



Ministry
of Defence

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Dear Julian,

I enclose a response providing the expert advice of the Surgeon General to the Committee's letter of 8 September 2015 about the use of the anti-malarial mefloquine in the Armed Forces.

Mefloquine is one of a number of anti-malarials we offer personnel. It is licensed in the UK by the Medicines and Health Products Regulatory Agency, based on the expert guidance of Public Health England's Advisory Committee for Malaria Prevention (ACMP). It is under continual review, but there are no countries where mefloquine has had its licence withdrawn. It is not a first line drug, and is used primarily in cases where other drugs would not be effective or appropriate for that person. Mefloquine makes up 1.2% of our anti-malarial stocks.

The Department complies with national guidelines on Malaria Prevention, which are reviewed annually, with the latest updated version being issued on 16 September 2015. These continue to recommend mefolquine use as long as individual assessments are undertaken before prescribing. Since 2004/05, Defence policy has required mefloquine to be prescribed to Service personnel with the accompanying risk assessment.

The health and wellbeing of our people is paramount, in this and all matters.

Yours
Michael

THE RT HON MICHAEL FALLON MP

The Rt Hon Dr Julian Lewis MP
Chairman, Defence Committee
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Q1. When did MOD last undertake an assessment of the safety of Lariam [mefloquine] and were any health risks highlighted in that assessment?

1. An audit of mefloquine prescription during Operation HERRICK 2007-14 was conducted in 2015, reporting in July. This audit identified that 28 (5.8%) of 486 mefloquine prescriptions were unjustified because of an existing contraindication, with 2 patients determined to have experienced *avoidable* side effects requiring the drug to be withdrawn. A total of 11 (2.46%) personnel receiving mefloquine for protection on Op HERRICK experienced documented side effects subsequently reported¹.

2. Other academic analysis of mefloquine safety undertaken by Defence includes a study by Croft in 1997 (then a trainee in Public Health within Army).² This was a questionnaire study of 317 soldiers in Kenya who took mefloquine and 307 soldiers who took chloroquine-proguanil. The author concluded:

“The incidence of putative side effects was not significantly different between the groups” and that “...these results support evidence which indicates that mefloquine is no more toxic than chloroquine-proguanil.”

3. The author stated limitations of the study in that response rates were incomplete³ and the study population was fit young men [with a low co-morbidity]—but the fit, young population is only a ‘limitation’ if the findings are to be extrapolated to a wider population.

4. A further study led by Defence (2015, in press)⁴ has evaluated the relative occupational impact of side effects experienced by soldiers from mefloquine compared to doxycycline, drawing on a cohort of over 1,500 personnel from 10 consecutive units training in Kenya during 2012 and 2013. The results identified that:

“Significantly more ($p < 0.0001$) doxycycline users⁵ reported that one or more adverse effects had interfered with their ability to do their job than mefloquine users.”

...and the authors concluded that...

*“...this study supports the view that, for organizations which provide malaria chemoprophylaxis to employees free of charge, **mefloquine should be the first-choice antimalarial drug where the only alternative is doxycycline.**”*

5. A review of data held by Defence Statistics in April 2015 on personnel presenting for care at a Department of Community Mental Health showed that of all those prescribed mefloquine there was a rate of 6% who presented for mental healthcare, compared to 3% amongst the general military population. It is **not** possible, however, to directly demonstrate how important the mefloquine prescription was with regard to the causation of the mental health condition. Other factors may be equally important such as deployment, combat role, patient perceptions of mefloquine, or doctors’ referring behaviour.

¹ National Yellow Card reporting system.

² Croft AMJ, Clayton TC, World MJ. Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. *Trans R Soc Trop Med Hyg* 1997;91:199-203.

³ Response rates were 58% at 2 weeks and 46% at 8 weeks after stopping treatment.

⁴ Terrell A et al. Malaria Chemoprophylaxis and Self-Reported Impact on Ability to Work: Mefloquine Versus Doxycycline. *Journal of Travel Medicine* 2015; in press.

⁵ 109/867 mefloquine users (12.6%) and 152/685 (22.2%) of doxycycline users reported that one or more adverse effects had impacted upon their ability to do their job

6. Internationally, published work into possible adverse effects of mefloquine has been conducted on very large numbers of individuals through academic studies and post-marketing surveillance: very large numbers have to be recruited in order to demonstrate the incidence of a side effect that is correspondingly rare. Conducting such a trial on Service personnel would therefore be unfeasible. This is an important reason why Defence continues to rely on the expert advice and direction given by the national expert committee on malaria (Advisory Committee for Malaria Prevention - ACMP) and takes note of the opinion of various international expert bodies (such as the World Health Organisation and the Centre for Disease Control - CDC). The MOD policy regarding malaria prevention is consistent with the revised 2015 national Malaria Prevention Guidelines published by Public Health England for travellers from the UK.

7. There is a link made between mefloquine and Post Traumatic Stress Disorder (PTSD) by some commentators, but **there is no evidence that mefloquine causes PTSD *per se***. However, the symptoms (SEs) experienced by some mefloquine users are quite similar to PTSD, so it is possible to mis-ascribe one as the other, hence the link that has formed in some minds.

8. **The fact that mefloquine has side effects is not disputed.** Every drug that has a clinical effect will also have a side effect profile. The balance lies in providing effective prophylaxis against a known debilitating and potentially lethal infection, with the least impact through side effects on the patient. Given that there is variable resistance internationally to some drug options, and given that individuals vary in their tolerance to each drug, there is no universal safe and effective malaria prophylaxis.

Q2. What plans does the MOD have to reassess the safety of Lariam [mefloquine] in the light of recent concerns raised by military personnel?

9. A prospective audit of the side effect profile of mefloquine is planned, following on from the retrospective audit described above.

10. Following on from the results of the impact of side effects of doxycycline vs mefloquine on occupational efficiency, Defence is planning an additional study to compare malarone with mefloquine in a similar exercise population in Kenya. The protocol is currently being prepared for ethics submission (MOD Research Ethics Committee).

Q3. How many complaints has the MOD received from military personnel about side effects following the use of Lariam and how have these have been resolved?

11. The MOD's Automated Significant Event Reporting System (ASER) is used by clinicians to report significant events that occur within a medical treatment facility and does ask the reporter if the event is known to have led to a formal patient complaint. A search of ASER was conducted and this produced no record of any patient complaint relating to mefloquine or any other antimalarial. However, it should be noted that it is not mandatory for patient complaints to be recorded on ASER, nor is this the system's primary purpose.

12. The MOD's Directorate of Judicial Engagement Policy is currently investigating two complaints by the Department in relation to side effects of mefloquine.

Q4. What is the Department's policy for the (a) immediate, (b) medium-term and (c) long term treatment of military personnel who have suffered detrimental side-effects of using Lariam [mefloquine]?

13. The clinical management plan for a patient who reports side effects from mefloquine is no different in principle to that for any drug producing side effects. The clinical options are:

- a. To recognise and tolerate minor side effects, with the patient's agreement, particularly if there is no other credible pharmaceutical option and the clinical risk of the disease outweighs the side effect demonstrated(note: additional symptomatic treatment may be offered that mitigates minor side effects while continuing to take the drug). **Substitution with alternative malaria prophylaxis is commonly for this reason.**
- b. To stop the drug immediately, because of the severity of the side effect, and either provide a credible alternative or accept, with the patient's understanding, that providing no therapy is in the better interests of the patient than experiencing the side effect. **This would be a last resort in malaria prophylaxis because of both the serious nature and the high probability of infection.** In a review of UK citizen malaria deaths over 20 years (published in 2012) many deaths were associated with poor compliance with chemoprophylaxis⁶—this re-emphasises the need for chemoprophylaxis and the fatal consequences of not following effective prevention.
- c. To stop the drug immediately and intervene with life-saving therapy, specifically in the case of anaphylactic reaction to the drug.

14. It is important to discriminate between adverse effects that are spontaneously reported (because individuals feel ill) and adverse effects reported during research studies. There is observer bias in research studies, whereby side effects are reported that were either not initially recognised nor considered important by the patient.

15. It is also important to note that singling out mefloquine for scrutiny is a flawed logic. Any prospective mefloquine study must capture the side effects profile of all anti-malarials. They all have significant side effect profiles and it is inappropriate to only track mefloquine. Clinical Advisers have considerable concern if mental ill health symptoms that are reported while taking Mefloquine are regarded as uniquely attributable to Mefloquine. There is a background prevalence of mental ill health and caution must be exhibited in drawing any cause-and-effect conclusion.

Q5. Why were individual risk assessments not carried out before 2013 when usage guidelines issued by the manufacturer stated that such assessments should be undertaken?

16. Relevant Joint Service Publication 950 leaflets and predecessor MOD policy documents about mefloquine were in place prior to 2013. These have changed over time to reflect substantive changes in national and manufacturer guidance. For example, the Summary of Product Characteristics for Lariam has been updated 20 times since 1999. Since 2004/05, Defence policy has required mefloquine to be prescribed, with the implied accompanying risk assessment. In 2013, with the

⁶ Checkley AM, et al. *BMJ* 2012; 344.

formation of the Defence Primary Healthcare (DPHC) organisation, HQ DPHC has been responsible for ensuring that this policy has been followed. Prior to April 2013 the single Services were responsible for the provision of primary care and the procedures for prescribing mefloquine.

17. The Defence Medical Services endeavours at every opportunity to educate Service personnel and clinicians on the importance of compliance with taking mefloquine as per current policy guidelines. Non-compliance with taking mefloquine places Service persons at an unacceptable risk from contracting malaria.

Q6. What information has the MOD sought from the US and Canada on their experience of issuing Lariam [mefloquine] to their Armed Forces?

18. Canada had well publicised problems with Airborne Forces in Somalia in the 1990s, in which one of the mitigating factors cited by the defendants accused of War Crimes was that mefloquine was a causative factor. This assertion was discredited at the time.

19. In the US, similar assertions have been made by those accused of criminal activity to implicate mefloquine as a causative factor. Notably, there are the cases of Major Hasan (who injured 30 and killed 13 in shootings at Fort Hood in 2009 – but there is believed to be no evidence he took mefloquine) and Sgt Bales (who murdered 16 Afghans in Kandahar in 2012 – but there is believed to be no evidence of any association with mefloquine use). A review in 2015 of extant US policies and findings of DoD investigations into putative links between mefloquine use and suicides of Servicemen has found no links.

20. The US changes in policy were communicated to the MOD when they happened in 2009. Although there was no scientific evidence provided to justify their variation from national US policies and guidance, there was the statement that “...in an Operational context the US would find it too difficult to offer individual advice to deploying Service personnel about possible adverse drug effects from mefloquine.”

21. In April 2013, the Assistant Secretary of Defense (Health Affairs) issued new guidance on medications to prevent malaria:

“Atovaquone-proguanil and doxycycline are both first-line choices in areas other than sub-Saharan Africa. Mefloquine should be reserved for people with intolerance or contraindications to both first-line medications. Before using mefloquine for prophylaxis, care should be taken to identify any contraindications on an individual basis and ensure required FDA mefloquine medication guide is given to people prescribed mefloquine.”^{7 8}

22. In contrast, the section of the US CDC Yellow Book dealing with civilian travellers is much less proscriptive. The advice to contrast with the above is:

“For destinations where chloroquine-resistant malaria is present, in addition to mosquito avoidance measures, chemoprophylaxis options are atovaquone-proguanil, doxycycline, and mefloquine.”⁹

⁷ www.accessdata.fda.gov/drugsatfda_docs/label/2013/076523s007lbl.pdf

⁸ <http://wwwnc.cdc.gov/travel/yellowbook/2016/advising-travelers-with-specific-needs/special-considerations-for-us-military-deployments>

⁹ <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria>

23. Therefore, mefloquine is considered by US CDC to be equally suitable (within individual clinical assessment) as each of the other drugs.

24. US and Canadian experiences have therefore been sought and noted, but are not considered as sufficient evidence to justify changes from current MOD policy, particularly with respect to variation from evidence-based national guidance.