for malaria prophylaxis. After the second dose he experienced panic attacks with a feeling of confusion, mefloquine remained ongoing until the course was completed. Six months thereafter panic attacks were persisting, and he started treatment with clobazam. Paroxetine was then started and remained ongoing at last follow-up.

██████████ (2D): A 17-year-old female patient with a BMI of 18.4, on oral contraception, and with no psychiatric medical history, took 1x250mg/week mefloquine for malaria prophylaxis for approximately 7 weeks, then she experienced hallucinations due to which mefloquine was discontinued. One month later she had nightmares and flashbacks which were persistent and caused disability. Another month later she experienced depression and irritability. Treatment with risperidone, quetiapine and venlafaxine was started. Risperidone was discontinued, and one month later also quetiapine, while venlafaxine remained ongoing. At last follow-up tiredness, terrifying nightmares, flashbacks, depressive symptoms and irritability were persisting while the hallucinations had improved.

██████████ (2D): A male patient in his mid twenties with no relevant medical history (ex-soldier) experienced a panic disorder during the use of 1x250mg/week mefloquine for malaria prophylaxis while on vacation. Within 24 hours of taking the first dose he presented with weakness, gait disturbance, vertigo, fever, confusion, aggressiveness, lethargy, sweating and loss of appetite. One week later he also had severe anxiety with feeling of suffocation and insomnia which worsened progressively. He was hospitalized, all neurological and laboratory tests were normal. He was diagnosed with a panic state and received diazepam. He was repatriated. At that time his mefloquine level in serum was 200ng%. He was treated with clonazepam and fluoxetine. The events were persisting 9 weeks later, at last follow-up. This report is also included in Group II malaria prophylaxis: nervous system disorder events: SAE confusion, classified as 2D.

██████████ (2D): A 35-year-old female patient with a BMI of 20.6, no relevant medical history nor on comedication took 1x250mg/week mefloquine for malaria prophylaxis for four weeks. After the second dose she experienced gait disturbances which lasted three weeks, and also anxiety states. A week later she was briefly hospitalized for depression, sleep disorder, tachycardia, headache and nausea. Ten days later mefloquine was discontinued, neurological exams and CT were without pathological findings. Promethazine and metoclopramide was started, and approximately four months later she had fully recovered.

██████████ (4D): A 20-year-old female patient with a BMI of 18.4, no relevant medical history and on no comedication took 1x250mg/week mefloquine for malaria prophylaxis. Approximately one month later, she experienced some psychiatric problems. After further three months she took her last dose of mefloquine, and needed hospitalization for an acute psychotic reaction. She was then repatriated, and received unspecified psychopharmaca. The overt psychotic reaction resolved over time, but she remained in a subacute psychotic state which was waxing and waning. She received lithium which was replaced by thioridazine because of lack of effect. At the time of last report she had not recovered.

Comments: All relevant psychiatric disorder SAEs presented in this section are known to occur on occasions with mefloquine and are listed in the CDS. In addition because of the long half-life of mefloquine, adverse reactions may occur or persist up to several weeks after discontinuation of the drug.

2) Indication: Malaria (N=28; D=1)

...27 patients of the 28 patients in this group are not discussed in further detail as they fail the review criteria to focus on.

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6
Category A	0	3	1	0	0	6
Category B	0	3	1	1	0	4
Category C	0	0	0	0	0	0
Category D	0	1	0	0	0	0
Category E	8	0	0	0	0	0
Category F	0	0	0	0	0	0

Result of case review: Category **A**: insuff/controversial data, **B**: alternative explanation, **C**: SAE occurred > 6 months after mefloquine discontinuation, **D**: no alternative explanation, **E**: out of scope of the review, **F**: overdose. Event persistence: Duration **1**: SAE < 90 d, **2**: SAE 90 d to 1 yr, **3**: SAE 1 yr to 2 yrs, **4**: SAE 2 to 3 yrs, **5**: SAE > 3 yrs, **6**: SAE duration unknown

██████████ (2D): A 30-year-old male patient with no psychiatric medical

history had been overseas for 15 months and on malaria prophylaxis with chloroquine and proguanil when he experienced fever and headache. He was hospitalized and treated with quinine for 3 days in addition to 6 tablets mefloquine for suspected malaria tropica. While under this regimen he presented with psychotic symptoms, circulatory disturbances, vomiting and dizziness. He was repatriated and re-hospitalized. He was temporarily treated with thioridazine. The suspicion of malaria was not confirmed at the new hospital, nor was there any other tropical infections diagnosed. The psychiatrist considered a mefloquine-induced psychosis. He was then treated with imipramine and hydroxyzine. Two months later imipramine was reduced, and patient could return to work. This report is also included in Group II: malaria treatment: nervous system disorder SAES: dizziness, classified as 1E.

Comment: This is another report of CDS listed psychosis which resolved with appropriate treatment. In addition because of the long half-life of mefloquine, adverse reactions may occur or persist up to several weeks after discontinuation of the drug.

3) Indication: unknown (N=34; D=0)

Group III

1) Indication: malaria prophylaxis (N=19; D=0)

2) Indication: malaria treatment (N=0)

3) Indication: Unknown (N = 8; D=0)

B) Nervous System Disorders

Group I

1) Indication: Malaria Prophylaxis (N = 21; D=3 two of them are already included in Group I malaria prophylaxis: psychiatric events)

There were 21 patients in this group: of those three patients were out of the scope of this report as the duration of the relevant SAE was less than 90 days. In addition four patients with a relevant SAE duration of 90 days – 1 year from the 21 reports had only very limited information which did not allow for a causality assessment of the report, and 5 patients with a relevant history and/or other explanations confounding their report will be excluded from discussion, while 2 patients are presented below as they had no explanation other than mefloquine for the occurrence of the relevant event. Likewise one further patient from group D with a SAE duration of 1 – 2 years is presented below...

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6
Category A	0	4	1	2	0	1
Category B	0	5	0	2	0	0
Category C	0	0	0	0	0	0

Category D	0	2	1	0	0	0
Category E	3	0	0	0	0	0
Category F	0	0	0	0	0	0

Result of case review: Category **A**: insuff/controversial data, **B**: alternative explanation, **C**: SAE occurred > 6 months after mefloquine discontinuation, **D**: no alternative explanation, **E**: out of scope of the review, **F**: overdose. Event persistence: Duration **1**: SAE < 90 d, **2**: SAE 90 d to 1 yr, **3**: SAE 1 yr to 2 yrs, **4**: SAE 2 to 3 yrs, **5**: SAE > 3 yrs, **6**: SAE duration unknown

██████████ (2D): A 67-year-old female patient with no history of psychosis nor on comedications received mefloquine 250mg/week (exact dates unknown) which was discontinued prior to her leaving for abroad. Some days later she became very confused, and manifested psychotic features, and was hospitalized. She initially recovered within a few days, but psychosis and confusion recurred approximately 5 months later, and she was re-hospitalized, and recovered subsequently. Neurologic examinations were carried out which did not reveal dementia. This report is also included in Group I malaria prophylaxis: psychiatric events: SAE psychotic features, classified as 2D (Appendix 1).

██████████ (2D): A 40-year-old male patient was taking 1x250mg mefloquine/week for malaria prophylaxis. He had no relevant medical history nor was he taking any comedication. A few days after discontinuation of mefloquine he experienced dizziness, some days later, multidirectional nystagmus was observed, a brain MRI was normal. He then experienced headache, balance difficulties and memory disturbances. When his condition deteriorated he was hospitalized. Brainstem evoked responses were normal as was a spinal fluid exam. Nystagmus resolved after about 6 weeks. Except for headache and dizziness the patient had recovered approximately a further 3 months later.

██████████ (3D): ██████████ (3D): A 23-year-old male patient with no relevant history and no comedications was taking 1x250mg mefloquine/week for malaria prophylaxis. He experienced amnesia, but only after discontinuation of mefloquine he consulted his general practitioner about this problem. A CT scan, 24hr blood pressure monitoring, and blood tests (NOS) were all normal. Some months later he was treated with Ubidecarone which remained ongoing, and he slowly recovered. This report is also included in Group I malaria prophylaxis: psychiatric system disorder events: SAE amnesia, classified as 3D.

Comment: While all nervous system disorder events are listed in the CDS, it is also specifically mentioned: "Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist up to several weeks 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."

2) Indication: Malaria Treatment (N = 3; D=0)

3) Indication: unknown (N=0)

Group II

1) Indication: Malaria prophylaxis (N=225; D=4) two of the cases are already included in Group II malaria prophylaxis: psychiatric events)

...

Four patients from category 2 are presented below as they had no explanation other than mefloquine for the occurrence of the relevant event....

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6
Category A	0	46	4	3	7	48
Category B	2	15	6	4	10	20
Category C	2	2	2	0	1	2
Category D	0	4	0	0	0	1
Category E	45	0	0	0	0	0
Category F	0	0	1	0	0	0

Result of case review: Category **A**: insuff/controversial data, **B**: alternative explanation, **C**: SAE occurred > 6 months after mefloquine discontinuation, **D**: no alternative explanation, **E**: out of scope of the review, **F**: overdose. Event persistence: Duration **1**: SAE < 90 d, **2**: SAE 90 d to 1 yr, **3**: SAE 1 yr to 2 yrs, **4**: SAE 2 to 3 yrs, **5**: SAE > 3 yrs, **6**: SAE duration unknown

██████████ (2D): A 24-year-old female patient with a BMI of 18.5 with no relevant medical history nor on comedications took 1x250mg mefloquine/week for malaria prophylaxis for a few weeks when she experienced severe panic attacks, dizziness and vertigo, headache, depression and anxiety. Mefloquine was discontinued, and she was treated with psychotherapy, naproxen, sumatriptan, which gave no relief. The patient had been hospitalized for the SAEs, and citalopram and alprazolam was given. Complete blood count and liver function tests were all normal. The mefloquine drug level was 0.31 mg/ml. A MRI brain scan was normal. The treatment with alprazolam was maintained, and other unspecified treatment given. Six months later the SAEs were persisting. This report is also included in Group II malaria prophylaxis: psychiatric system disorder events: SAEs panic attacks, anxiety, and depression, classified as 2D (Appendix 3).

██████████ (2D): A 42-year-old female patient with no relevant medical history and not taking comedications received mefloquine 1x250mg/week for malaria prophylaxis. She took in total two doses and presented with disabling difficulty writing, optic neuritis, blurred vision, a panic reaction, anxiety, nightmares, delusion, memory loss, neurologic symptoms, irrational thinking, depression, demyelination disorder, hemiparesis, dizziness, memory dysfunction, hair loss, nausea, diarrhea, bloating and abdominal cramps. After repatriation she took a third dose of mefloquine, and her condition deteriorated. Brain MRI was normal, and she was treated with cortical steroids, but contracted Herpes zoster in the right C3-C4 thereafter. Her symptoms improved with gabapentin as well as many other medications. At last follow-up her neurological symptoms gradually improved, but dizziness, memory loss and nightmares were persisting. The cause of her symptoms were unclear several theories from mefloquine toxicity to demyelination disorder were discussed. This report is also included in Group II malaria prophylaxis: psychiatric system disorder events: SAE nightmare, classified as 2D (Appendix 3).

██████████ (2D): A male patient in his mid twenties with no relevant medical history presented with a panic disorder during the use of 1x250mg/week mefloquine for malaria prophylaxis. Within 24 hours of taking the first dose he experienced weakness, gait disturbance, vertigo, fever, confusion, aggressiveness, lethargy, sweating and loss of appetite. One week later he also had severe anxiety with feeling of suffocation and insomnia which worsened progressively. He was hospitalized, all neurological and laboratory tests were normal. He was diagnosed with a panic state and received diazepam. He was repatriated. At that time his mefloquine level in serum was 200ng%. He was treated with clonazepam and fluoxetine. The events were persisting 9 weeks later, at last follow-up. This report is also included in Group II malaria prophylaxis: psychiatric system disorder events: SAE confusion, aggressiveness, panic state, classified as 2D (Appendix 3).

██████████ (2D): A 57-year-old male patient with a BMI of 27.7 and no relevant medical history took 1x250mg mefloquine /week for malaria prophylaxis. Approximately six weeks later he had hypesthesia of the thigh. Mefloquine was discontinued 5 weeks later as planned. Three months later, hypesthesia worsened and extended to the left knee causing slight paresis of the leg. Left-sided mononeuropathy (pt peripheral neuropathy) was diagnosed subsequent to various investigations, and treatment of cytidylic acid/hydroxycobalamin was started. Further six weeks later the symptoms persisted.

Comments: All relevant nervous system disorder SAEs presented above are listed in the CDS, and because of the long half-life it is also mentioned that adverse reactions to mefloquine may occur or persist up to several weeks after discontinuation of the drug.

2) Indication: Malaria treatment N=21; D=0

3) Indication: unknown N=21; D=1

██████████ (2D): A 37-years-old female patient with no relevant medical history, no comedication took mefloquine for approximately 2 months, after six weeks upon her return home she experienced a static cerebellar ataxic syndrome and was hospitalized. A lumbar puncture, EMG and an MRI of the brain and spinal cord were normal. No inflammatory syndrome was noted. Two weeks after onset of the events, mefloquine treatment was discontinued. A gradual favourable outcome was reported. The events of ataxia and cerebellar syndrome improved. Consultation six months after onset of the events revealed the patient still had a mild ataxic syndrome of the lower extremities.

Group III

1) Indication: Malaria Prophylaxis (N=16; D=0)

....

In addition none of the remaining patients in Group III: malaria prophylaxis qualified for detailed discussion as they failed the review criteria to focus on....

2) Indication: Malaria Treatment (N=1; D=0)

3) Indication: unknown (N=4; D=0)

MAH - Discussion and Conclusion of Drug Safety report 104001

The review of the safety data from Roche's Global Safety Database ADVENT yielded a total of 369 patients reporting 623 medically confirmed psychiatric disorders SAEs, and 309 patients with 436 medically confirmed nervous system disorders SAEs which were selected as described in section 5.2.1 search and selection strategy. These reports are

included in a tabular format in Appendices 1 – 15, according to the reported indication and the selection strategy criteria. All cases have been commented on individually.

According to the search and selection strategy the relevant SAEs, all of them were supposedly having a duration of ≥ 90 days. In a first step the case reports were then manually reviewed to verify the actual SAE duration, as reported in the narrative and in all report updates. This led to a significant reduction of the number of the reports as is shown in the overall tables presented below. Of all reports included in the psychiatric system disorder group 73 reports had a SAE duration of less than 90 days, as did 70 reports in the nervous system disorder group. In a second step reports with insufficient information were excluded (190/146) as were reports with relevant medical histories, confounding factors, and/or alternative explanations (82/75), with mefloquine overdoses (2/1) and with pre-existing events (3/13). Thus the focus of this report was directed at patients without a relevant medical history (reported as such), not receiving comedications which might impact on SAE duration, receiving appropriate doses of mefloquine according to the indication, and displaying a SAE duration of ≥ 90 days, which left 17 patients with psychiatric system disorder SAEs, and 8 patients with nervous system disorder SAEs, respectively which had a duration of more than 90 days. By this method 25 cases were identified which were described in detail, and of which some patients presented with both, psychiatric and nervous system disorder SAEs. It may be important to mention that a total of 1073 patients with 1977 psychiatric system disorder adverse events, and a total of 1022 patients with 1699 nervous system disorder adverse associated with the use of mefloquine are stored in the Roche Global Drug Safety database ADVENT and that only 25 of these reports include SAEs with a duration of more than 90 days in patients who used mefloquine as prescribed, had no relevant medical history or alternative explanations, and were not taking comedications; and only four of these 25 cases presented with a duration of more than one year.

It must be borne in mind that this analysis is mainly based on spontaneous reports (673), whereas only 5 reports originated from studies. Thus, even with fairly detailed information received on the individual patients, factors such as social environment, personal circumstances, wrongly reported medical history, omitted comedications cannot be excluded. In addition the reporter who provided the case reports to the MAH may not always have been the physician treating the patient in the first place. This is also evidenced by the fact that only one report of a nervous system disorder SAE has been obtained from a country with potential malaria infections, and this report originated from a clinical trial. Some of the reports were also submitted by the reporter months if not years after the relevant SAEs occurred, thus some relevant case details may have been missed. The events were reported after the return from a trip and therefore retrospectively.

Nevertheless it may be concluded from this review that the observed relevant psychiatric and nervous system disorder SAEs of group D (no alternative explanation) patients are listed in the CDS, and as also specified in the CDS that they may persist for a prolonged period of time after discontinuation of mefloquine. In some of the cases it remains unclear whether other unreported factors contributed to the recurrence or persistence of the events.

Patients with a history of depression, psychosis or other major psychiatric disorders seem to be at particular risk of developing psychiatric AEs.

MAH - CONCLUSION:

Based on the review of reports from Roche Global Drug Safety Database ADVENT MAH decided to update the CDS and upgrade the information about the occurrence of neuropsychiatric disorders into the Warnings/Precautions section of CDS. As a further risk mitigation, the contraindication section will be updated not to allow mefloquine prophylaxis in patients with a history of depression and the other major psychiatric disorders.

Assessor's comments:

This DSR report describes 17 case reports of Psychiatric Disorders in category D 2; 3 and 4 (cases without an alternative explanation and a known duration).

Furthermore three additional reports of Nervous System Disorders were reported in category D2 and 3. Patients who were already presented under the SOC psychiatric disorders are not double calculated.

Additionally four other cases () have to be assigned to this group.

Most of the 24 cases (20) had a duration between 90 days and 1 year (in 7 cases the SAE resolved; and in 13 cases the SAE were still ongoing at the last follow up). In four cases the events had a duration over a year (in one case the patient recovered within this time; in another case the SAE slowly resolved during this period, in one case the symptoms were persisting over a time of 2 to 3 years and one patient recovered over a time of 2 to 3 years).

Therefore the discussion of this DSR in the finalized worksharing procedure 001 for mefloquine resulted in an update for the product-information of Lariam.

4.4 warnings

"Due to the long half-life of mefloquine, adverse reactions may occur and persist up to several months after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance continued for months after discontinuation of the drug."

Drug Safety Report 105825507

(06 May 2010 until 27 October 2013)

A) SOC Psychiatric Disorder**Group I (N=0)****Group II****1) Indication: Malaria Chemoprophylaxis (N=14; D=3)**

Of the 14 cases, three cases (AERs) were substantive follow-up reports of cases included in DSR 1040001. None of the follow-up reports included new events fulfilling the inclusion criteria of the current analysis (see Section 4.1.2). Relevant new information was received in a follow-up report of AER , which reported a negative psychiatric history, temporal relationship of event onset with mefloquine therapy, and a long-lasting disability (after 3 years the patient was not able to work full-time). Accordingly this case has been reclassified from category B to D.

Of the 11 initial cases, five cases provided information that allowed further evaluation of the event duration. In three of these cases (AERs) no risk/contributory factors were identified (category D). One case included insufficient information for a causality assessment (category A), but concluded that sleep disorder was persisting (AER). In one case (AER) the patient had a history of major psychiatric disorders, but the persistence of the event was medically confirmed.

The narratives of these cases are presented below. The remaining cases (AERs [REDACTED], [REDACTED] and [REDACTED], [REDACTED], [REDACTED], [REDACTED]) did not provide sufficient information for the assessment of the event duration.

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6 or n/a*
Category A	0	0	1	1	1	0
Category B	0	0	1	0	1	0
Category C	0	0	0	0	0	0
Category D	0	0	1	0	2	0
Category E	1	0	0	0	0	2
Category F	0	0	0	0	0	0

Result of case review: **Category A:** insufficient/controversial data, **B:** alternative explanation, **C:** SAE occurred > 6 months after mefloquine discontinuation, **D:** no alternative explanation, **E:** out of scope of the review, **F:** overdose. Event persistence: Category for SAE duration - **1:** SAE < 90 d, **2:** SAE 90 d to 1 yr, **3:** SAE 1 yr to 2 yrs, **4:** SAE 2 to 3 yrs, **5:** SAE > 3 yrs, **6:** SAE duration unknown or *n/a [not applicable (for suicide cases where onset date is the date of suicide)]

[REDACTED]: Major Depression

This spontaneous case concerns a 60-year-old female patient who received mefloquine (250 mg/week) for malaria chemoprophylaxis. She had no psychiatric medical history. Past treatment included doxycycline. No concomitant drugs were reported. She experienced insomnia and low mood about three weeks after start of mefloquine, and depression approximately three months after mefloquine discontinuation. Approximately a month thereafter, she experienced deterioration to psychotic depression, anxiety and was hospitalized due to agitation and paranoia. She was treated with risperidone, mirtazapine, and lorazepam. About four years after onset of the event, it was reported that the patient had not been the same since use of mefloquine. However, in the followup information received in [REDACTED], psychotic depression had improved, suggesting an SAE duration of more than three years.

[REDACTED]: Psychotic disorder, Self injurious behavior

This spontaneous case (reported by a health authority) concerns a 20-year-old male patient who received mefloquine (250 mg/week) for malaria chemoprophylaxis (started on an unspecified date in [REDACTED]). He had a medical history of childhood asthma, and high blood pressure. No concomitant or past drugs were reported. An unspecified time after starting mefloquine, he experienced vivid dreams and anxiety. Reportedly, he was on mefloquine for nine months and experienced events during respectively four weeks after therapy. A small amount of alcohol caused significant effects with regard to hallucination and disorientation. An unspecified time thereafter, he was hospitalized for dehydration and had two episodes of self-harm (PT-self injurious behavior). An unspecified time thereafter, mefloquine was discontinued for an unspecified reason. Approximately a month after mefloquine discontinuation, he experienced psychotic behavior. He was treated with escitalopram and zolpidem. At the time of reporting ([REDACTED]), the events of psychotic disorder, self injurious behavior, anxiety and vivid dreams were persisting.

[REDACTED]: Delirium, Agitation, Aggression, Suicide attempt

This spontaneous case (reported by a health authority) concerns a 45-year-old male patient who received mefloquine for malaria chemoprophylaxis. He had medical history of mesencephalic cerebrovascular accident (CVA) and parinaud syndrome (diagnosed

five years before mefloquine use). Concomitant medications included aspirin dL-lysine and simvastatin. He was hospitalized due to acute delirious episode (PT-delirium), agitation, aggressiveness (PT-aggression) and suicidal attempt approximately ten weeks after starting mefloquine on a business trip to [REDACTED]. The patient did not have any past psychiatric history and did not take any anti-psychotic, antidepressant or any other CNS drug. The events resolved with sequelae about one month after onset. Sequelae were not specified. Follow-up information about one year later did not provide new information on the outcome.

MAH comment: Most of the relevant psychiatric disorder SAEs reported in the cases assigned to category D are known to occur with mefloquine and are listed in the current Lariam CDS V. 4.0 [2]. Self-injurious behavior and suicide attempt are not listed but for these events the provided information is limited and the duration is questionable ("two episodes", "an attempt to jump out of the window"). Of note is the positive CVA of the patient in case AER [REDACTED]. This case is also included in Section 6.2.1.2.2.1 (Nervous system disorders is the primary SOC for agitation). Based on the calculation applied to this group events or sequelae of events persisted from about one to >3 years and in one case long-lasting impairment of the patient is confirmed by the reporter.

2) Indication: Malaria Treatment (N=1; D=1)

One case (AER [REDACTED]) was identified in this group. This patient experienced depression, which was resolving 92 days after event onset. No alternative explanations for the occurrence of the relevant psychiatric disorder were identified (category D 2). This case is briefly reviewed below.

[REDACTED]: Depression

This spontaneous case concerns a 38-year-old female patient who experienced depression seven weeks after starting and a week after the most recent dose of mefloquine (250 mg/week). Mefloquine was discontinued and she was treated with citalopram. The event of depression was resolving at the time of reporting. The patient did not have a history of psychiatric treatment, alcohol/substance abuse, suicidal ideation or suicide attempts and family history of suicide, or any recent losses, emotional upsets or legal trouble.

MAH comment: Given the reported dose, the indication is suggestive of chemoprophylaxis, rather than treatment. However, depression is a listed event in the current Lariam CDS V. 4.0 [2]. In this case the patient was on mefloquine for about seven weeks and for the event duration of about three months (after discontinuation), the long half-life of mefloquine should be considered.

3) Indication: Unknown (N=1; D=1)

One case (AER [REDACTED]) was identified in this group. This patient experienced an SAE duration of about five months⁴ and no alternative explanations for the occurrence of anxiety and panic disorder were identified (category D 2). This case is briefly discussed below.

[REDACTED]: Anxiety, Panic disorder, Dizziness, hypoaesthesia

This spontaneous case concerns a 20-year-old male patient who received mefloquine for an unknown indication. Approximately two weeks after the first dose, he received a second dose of mefloquine (reported as [REDACTED]) and visited [REDACTED] on [REDACTED]. Approximately two weeks thereafter (end of [REDACTED]), he experienced anxiety along with nervous system disorder AEs (dizziness and episodic feeling of numbness). Mefloquine was discontinued on [REDACTED] and doxycycline was started. An unspecified time after mefloquine discontinuation, he

experienced episodic panic disorder-type symptoms (PT-panic disorder). Reportedly, the events started upon traveling to India while he was on mefloquine and were triggered by enclosed spaces, and also after returning home by other exciting occasions. He had not experienced similar symptoms or any psychiatric symptoms in the past.

MAH comment: Given the frequency of mefloquine use and patient's traveling, the indication is suggestive of chemoprophylaxis. However, anxiety and panic attacks are listed events in the current Lariam CDS V. 4.0 [2]. The information provided points to a duration of more than four months; however, medical confirmation is limited to a few symptoms. This case has also been discussed in Section 6.2.1.2.2.3.

Group III

1) Indication: Malaria Chemoprophylaxis (N=9: D=1)

Of the nine cases, two cases provide information that allowed further evaluation of the event duration. In one of the nine cases (AER [REDACTED]) the patient experienced depression and suicidal ideation with a calculated duration of around 3.5 months and no alternative explanations were identified for the events (category D). In one case (AER [REDACTED]), the duration of psychiatric therapy suggested a long duration of events; however, this case had insufficient information for causality assessment (category A). The narratives of these cases are presented below.

The remaining cases (AERs [REDACTED] (a follow-up report), [REDACTED], [REDACTED] did not provide sufficient information for an assessment of the event duration.

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6
Category A	0	3	2	0	0	0
Category B	0	1	0	0	0	0
Category C	0	0	0	0	0	0
Category D	0	1	0	0	0	0
Category E	1	0	0	0	0	0
Category F	0	0	0	0	0	0

Result of case review: **Category A:** insufficient/controversial data, **B:** alternative explanation, **C:** SAE occurred > 6 months after mefloquine discontinuation, **D:** no alternative explanation, **E:** out of scope of the review, **F:** overdose. Event persistence: Category for SAE duration- **1:** SAE < 90 d, **2:** SAE 90 d to 1 yr, **3:** SAE 1 yr to 2 yrs, **4:** SAE 2 to 3 yrs, **5:** SAE > 3 yrs, **6:** SAE duration unknown

[REDACTED]: Suicidal ideation, Depression

This spontaneous case (reported by a health authority) concerns a 37-year-old female patient who received mefloquine for malaria chemoprophylaxis for an unknown duration. No concomitant or past drugs were reported. She did not have a medical history of any psychiatric disorder. Approximately five weeks after starting mefloquine, she developed depression and suicidal ideation (reported as "she wanted to throw herself in front of the metro") while on mefloquine. An unspecified time thereafter, mefloquine was discontinued and at the time of reporting (about three months after onset), the events resolved.

MAH comment: Depression is a listed event in the current Lariam CDS V. 4.0 [2]. In this case, the patient was on mefloquine for about seven weeks. For the event duration of approximately 3.5 months (after discontinuation), the long half-life of mefloquine should

be considered.

2) Indication: Malaria Treatment (N=0)

3) Indication: Unknown (N=1; D=0)

Summary table of case reports of psychiatric disorders

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6 or n/a*	Total
Category A	0	4	3	1	1	0	9
Category B	0	1	1	0	1	0	3
Category C	0	0	0	0	0	0	0
Category D	0	3	1	0	2	0	6
Category E	1 ⁹	0	0	0	0	2	3
Category F	0	0	0	0	0	0	0
Total	1	8	5	1	4	2	21

Result of case review: **Category A:** insufficient/controversial data, **B:** alternative explanation, **C:** SAE occurred > 6 months after mefloquine discontinuation, **D:** no alternative explanation, **E:** out of scope of the review, **F:** overdose. Event persistence: Category for SAE duration - **1:** SAE < 90 d, **2:** SAE 90 d to 1 yr, **3:** SAE 1 yr to 2 yrs, **4:** SAE 2 to 3 yrs, **5:** SAE > 3 yrs, **6:** SAE duration unknown or *n/a [not applicable (for suicide cases where onset date is the date of suicide)]

B) SOC "NERVOUS SYSTEM DISORDERS

A total of 17 cases reporting 24 SAEs were retrieved under the "nervous system disorder" SOC. Of the 17 cases, two cases (five SAEs) were substantive follow-up cases and 15 cases (19 SAEs) were initial case reports. A tabular overview of these initial and follow-up cases is presented below.

Of the 19 SAEs, the latency from first dose was reported as '0-6 days' for nine SAEs (n=9); '1-4 weeks' for four SAEs (n=4); '>1 year' for two SAEs (n=2); '1-3 months' for one SAE and '4-12 months' for one SAE. The latency from first dose was unknown for two SAEs (n=2).

The outcome of the 19 SAEs was reported as: 'recovering/resolving' for six SAEs (n=6); 'not recovered/not resolved' for six SAEs (n=6); 'recovered/resolved' for five SAEs (n=5) and 'recovered/resolved with sequelae' for two SAEs (n=2).

Group I (N=0)

Group II

1) Indication: Malaria Chemoprophylaxis (N=8; D=2)

A total of eight cases were identified in this group. Of the eight cases, six cases were initial cases and two cases (AERs ██████████) were substantive follow-up cases included in DSR 1040001. Both cases reported neurologic and psychiatric events and were also discussed in Section 6.1.1.2.2.1. However, relevant new information was received in the follow-up report of case AER ██████████ only.

██████████: Dizziness, Hyperaesthesia

This spontaneous case concerns a 28-year-old female patient (BMI: 21.2) who received mefloquine (250 mg/week) for chemoprophylaxis of malaria. No concomitant drugs were reported. The patient did not have any medical history of psychiatric problems and was physically and mentally healthy. She experienced dizziness and hyperesthesia (as well as psychiatric events), which commenced at the start of mefloquine therapy. On an unspecified date, dizziness and hyperesthesia resolved with sequelae. Three years after discontinuation of mefloquine therapy, the patient was still not able to work full-time.

MAH comment: Based on the new information (negative psychiatric history and patient was unable to work full-time for approximately three years after the event onset), this case has been reclassified from category B to D. The psychiatric events of this case are included and discussed in Section 6.1.1.2.2.1.

Of the six initial cases, one patient (AER [REDACTED]) experienced SAEs with a duration of more than 90 days and no identified risk factors (category D). The event of interest in this case is agitation, which is a secondary PT in the SOC "Psychiatric Disorders".... (The psychiatric events of this case were also discussed above.)

The remaining cases (AERs [REDACTED]) did not provide sufficient information for the assessment of the event duration. Of the remaining cases, one patient (AER [REDACTED]) experienced Parkinson's disease approximately two years after an overdose of mefloquine (category C and category F).

2) Indication: Malaria Treatment (N=2; D=0)

3) Indication: Unknown (N=2; D=1)

Two cases were identified in this group. One of these two cases (AER [REDACTED]) had possible risk/contributory factors for the events (category B; underlying thymoma and positive acetylcholine receptor antibodies, suggesting autoimmune etiology of myasthenia gravis for the event of muscular weakness). In the other case (AER [REDACTED]), the patient experienced an SAE duration of more than 90 days and no risk factors were identified for the SAEs (category D).

(The psychiatric events of this case were also discussed above.)

Group III

1) Indication: Malaria Chemoprophylaxis (N=3; D=0)

2) Indication: Malaria Treatment (N=0)

3) Indication: unknown (N=2; D=1)

Two cases were identified in this group. In one of the two cases (AER [REDACTED]) the patient received an accidental overdose of mefloquine and experienced generalized convulsions (PT-convulsions) with inhalation stop and cardiorespiratory stop for a few seconds, which was recovered after aspiration. This information points to a short duration of the events including convulsion after overdose (category F). In the other case (AER [REDACTED]) the patient experienced vertigo and no alternative explanations were provided. A short narrative of this case is presented below.

[REDACTED]: Vertigo

This spontaneous case (reported by a health authority) concerns a 50-year-old female patient who received mefloquine for an unknown indication. She had medical history of ophthalmic migraine. Concomitant medications included acetylcellulose. Past drugs included Seglar and propranolol hydrochloride. One day prior to starting mefloquine, the patient experienced unspecified infectious syndrome with fever (39°C) and started mefloquine at a dose of 6 dose forms a day and on the same day experienced vertigo.

Mefloquine was discontinued on the same day. Four days after onset, the patient was no longer febrile, but vertigo persisted. Later (date not specified), the event resolved.

MAH comment: Given the dose of mefloquine the indication is suggestive of malaria treatment. Although the medical history of ophthalmic migraine and underlying influenza (confirmed by laboratory investigation) need to be considered risk factors, persistence of vertigo in an afebrile patient and short drug-event latency suggests a possible role of mefloquine used at therapeutic dose. Vertigo, including persistence for months, is listed in the current Lariam CDS V. 4.0 [2]. In this case the patient received a high dose and for the calculated event duration of maximal 4.5 months, the long half-life of mefloquine should be considered.

Summary table of case reports of nervous system disorder (2 cases of category D are already mentioned under the SOC psychiatric disorder)

	Duration 1	Duration 2	Duration 3	Duration 4	Duration 5	Duration 6	Total
Category A	0	2	1	1	1	0	5
Category B	0	2	0	0	1	0	3
Category C	0	0	2	0	0	0	2
Category D	0	2	1	0	0	0	3
Category E	1	0	0	0	0	0	1
Category F	0	1	0	0	0	0	1
Total	1	7	4	1	2	0	15

Result of case review: Group **A**: insufficient/controversial data, **B**: alternative explanation, **C**: SAE occurred > 6 months after mefloquine discontinuation, **D**: no alternative explanation, **E**: out of scope of the review, **F**: overdose. Event persistence: Category **1**: SAE < 90 d, **2**: SAE 90 d to 1 yr, **3**: SAE 1 yr to 2 yrs, **4**: SAE 2 to 3 yrs, **5**: SAE > 3 yrs, **6**: SAE duration unknown

Assessor's comments:

The second drug safety report regarding long lasting neuropsychiatric adverse reactions with the period May 2010 until 27 October 2013 describes six cases of psychiatric disorders in category D and one additional case of nervous system disorder in category D. Patients who were already presented under the SOC psychiatric disorders are not double calculated.

In four cases the symptoms had a duration between 90 days to 1 year; two cases were reported with continuance of 2 to 3 years and one case with a duration over 3 years.

Additionally one follow up with relevant new information was received during this period. The case AER [REDACTED] from the former DSR has been reclassified from category B to D. As a result the number of category D cases of DSR 104001 has increased to 25 reports. Additionally the number of cases presented with duration of more than one year increased in this analysis from four to five cases.

The DSR 104001 (period 1984 until 6 of May 2010) with an exposure of over 34 Mio patients presented 25 category D case reports of long lasting neuropsychiatric adverse reactions (without double calculations). In contrast seven category D case reports of long lasting

neuropsychiatric adverse reactions (without double calculations) were submitted with the three-year DSR 105825507 and an exposure of over 3 Mio patients. Considering the intensive increase of category D cases in comparison with the former DSR especially regarding reports with duration over two years and the data presented in the FDA assessment, an update of product-information to include permanent/persistent neuropsychiatric adverse events is required.

SMQ "VESTIBULAR DISORDERS"

(Cumulative search: cut- off date 27 October 2013)

A total of 88 cases (95 SAEs) were retrieved. The most frequently reported SAEs (PT) were dizziness (58 SAEs), vertigo (21 SAEs), and balance disorder (14 SAEs). Of the 88 cases, 86 were spontaneous reports, and the remaining 2 were literature reports.

Overall six of the 88 cases were classified in Category D (DSR 104001: [REDACTED], [REDACTED], [REDACTED], DSR 105825507: [REDACTED], and [REDACTED]; Case [REDACTED]: see below)

Group I (N=0)

Group II (N=3; D=1)

A total of three cases were identified in this group (AERs [REDACTED]). In two cases, the indication was malaria chemoprophylaxis (AERs [REDACTED]); while in the remaining case (AER [REDACTED]), the indication was unknown.

Two of these cases were classified as Category E since the duration of events was reported to last less than 90 days. In one of these two cases (AER [REDACTED]), the relevant SAE (PT: vertigo) resolved after 4 weeks. In the other case (AER [REDACTED]), the relevant SAE (PT: vertigo) resolved after 1 day. In the remaining case (AER [REDACTED]), the event duration was 611 days. This case was classified as category D. A narrative of this case is presented below.

AER [REDACTED]: Dizziness

This spontaneous case was reported by a health care professional, and concerns a 43-year-old female who took mefloquine for malaria chemoprophylaxis. No medical history or previous medications were reported. No concurrent medications or conditions were reported. Mefloquine (250 mg/week p.o.) was started. The patient experienced dizziness, agitation, and insomnia. The latency of these events was reported as <12 hours. Mefloquine was discontinued 3.5 weeks later. At the time of reporting, the events were described as improving but persisting.

MAH comment: Dizziness is a listed event in the current Lariam CDS V. 4.0 [2]. Limited information is provided e.g. regarding the event cessation date. However, no alternative explanations were identified and the SAE duration was calculated to be 1.7 years.

Group III (N=0)

Assessor's comments:

DSR104001 and 105825507 describe together 6 case reports of vestibular disorder in category D – 3 in the old one and three in the newer report. For one report the duration is unknown due to limited information. In four cases the duration of symptoms was reported between 90 days to 1 year. Only one case was submitted with duration over 1.7 years. Five of the presented cases are already discussed in section A) psychiatric disorder or B) nervous system disorder. The intensive increase of category D case reports during the last DSR-period can also be observed in this SMQ.

PT "TINNITUS"

(Cumulative search: cut- off date 27 October 2013)

A total of 16 cases (16 SAEs) were retrieved under the PT "Tinnitus".
Of all 16 cases, none was classified in Category D.

Assessor's comments:

For the PT-Term "Tinnitus" no case reports are classified under the category D – cases with no alternative explanation. Nevertheless this adverse reaction is already labelled in section 4.8 of the SPC.

EVIDENCE FROM LITERATURE REGARDING THE DRUGEVENT ASSOCIATION

A total of 537 literature articles were retrieved from the cumulative search as described in Section 5. Of those, one literature case report was found to be relevant for the current addendum DSR and is summarized below.

This literature case report, reported by Nevin [4], concerns a previously healthy 24-yearold male patient, with no relevant medical history, no drug allergies, no history of mental health disorder, use of psychotropic medication, or head injury. After joining an army group in Spain from his home in the United States, he had been directed to take generic mefloquine for chemoprophylaxis under supervision while he remained on standby for short notice travel to Africa. Reportedly, within 12 hours of taking first 250 mg dose of mefloquine, he experienced unease, anxiety, and foreboding, which increased over the next two days. By the third day he experienced "intermittent mumbling auditory hallucinations" and a sense of the "presence of a nearby nondescript female". Shortly after the second dose, he was noted to be paranoid, distant and confused, with a markedly changed personality. Soon after the third dose, he became troubled by the onset of impairment in short-term spatial and working memory, as well as tinnitus, palpitations, and an intermittent lateral "wavy" vertigo which worsened after his fourth dose. Vertigo evolved to include a sensation of intermittent rotation. Two weeks after discontinuing mefloquine, the patient complained of persistent auditory hallucinations, and described his state as "delirious" and "confused", with a "loss of sensation", which he described as "no emotions and no intellectual stimulation". He complained of being "restless", obtaining less than four hours of sleep per night, suffering "memory loss, personality change, and irritable mood" and of being "angry" and "aggressive". Over subsequent weeks and months these psychiatric symptoms and his sleep disturbances gradually decreased in frequency and severity, and his physical symptoms including palpitations, tinnitus, vertigo and disequilibrium became relatively more prominent. Vestibular testing (videonystagmography, optokinetic testing, motor control test, saccades, and pursuits) were grossly normal. Right-sided vestibular evoked myogenic potentials were enhanced relative to the left. Computerized dynamic posturography revealed a pattern of global dysfunction with falls during sensory organization tests 5 and 6 that were considered aphysiologic. Approximately six months after symptom onset the patient's hallucinations had fully resolved, but he reported continued deficits in short-term spatial and working memory with rare episodes of spatial disorientation described as "dizzy" spells, with episodes of tinnitus, vertigo and severe disequilibrium occurring approximately every day to every other day without a clearly identifiable cause, frequently heralded by frontal headache, and occasionally associated with palpitations and anxiety. Ten months after symptom onset and at the conclusion of reported followup, the patient's improvement had plateaued. He remained restricted from driving due to persistent episodes of vertigo and disequilibrium.

The author concluded that the strong temporal association reported in this case between the use of mefloquine and the onset of anxiety, paranoia, psychosis, dissociation and

short-term memory impairment, accompanied by chronic disequilibrium and vertigo, is consistent with the development of a progressive limbic encephalopathy and an associated, likely multifocal brainstem injury caused by exposure to the drug. He argued that adverse reactions to mefloquine may occur even among patients without contraindications to the drug, and that these reactions may occur after administration of only a single 250 mg tablet. He hypothesized neuronal gap junction blockade and direct neurotoxicity as potential mechanism.

MAH comment: The patient took a generic version of mefloquine. His psychiatric symptoms and sleep disturbances gradually decreased in severity and frequency within a few months of their onset. Six months after the onset of events, episodes of tinnitus, vertigo and severe disequilibrium were persisting. Approximately ten months after the onset of events, the patient remained restricted from driving due to persistent vertigo and dysequilibrium. The patient did not have medical history of any psychiatric disorder or any other relevant medical history. A causal role of mefloquine in the occurring events cannot be excluded.

Assessor's comments:

Conclusions are endorsed.

MAH's overall discussion and conclusion

The safety profile of mefloquine is characterized by a predominance of neuropsychiatric AEs, which is indicated in the current Lariam CDS V. 4.0 [2]. Therefore, the purpose of the current addendum DSR was to evaluate the evidence of neuropsychiatric SAEs that were at least 90 days or longer in duration, including those reported as persisting for at least 1 year.

Cases classified as category D (no alternative explanation) were considered the most suitable for the analysis; however, cases with alternative explanations (category B) and limited information (category A) were also included into the evaluation of the event duration as long as strong evidence for persistence was given. In this context an event with a calculated duration of more than one year was considered to be persistent.

The duration of SAEs were calculated based upon SAE onset date and company received date. It is a considerable limitation to this analysis that no SAE cessation date or exact event duration was reported for any of these SAEs (no cases in group I). In a few cases, the event description did allow verification or correction of the calculated duration, and in some cases the corrected value was actually shorter than the originally calculated duration (e.g. AERs [REDACTED]).

In DSR 1040001, 369 cases with 623 medically confirmed psychiatric disorder SAEs, and 309 cases with 436 medically confirmed nervous system disorder SAEs were retrieved. Of all cases, four were classified as category D (no alternative explanation), and presented with an SAE duration of more than one year. An additional 79 cases from the categories A (insufficient information) and B (cases with alternative explanations) also provided evidence for an event duration of more than one year.

Since the cut-off date of DSR 1040001 (cut-off date 06 May 6 2010), a total of 34 cases, with 25 cases reporting 46 SAEs from the SOC "Psychiatric Disorders", and 17 cases with 24 SAEs from the SOC "Nervous System Disorders" fulfilled the search criteria. The criteria were defined to retrieve serious, medically confirmed cases with an event duration of more than 90 days reported to the MAH within the period of 07 May 2010 – 27 October 2013.

Of the identified cases, four cases provided follow-up information to cases already included in DSR 1040001; however, relevant new information was received in one follow-up report (AER [REDACTED]). Based on the new information (negative psychiatric history, patient unable to work full-time for three years after event onset), this case was reclassified from category B to D. For the data set of DSR 1040001, this meant an increase from 17 to 18 patients with psychiatric disorder SAEs, and from 8 to 9 patients with nervous system disorder SAEs, who suffered from their events for more than 90 days with no alternative explanation for the events (category D). The number of cases presented with a duration of more than one year increased in this analysis from four to five cases.

In six of the 21 new, initial cases reported under the SOC "Psychiatric Disorders," no alternative explanation was identified for the SAEs (category D). Three of these cases provided strong evidence for psychiatric event duration for more than one year (AER [REDACTED]: major depression >3 years; AER [REDACTED]: psychotic disorder >3 years; AER [REDACTED]: delirium, agitation aggression [sequelae] >1 year).

An additional three cases from the categories A and B also provided some evidence for event duration of more than one year. Although these cases provided limited information (AER [REDACTED]: sleep disorder >3 years; AER [REDACTED]: dissociation, psychotic disorder, anxiety, and delusion with psychiatric therapy for >1 year) or a psychiatric history (AER [REDACTED]: anxiety >3 years), a contributing role of mefloquine to the persistence of these events cannot be excluded.

In three of the 13 new, initial cases reported under the SOC "Nervous System Disorders," no alternative explanation was identified for the SAEs (category D). The only case with a calculated duration of more than one year was already discussed above, as the event of interest was agitation (included in the SOC "Psychiatric Disorders"). In addition, one case (AER [REDACTED] from category A also provided some evidence for event duration of more than one year. Although this cases provided limited information (AER [REDACTED]: myoclonus >3 years), a contributing role of mefloquine to the persistence of this event cannot be excluded.

The analysis of the current addendum DSR showed that few additional cases with information on the duration of events were received during the follow-up period (07 May 2010-27 October 2013). Of the 34 cases, six cases provided evidence on persistence of neuropsychiatric events for more than 1 year, and in 50% of these cases no evidence for a causal relationship could be established. However, in the remaining cases, a close temporal relationship between onset of events and mefloquine therapy and the lack of alternative explanations suggested a possible role of mefloquine.

Overall, cumulatively 91 cases contained evidence on neuropsychiatric SAEs that were at least 1 year or longer in duration.

The current addendum DSR also provides a cumulative review of persistent or permanent neurologic (vestibular) disorder events in patients receiving mefloquine. Cumulatively, a total of 88 cases with 95 SAEs for the SMQ "Vestibular Disorders" and 16 cases with 16 SAEs reporting the PT "Tinnitus" were retrieved according to the defined search criteria (to include serious, medically confirmed cases with an event duration of >90 days; some patients were counted twice as due to the multiaxial search vestibular disorders, including tinnitus, are also covered within the psychiatric and nervous system disorder SOC).

No alternative explanation (category D) was identified for the SAEs in six of the 88 cases reported for the SMQ "Vestibular Disorders." One of the six cases provided evidence for an SAE duration of more than 1 year (AER [REDACTED]). The patient experienced dizziness

that lasted for 611 days. No cases reporting 'Tinnitus' were identified for category D. An additional 13 cases for the SMQ "Vestibular Disorders" and for the PT "Tinnitus" from the categories A and B provided evidence for SAE duration of more than 1 year. Eight cases provided limited information (AER [REDACTED]: dizziness >2 years; AER [REDACTED]: dizziness >2 years; AER [REDACTED]: dizziness >6 years; AER [REDACTED]: balance disorder, vertigo >5 years; AER [REDACTED]: vertigo >6 years; AER [REDACTED]: vertigo >11 years; AER [REDACTED]: dizziness >2 years; AER [REDACTED]: dizziness, tinnitus >5 years) and confounders were reported in four cases (relevant medical history, concomitant medication; AER [REDACTED]: vertigo >1 year; AER [REDACTED]: balance disorder >3 years; AER [REDACTED]: dizziness >5 years; AER [REDACTED]: vestibular disorder >7 years). However, an association between mefloquine and the persistence of these events cannot be excluded. One of the 537 retrieved literature articles was included in the current addendum DSR. This article concerned one patient who experienced psychiatric symptoms, sleep disturbances, disequilibrium, vertigo and tinnitus after taking a generic version of mefloquine, with short drug-event latencies. Psychiatric symptoms and sleep disturbances gradually decreased in severity and frequency within a few months of their onset. However, the events of vertigo and dysequilibrium were persisting approximately ten months after the onset of events. No risk factors were identified in this case. Based upon the assessment in DSR 1040001 (cut-off date 06 May 2010), the MAH amended the Lariam CDS regarding the duration of neuropsychiatric disorders into the "Warnings and Precautions" section. The information that adverse reactions to Lariam may occur or persist up to several weeks after discontinuation of the drug and that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug was added. The analysis provided in the current addendum DSR (DSR 1058255, cut-off date 27 October 2013) confirms this outcome for most of the cases; however, longer duration or even persistence of such adverse reactions in a small proportion of patients may be possible.

MAH's Conclusion

Based on this review, including case reports from the Roche Global Drug Safety Database ARISg, the MAH will amend the "Warnings and Precautions" section of the current Lariam CDS V. 4.0 to include information on the persistence of certain neuropsychiatric events after discontinuation of the product.

MAH's proposed changes of section 4.4 and 4.8 of the approved CSP:

4.4 Special warnings and precautions for use

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

Due to the long half-life of mefloquine, adverse reactions may occur and persist up to several months 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 ~~continued~~ for months or longer 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).

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. Due to the long half-life of mefloquine, adverse reactions may occur or persist ~~up to several weeks~~ after discontinuation of the drug. 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 drug levels.

Assessor's comment's:

As already comment above, considering the intensive increase of category D cases in comparison with the former DSR especially regarding reports with a duration over two years and the data presented in the FDA assessment, an update of product-information to include permanent/persistent neuropsychiatric adverse events is strongly required.

The proposed changes by the MAH of the product-information for Lariam are mostly accepted.

Nevertheless, since a clear differentiation of neuropsychiatric side effects which persist, cannot be made, the following wording is proposed:

Due to the long half-life of mefloquine, adverse reactions may occur and persist ~~up to several months~~ after discontinuation of the drug. In a small number of patients it has been reported that ~~some neuropsychiatric events~~ reactions (including e.g. depression, dizziness or vertigo and loss of balance) may continue-continued-for months or longer or even persist after discontinuation of the drug.

2.3. Rapporteur's position

- This DSR report described 17 case reports of Psychiatric Disorders in category D 2; 3 and 4 (cases without an alternative explanation and a known duration). Furthermore three additional reports of Nervous System Disorders were reported in category D2 and 3. Patients who were already presented under the SOC psychiatric disorders are not double calculated. Additionally four other cases () have to be assigned to this group.
- Most of the 24 cases (20) had a duration between 90 days and 1 year (in 7 cases the SAE resolved; and in 13 cases the SAE were still ongoing at the last follow up). In four cases the events had a duration over a year (in one case the patient recovered within this time; in another case the SAE slowly resolved during this period, in one case the symptoms were persisting over a time of 2 to 3 years and one patient recovered over a time of 2 to 3 years).
- The second drug safety report regarding long lasting neuropsychiatric adverse reactions with the period May 2010 until 27 October 2013 describes six cases of psychiatric disorders in category D and one additional case of nervous system

disorder in category D. Patients who were already presented under the SOC psychiatric disorders are not double calculated. In four cases the symptoms had a duration between 90 days to 1 year; two cases were reported with continuance of 2 to 3 years and one case with duration over 3 years. Additionally one follow up with relevant new information was received during this period. As a result the number of cases presented with a duration of more than one year increased in this analysis from four to five cases.

- The DSR 104001 (period 1984 until 6 of May 2010) with an exposure of over 34 Mio patients presented 25 category D case reports of long lasting neuropsychiatric adverse reactions (without double calculations). In contrast seven category D cases of long lasting neuropsychiatric adverse reactions (without double calculations) were submitted with the three-year DSR 105825507 and an exposure of over 3 Mio patients.
- Considering the intensive increase of category D cases in comparison with the former DSR especially regarding reports with a duration over two years and the data presented in the FDA assessment, an update of product-information to include permanent/persistent neuropsychiatric adverse events is strongly required.

3. Conclusion and recommendations

There is enough evidence from the presented drug safety reports, the submitted literature report and the FDA assessment report supporting a causal relationship between mefloquine and the occurrence of long lasting and even persistent neuropsychiatric side effects.

Additionally based on the pharmacodynamic profile of mefloquine, the neuropsychiatric side effects of Lariam can be explained to a large extent by the neuro(patho)physiology and can be predicted by mechanistic aspects as well.

In consideration of this and the increase of case reports with long lasting side effects, there is a strong suspicion that mefloquine can cause different kind of permanent brain damage, even under plasma concentration achieved in malaria prophylaxis.

No specific risk factors - dosage, duration etc. could be identified. For that reason, only the advice - to stop taking mefloquine if neuropsychiatric reactions or changes to their mental state occur - can be given as precautionary measure.

The current wording regarding the continuance of neuropsychiatric side effects in section 4.4 and 4.8 of the SmPC and the respective section of the PIL should be updated as follows:

3.1. Changes to the product information

4.4 Special warnings and precautions for use

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

Due to the long half-life of mefloquine, adverse reactions may occur and persist up to several months after discontinuation of the drug. In a small number of patients it has been reported that some neuropsychiatric events reactions (including e.g. depression, dizziness or vertigo and loss of balance) may continue continued for months or longer or even persist 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).

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. Due to the long half-life of mefloquine, adverse reactions may occur or persist up to several weeks after discontinuation of the drug. 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 drug levels.

PL:

The PL should be updated accordingly.


3.2. Request for supplementary information


n/a

3.3. Communication

Based on this relevant new information on permanent side adverse reactions a DHPC is recommended on national level. (The existing Educational material should be updated accordingly.)

4. Comments from member states


We endorse conclusions in PRAC Rapporteur AR.


We fully agree with the Rapporteur assessment. However we would like to underline several points:

- 1. The information that occurrence of adverse effects could be very late after discontinuation of the drug is removed with the proposed labelling, whereas this information is very important for prescribers and patients to keep in mind the potential causal relationship between mefloquine and late adverse reactions. The*

information regarding the wording "up to several months" is applicable for persistence and occurrence. Therefore we would prefer to keep the wording in sections 4.4 and 4.8.

2. Moreover the information included in the two sentences regarding general adverse reactions and neuropsychiatric reactions are quite similar. Redundant information in the warning box should be avoided for a better readability of prescribers.

Based on these previous comments, we propose the following modifications for SmPC:

4.4 Special warnings and precautions for use

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

Due to the long half-life of mefloquine, adverse reactions notably neuropsychiatric reactions (e.g. depression, dizziness or vertigo and loss of balance) may occur and persist up to several months after discontinuation of the drug. ~~In a small number of patients it has been reported that some neuropsychiatric events reactions (including e.g. depression, dizziness or vertigo and loss of balance) may continue continued for months or longer 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).

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. Due to the long half-life of mefloquine, adverse reactions may occur or persist up to several weeks months after discontinuation of the drug. 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 drug levels.

3. The Rapporteur concluded that possible permanent adverse reaction can occur with mefloquine. We underline that this new information is not clearly mentioned in the changes to the product information.

Assessor's comment's:

To bring both issues in accordance (very late occurrence and the permanence of the adverse events), the Rapporteur proposes the following wording:

4.4 Special warnings and precautions for use

Mefloquine may induce psychiatric symptoms such as anxiety disorders, paranoia, depression, hallucinations and psychosis. Psychiatric symptoms such as nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more

serious event. Cases of suicide, suicidal thoughts and self-endangering behaviour such as attempted suicide (see 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.

Due to the long half-life of mefloquine, adverse reactions notably neuropsychiatric reactions (e.g. depression, dizziness or vertigo and loss of balance) may occur and persist up to several months after discontinuation of the drug or become permanent. ~~In a small number of patients it has been reported that some neuropsychiatric events reactions (including e.g. depression, dizziness or vertigo and loss of balance) may continue continued for months or longer 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).

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. Due to the long half-life of mefloquine, adverse reactions may occur or persist up to several ~~weeks~~ months after discontinuation of the drug or become permanent. 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 drug levels.

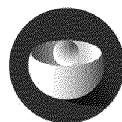
4. *Regarding the proposed communication plan, it is remained that further to the PSUR Worksharing, a DHPC regarding neuropsychiatric reactions would be sent less than 9 months ago (in [REDACTED] circulation of the DHPC with guide for health care professionals and patient cards was performed on 8th July 2013). Thus, the necessary to send a new DHPC is questionable. Indeed, we consider that there is no new major safety information and that the proposed modifications of SmPC and PIL do not warrant a new communication. If PRAC would recommend a new communication plan, it would be appreciated that final decision should be taken at the national level.*
5. *Regarding the risk minimisation documents regarding neuropsychiatric side effects, we consider that the update of these documents could be performed at the same as update of the product information. Of note, it should be taken into account that in [REDACTED] the patient card and the guide for health care professionals, proposed during the PSUR Worksharing procedure finalised in April 2013, was nationally adjusted with lots of modifications in order to better underline the relevant new information.*

Assessor's comment's:

The Rapporteur recommends a DHPC and an update of the educational material. Due to only national authorisations for Lariam, the need for an update of the educational material or the circulation of a DHPC is in national responsibility, so this decision should be taken on national level.

5. Points for discussion/agreement

6. References



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/63963/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Summary PRAC assessment report on the signal of <issue> with <INN and/or product name(s) or product class>¹

The summary shall not exceed two A4 pages.

The summary PRAC assessment report (SmAR) is intended for publication with recommendations for amendments of the SPC/PL on the EMA website. The SmAR focuses on the outcome of the assessment and regulatory comments, taking into account the regulatory and clinical context.

Trigger for current safety review, evidence assessed and public-health impact

Please provide the trigger for this signal and the evidence leading to the requested changes to product information and the importance of this signal for public health.

The signal was raised following a new publication, in the framework of routine pharmacovigilance activities, or following a signal from other regulatory authorities.

The Pharmacovigilance Risk Assessment Committee (PRAC) assessed the following evidence/data (i.e. spontaneous/published cases, meta-analysis, data submitted by the marketing authorisation holders, additional data provided in the context of supporting analysis in THIN, and GPRD data). The assessed evidence provides the scientific motivation to request changes to the product information.

Patient population/exposure and reaction severity, among other elements, should be taken into account when discussing public-health impact.

Changes to the product information

Summary of product characteristics (SmPC)

<Text here.>

Please provide the wording of the relevant sections of the SmPC.

¹ For product classes, a footnote should list the INN of the relevant active substances.



Package leaflet

<Text here.>

Please provide the wording of the relevant sections of the package leaflet.

Timelines for implementation

<Text here.>

Please provide the timelines for implementation of the changes to the product information as agreed by the PRAC.