01 July 2013

Direct Healthcare Professional Communication on Lariam® (mefloquine) for malaria chemoprophylaxis and the risk of neuropsychiatric adverse reactions

Dear Healthcare Professional

Roche Products (Ireland) Limited would like to inform you of important safety information regarding the use of Lariam® (mefloquine). For the complete prescribing and safety information, please refer to the Lariam Summary of Product Characteristics which is enclosed with this communication and also available at www.medicines.ie.

Summary

- **Lariam® (mefloquine) may induce potentially serious neuropsychiatric disorders.**
- **The most common neuropsychiatric reactions to mefloquine include abnormal dreams, insomnia, anxiety, and depression. Additionally hallucinations, psychosis, suicide, suicidal thoughts and self-endangering behaviour have been reported.**
- **Do not use mefloquine for malaria chemoprophylaxis in patients with active or a history of psychiatric disturbances.**
- **Due to the long half-life of mefloquine, adverse reactions may occur and persist up to several months after discontinuation of the drug.**
- **Healthcare professionals should react promptly to signs of neuropsychiatric reactions with mefloquine chemoprophylaxis. Mefloquine should be discontinued immediately and replaced by alternative malaria prophylaxis medication.**
- **Advise patients that if they experience a neuropsychiatric reaction such as suicidal thoughts; self-endangering behaviour; severe anxiety; feelings of restlessness, confusion, or mistrust towards others; visual/auditory hallucinations; depression; or changes to their mental state during mefloquine chemoprophylaxis, they should stop taking mefloquine immediately and seek urgent medical advice.**
- **Please read the Guide for Healthcare Professionals and follow the checklist before prescribing mefloquine chemoprophylaxis to your patient (see enclosure 1).**

Further information on the safety concern and recommendations

Therapeutic indications:

Therapy:

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

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

Chemoprophylaxis:

Mefloquine is particularly recommended for travellers to malarious areas in which multiple resistant *P. falciparum* strains occur.

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

For all indications Lariam (mefloquine) is <u>contraindicated</u> in patients who:

- are hypersensitive to mefloquine or related compounds (e.g. quinine, quinidine) or to any excipients contained in the formulation
- have a history of Blackwater fever
- have severe impairment of liver function
- are currently receiving halofantrine treatment

Additionally for the chemoprophylaxis indication Lariam (mefloquine) is contraindicated in the following patients:

- those who experience or have experienced the following neuropsychiatric disorders at any time:
  - depression
  - generalised anxiety disorder
  - psychosis
  - schizophrenia
  - suicide attempts
  - suicidal thoughts
  - self-endangering behaviour
  - any other psychiatric disorder
- those who have a history of convulsions of any origin

Counselling your patient

As part of your discussions with patients or their carers, please ensure that:

- You provide a full description of the neuropsychiatric profile of Lariam (mefloquine);
- You instruct the patient to read the patient information leaflet;
- You hand out a patient alert card.

Additional information can be found in the Summary of Product Characteristics (see enclosure 4).

Please advise patients that if neuropsychiatric reactions or changes to their mental state occur during mefloquine chemoprophylaxis, to stop taking mefloquine and seek medical advice immediately so that mefloquine can be replaced by alternative malaria prevention medication.

Additional information for mefloquine

Cardiac toxicity

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

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

Due to increased plasma concentrations and elimination half-life of mefloquine following co-administration with **ketoconazole**, the risk of QTc prolongation may also be expected:

- if ketoconazole is taken during mefloquine chemoprophylaxis or treatment of malaria
- or ketoconazole is taken within 15 weeks after the last dose of mefloquine.

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

Eye disorders

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

Seizure disorders

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

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

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

Neuropathy

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving mefloquine.

Mefloquine should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see the Lariam Summary of Product Characteristics - enclosure 4).

Pneumonitis

Pneumonitis of possible allergic etiology has been reported in patients receiving mefloquine. Patients who develop signs of dyspnoea, dry cough or fever etc. while receiving mefloquine should be advised to contact a doctor to undergo medical evaluation (see the Lariam Summary of Product Characteristics - enclosure 4).

Long-term use

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

For information on **renal impairment** and **pregnancy and breastfeeding**, refer to the Lariam Summary of Product Characteristics which is enclosed and available at www.medicines.ie.

Call for reporting

Please report any suspected adverse events associated with the use of Lariam (mefloquine) to the Drug Surveillance Centre at Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24 by mail, telephone (01 4690700), fax (01 4690793) or email (Ireland.drug_surveillance_centre@roche.com). Alternatively, suspected adverse events should be reported to the Irish Medicines Board using the online form at www.imb.ie or by using the freepost yellow card system. The IMB can also be contacted on 01-6764971.

Communication information

Should you have any questions or require additional information regarding the use of Lariam (mefloquine) or if you require additional copies of any of the Lariam educational materials, please contact Medical Information at Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24 by mail, telephone (01 4690700), fax (01 4690791) or email (Ireland.druginfo@roche.com).

For the complete prescribing and safety information, please refer to the Lariam Summary of Product Characteristics which is enclosed with this communication and also available at www.medicines.ie.

Yours sincerely

Dr. Maria Luz Amador
Medical Director

Enclosures

1. Guide for Healthcare Professionals entitled 'Lariam (mefloquine) for Malaria Chemoprophylaxis' (including an example of the prescriber's checklist for Lariam® (mefloquine))
2. Pad of checklists for the prescription of Lariam (mefloquine)
3. Lariam Patient Alert Card
4. Lariam Summary of Product Characteristics Version 12 June 2013