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GOVERNMENT NOTICES

Australian Government

Repatriation Medical Authority

DECLARATION UNDER SUBSECTION 196B(6)

OF THE *VETERANS' ENTITLEMENTS ACT 1986*

The Repatriation Medical Authority (the Authority), under subsection 196B(6) of the *Veterans' Entitlements Act 1986* (the Act), makes the following declaration in respect of the investigation concerning **chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine** notified in the Commonwealth of Australia Gazette of **14 February 2017**.

The Authority declares that it does not propose to make a Statement of Principles concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine, for the purposes of subsection 196B(2) or (3) of the Act. The Authority is of the view that there is insufficient sound medical-scientific evidence that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury. Further, there is insufficient sound medical-scientific evidence that there is a characteristic and persistent pattern of signs and symptoms following exposure to mefloquine, tafenoquine or primaquine that could be determined to be a particular kind of disease of, or injury to, the brain.

The Common Seal of the)
Repatriation Medical Authority)
was affixed at the direction of:)

PROFESSOR NICHOLAS SAUNDERS AO
CHAIRPERSON 18 / 08 / 2017

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Australian Government
Repatriation Medical Authority

REPATRIATION MEDICAL AUTHORITY

STATEMENT OF REASONS

RE: DECISION NOT TO MAKE STATEMENTS OF PRINCIPLES FOR CHEMICALLY-ACQUIRED BRAIN INJURY CAUSED BY MEFLOQUINE, TAFENOQUINE OR PRIMAQUINE

PART I INTRODUCTION

1. The Repatriation Medical Authority (the Authority) does not propose to make Statements of Principles under subsections 196B (2) or (3) of the *Veterans' Entitlements Act 1986* (the Act) in respect of chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine. The Authority published a notice of an investigation into chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine in the *Commonwealth of Australia Gazette* on 14 February 2017.

2. Having carried out the investigation as notified, the Authority declares that it does not propose to make a Statement of Principles concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine, for the purposes of subsection 196B(2) or (3) of the Act. The Authority is of the view that there is insufficient sound medical-scientific evidence that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury. Further, there is insufficient sound medical-scientific evidence that there is a characteristic and persisting pattern of signs and symptoms following exposure to mefloquine, tafenoquine or primaquine that could be determined to be a particular kind of disease of, or injury to, the brain.

PART II BACKGROUND TO THE INVESTIGATION

3. A request dated 6 February 2017, was received from the President of the Repatriation Commission and Chair of the Military Rehabilitation and Compensation Commission, seeking an investigation of chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine to find out whether Statements of Principles may be determined concerning the condition. The applicant did not provide any relevant sound medical-scientific evidence (SMSE) in support of the request.

4. On 7 February 2017, the Authority agreed to notify an investigation under subsection 196G(1) of the Act to ascertain if Statements of Principles concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine could be determined. An investigation notice was placed in the *Commonwealth of Australia Gazette* on 14 February 2017.

5. Mefloquine has already been included as a factor in the Statements of Principles for 14 conditions where there was at least a reasonable hypothesis that the relevant condition can occur: acquired cataract, anxiety disorder, bipolar disorder, depressive disorder, epileptic seizure, heart block, myasthenia gravis, peripheral neuropathy, psoriasis, sensorineural hearing loss, schizophrenia, suicide and attempted suicide, tinnitus and trigeminal neuropathy.

6. Tafenoquine has already been included as a factor in the Statements of Principles for 6 conditions where there was at least a reasonable hypothesis that the relevant condition can occur: acquired cataract, epileptic seizure, methaemoglobinaemia, psoriasis, sensorineural hearing loss and tinnitus.

7. Primaquine has already been included as a factor in the Statements of Principles for 6 conditions where there was at least a reasonable hypothesis that the relevant

condition can occur: acquired cataract, epileptic seizure, methaemoglobinaemia, psoriasis, sensorineural hearing loss and tinnitus.

PART III SUBMISSIONS RECEIVED BY THE AUTHORITY PURSUANT TO SECTION 196F

8. Following notification of its investigation, the Authority received seven submissions from persons or organisations eligible to make submissions pursuant to section 196F of the Act as follows:

(a) An online submission was received from a veteran on 15 February 2017. The veteran explained that he had taken mefloquine for 6 months while on deployment in East Timor in 2001 and had subsequently been diagnosed with posttraumatic stress disorder (PTSD). No SMSE was supplied with the submission.

(b) A submission was received from a scientific researcher on 10 May 2017, on the basis of having expertise relevant to the investigation. The researcher has been involved in research efforts to find a well-tolerated chemotherapeutic agent for malaria. The submission included a number of published peer-reviewed articles of relevance to the investigation.

(c) The above researcher sent an additional submission, received 4 July 2017, explaining the parameters for an upcoming clinical trial of tafenoquine. The submission included three published peer-reviewed articles.

(d) A veteran sent a submission on 10 May 2017, listing a number of symptoms she had experienced during and after taking mefloquine. The submission included a number of personal medical records and a web page concerning PTSD. No SMSE was included with the submission.

The symptoms the veteran reported having experienced while taking mefloquine included muscle pain, muscle weakness, abdominal cramps/stomach pain, lethargy, disorientation, feeling of skin "crawling", diarrhoea, "eye lid aggravation", headache, sore throat, neck and shoulder ache, photophobia, decreased appetite, earache, increased agitation, increased anger, paranoia, panic/anxiety attacks, mood changes, increased anxiety, nightmares, ringing in the ears, memory lapses and out of character behaviour.

The symptoms the veteran reported having experienced after returning to Australia and ceasing mefloquine included ongoing anxiety, general feeling of being "unwell", tiredness, stomach/intestinal pain, nausea, worsening back pain (previous injury), thyroglossal cyst, lethargy, flushes/night sweats, chronic dysthymia (depressive mood), somatoform symptoms, problems adjusting back into unit post deployment, mood swings, and vertigo/tinnitus (diagnosed with endolymphatic hydrops and hearing loss).

(e) A veteran sent an email on 16 May 2017 in order to register his interest in participating in any investigation that would lead to a determination in respect of chemically-acquired brain injury or any other side effects caused by being prescribed mefloquine. He had served in East Timor during April to October 2001.

On taking mefloquine during this deployment he experienced hallucinations, weird vivid dreams, broken sleep, "brain fog", anxiety and "stress attacks". The veteran reported that many of these symptoms, along with anger and depression, have continued up to the current time. No SMSE was supplied with the submission.

(f) A submission was received from a medical practitioner on 17 May 2017, on the basis of the person having expertise relevant to the investigation. The submission cited a number of his own and other published peer-reviewed articles. In addition to these articles, a poster obtained by freedom of information from the Walter Reed Army Institute of Research in December 2014 was included.

(g) A submission was received from a scientific researcher on 18 May 2017, on the basis of the person having expertise relevant to the investigation. The researcher pointed out that, although there is no specific category for chemically-acquired brain injury in DSM-5 or ICD-10, a relevant category might be "substance/medication-induced major or mild neurocognitive disorder". The submission included a number of published peer-reviewed articles of relevance to the investigation.

PART IV EVIDENCE/INFORMATION AVAILABLE TO THE REPATRIATION MEDICAL AUTHORITY

9. The following information was available to the Authority.

(a) Submissions and correspondence as detailed in Part III above.

(b) Literature searches were conducted using the Ovid search engine from 1996 to March Week 5 2017, limited to English language. The search terms were:

- Mefloquine/ae, po, to [Adverse Effects, Poisoning, Toxicity];
- Mefloquine/ and Psychotic Disorders/ or neuropsychiatric.mp. or Mental Disorders/
- Tafenoquine.mp and adverse effects.mp;
- Primaquine/ae, po, to.
- Brain Injuries/ci, et [Chemically Induced, Etiology] AND drugs.mp. or Pharmaceutical Preparations/ or chemicals.mp. or Inorganic Chemicals/ or Organic Chemicals/.

Articles were selected based on relevance, study quality, reliability and journal authority. The above search was supplemented by PubMed searches using the terms "mefloquine or primaquine or tafenoquine toxicity" or "mefloquine or primaquine or tafenoquine and neuropsychiatric", internet searches, manual searches of reference lists and extracts from relevant sections of textbooks.

(c) Medical or scientific publications as set out in the bibliography attached hereto.

(d) A briefing paper prepared for presentation to the Authority by a research officer of the Secretariat.

PART V DISEASE AND INJURY

10. The Authority determines Statements of Principles where there is sound medical scientific evidence that, "a particular kind of injury, disease or death" is relevantly related to service[1].

11. Section 5D of the Act defines disease and injury relevantly as follows:

> ***disease*** means:
>
> (a) any physical or mental ailment, disorder, defect or morbid condition (whether of sudden onset or gradual development); or
>
> (b) the recurrence of such an ailment, disorder, defect or morbid condition;
>
> but does not include:
>
> (c) the aggravation of such an ailment, disorder, defect or morbid condition; or
>
> (d) a temporary departure from:
>
> (i) the normal physiological state; or
>
> (ii) the accepted ranges of physiological or biochemical measures;
>
> that results from normal physiological stress (for example, the effect of exercise on blood pressure) or the temporary effect of extraneous agents (for example, alcohol on blood cholesterol levels);
>
> [and]
>
> ***injury*** means any physical or mental injury (including the recurrence of a physical or mental injury) but does not include:
>
> (a) a disease; or
>
> (b) the aggravation of a physical or mental injury.

12. The proper meaning of what constitutes a disease or injury for the purposes of determining a Statement of Principles under the Act is to be determined by the Authority.[2] In considering these terms, the Authority had regard to ordinary dictionary definitions, medical dictionaries, and its expert knowledge. In determining whether a condition is a disease or injury as defined, the Authority is entitled to have regard to the connotations of the words ‘disease or injury’ as used and understood in their ordinary meaning.[3]

13. Being familiar with the ordinary English meanings of the terms that are used in section 5D, the Authority considered whether chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine was "a particular kind of injury, disease or death" within the ordinary meaning of those terms. It also relied upon its expert medical knowledge and had regard to internationally agreed concepts in considering whether

[1] See s 196B(2) & (3) of the Act.

[2] Ryan D, SC (2013) Memorandum. Available at http://www.rma.gov.au/foi/what.htm.

[3] *Comcare v Mooi* (1996) 42 ALD 495.

chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine may represent a disease state.

PART VI REASONS FOR THE DECISION

Basis for defining chemically acquired brain injury and assessing the sound medical-scientific evidence

14. The Australian Institute of Health and Welfare (2007) defines acquired brain injury as

> *multiple disabilities arising from damage to the brain acquired after birth. It results in deterioration in cognitive, physical, emotional or independent functioning. It can be as a result of accidents, stroke, brain tumours, infection, poisoning, lack of oxygen, degenerative neurological disease etc.*

15. The wide variety of causes may lead to different kinds of effects, be they chronic or acute only, reversible or irreversible, progressive or non-progressive and thereby propagate to a large number of particular kinds of injury, disease or death. This variety means that the particular kinds of acquired brain injury are generally described by reference to the relevant specific causes of the injury.

16. In order to determine whether a chemically-acquired brain injury with long-lasting health effects can occur as a result of exposure to a substance, it is necessary to consider whether there is any SMSE showing consistent evidence of damage or injury to human brain tissue that is associated with exposure to the chemical substance and an enduring pattern of symptoms and neurological deficits. Such evidence is available, for example, in relation to acquired brain injury from exposure to lead (de Souza et al 2013) and solvents (Beckley et al 2013). Consistent with this approach the Authority has for example, determined SoPs for Chronic Solvent Encephalopathy.[4]

17. Further, while animal studies can provide evidence of biological mechanisms, this type of evidence needs to be confirmed by pathological and epidemiological studies in humans because of interspecies differences, the high doses which tend to be used in animal studies, and the difficulty of relating animal behaviours to human symptoms. It is also important than studies relate to the particular chemical of interest, since individual chemical compounds can have very specific effects, even if they belong to the same chemical class.

18. These issues were demonstrated in studies of a variety of quinoline compounds conducted in animals as part of a wartime search for effective antimalarials (Schmidt and Schmidt 1948 and 1949). Toxicities were specific to each compound tested, and there were considerable interspecies differences in toxicities.

19. The most informative epidemiological studies of long term neurological and psychiatric effects are cohort and case-control studies in which there is a specified period of follow up. These types of study employ a comparison group, thus accounting for the fact that symptoms can occur in people for reasons other than the exposure of concern.

[4] SoPs Nos. 71 & 72 of 2013.

Information on longer term effects can also be obtained from adverse events registers and case reports, but because they lack a comparison group it is difficult to determine from these studies if symptoms are due to a drug exposure or to other illnesses or exposures, and whether or not particular symptoms are more common in the group exposed to the drug compared with people who are not exposed to the drug.

20. Having regard to this background the Authority proceeded to consider and evaluate the sound medical-scientific evidence concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine.

Mefloquine

Background

21. Concerns have been raised that mefloquine, although usually considered a second or third line option for malaria prophylaxis, may be unsuitable for use in the military context (McCarthy 2015, Nevin 2015, Quinn 2016). These concerns relate in part to the well-recognised acute neuropsychiatric effects of mefloquine (Australian Medicines Handbook 2017), which are particularly problematic in an environment in which weapons are available and unimpaired judgement and fine motor skills are needed.

22. It has also been postulated that mefloquine might cause long term effects on the brain (Quinn 2016, Nevin 2014, Ritchie et al 2013), amounting to a condition that has been variously termed "mefloquine toxicity syndrome", "chronic mefloquine toxicity syndrome", "mefloquine intoxication syndrome", "chronic mefloquine-induced encephalopathy" and "chemically-acquired brain injury". Nevin (2012) proposes that mefloquine causes limbic encephalopathy, explaining symptoms of confusion, memory impairment and psychosis, with or without associated multifocal brainstem injury, explaining symptoms of dizziness and vertigo.

23. The US Food and Drug Administration (FDA) issued a drug safety communication concerning mefloquine in 2013. The information in this communication relates to reports of persistent vestibular adverse effects in mefloquine users. This assessment was based on adverse event reports from the FDA Adverse Event Reporting System and case reports in the published literature of dizziness, loss of balance, tinnitus, or vertigo persisting for months to years after mefloquine was discontinued, with permanent vestibular damage being diagnosed in some cases. Patients who experienced vestibular symptoms usually reported concomitant psychiatric symptoms such as anxiety, confusion, paranoia, and depression, some of which were persistent.

24. The FDA communication raises concerns but does not necessarily mean that there is a causal link between the reported adverse effects and mefloquine. The FDA does not require that a causal relationship between a product and event be proven.[5] The FDA uses Drug Safety Communications to let health care providers, patients, and

[5] US Food and Drug Administration (2016) Questions and Answers on FDA's Adverse Event Reporting System (FAERS). Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

consumers know about newly observed potential risks of FDA-approved drugs and to offer advice as to how these drugs may best be used in light of this new information.[6]

25. Mefloquine is on the World Health Organisation's List of Essential Medicines (WHO 2015). Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness (WHO 2017).

26. The term "neuropsychiatric effects" referred to above is vague, and it is not clear if it is meant to encompass only psychiatric illness, neurological symptoms and signs or a broad range of physical symptoms and cognitive problems. Reported acute or persistent neuropsychiatric symptoms in people who have taken mefloquine include anxiety, panic attacks, agitation, aggression, acute psychosis, depression, forgetfulness, sleep disturbance, nightmares, dizziness/vertigo, fatigue, abnormal vision, headache and tinnitus (Australian Medicines Handbook 2017, Ringqvist et al 2015, Fujii et al 2007). The symptom of most concern to the FDA has been persistent vestibular adverse effects. SMSE concerning a broad range of neurological and psychiatric effects was considered for this investigation.

Clinical trials

27. There have been several randomised controlled trials of mefloquine in both military and civilian populations (Gonzalez et al 2014, Nasveld et al 2010, Schlagenhauf et al 2003, van Riemsdijk et al 2002, Boudreau et al 1993). While none reported neuropsychiatric events which they rated as severe or requiring hospitalisation, these studies do not include long term follow up beyond the trial period (up to 6 months) or the period of deployment (mostly 6 months), so are not informative for potential ongoing chronic effects.

28. Similarly, there is a body of literature reporting on the findings of non-randomised and uncontrolled clinical trials of mefloquine. They can assess medium term effects but are not designed to assess long term sequelae. Many of these trials have been conducted in military populations in order to establish the effects of mefloquine in relation to efficacy, safety, compliance or effects on work functioning while in a deployment situation. These include studies in soldiers from Australia (Kitchener et al 2005), the US (Saunders et al 2015), Japan (Fujii et al 2007), the UK (Terrell et al 2015, Adshead 2014) and Holland (Jaspers et al 1996).

29. Fujii et al (2007) reported one case of psychosis, and Kitchener et al (2005) reported three withdrawals due to acute neuropsychiatric reactions possibly related to mefloquine. Overall, the trials concluded that mefloquine was well tolerated despite some mild to moderate adverse effects. Two trials in military populations reported that it did not compromise work function (Terrell et al 2015, Boudreau et al 1993). A randomised trial of 119 Dutch travellers found that measures of concentration

[6] US Food and Drug Administration (2017) What is an FDA Drug Safety Communication? Available at https://www.fda.gov/AboutFDA/Transparency/Basics/ucm222375.htm.

impairment showed no significant difference in change between subjects taking atovaquone plus proguanil and those taking mefloquine (van Riemsdijk et al 2002).

Cohort and case-control studies

30. Of particular relevance to the question of long term effects were three studies based on prescriptions of mefloquine and their association with longitudinal data on specified neuropsychiatric events. There were two large cohort studies in US military populations (Eick-Cost et al 2017, Wells et al 2006) and a nested case-control study using data from the UK General Practice Research Database (Schneider et al 2013). These three studies had overall findings of similar or decreased risk of longer term neuropsychiatric outcomes for mefloquine-prescribed groups compared to control groups.

31. Eick-Cost et al (2017) compared neuropsychiatric outcomes in subjects prescribed mefloquine with outcomes in those prescribed doxycycline or atovaquone-proguanil, in both deployed and non-deployed groups. The risk period included the duration of the prescription and 365 days after the end of the prescription. Rates of neuropsychiatric outcomes were similar or less than rates among the other two antimalarials for the majority of outcomes. Mefloquine recipients were at increased risk of three outcomes, but only in particular subgroups: anxiety disorder in deployed but not in non-deployed compared to doxycycline only, PTSD in non-deployed but not in deployed compared to atovaquone-proguanil only, and tinnitus in deployed and non-deployed compared to atovaquone-proguanil only. This inconsistency by comparator drug and deployment status suggests that the associations are due to chance, especially given the large number of comparisons. Mefloquine recipients were at decreased risk for another six outcomes.

32. Wells et al (2006) compared hospitalisation data among deployed, mefloquine-prescribed groups with non-antimalarial prescribed groups who were either deployed or non-deployed, with follow up between 12 to 27 months. Mefloquine-prescribed individuals were at significantly decreased risk of hospitalisations for mood disorders compared with the non-deployed reference group. No other psychiatric or neurologic categories were significantly different when the mefloquine-prescribed group was compared with either reference group.

33. Schneider et al (2013) compared neuropsychiatric disorders in users of antimalarial chemoprophylaxis with non-users over a 540 day period. The risk of psychosis was non-significantly elevated in mefloquine users, while being non-significantly reduced for users of other antimalarials. Phobia, anxiety and panic attack diagnoses were non-significantly reduced in mefloquine users compared with non-users.

Case series and case reports

34. Most studies report that acute reactions to mefloquine occur after the initial few doses (Castelli et al 2010), and tolerance develops over subsequent days or weeks (Riemsdijk et al 2002, Ronn et al 1998, Weinke 1991). Given that mefloquine has been used by more than 35 million travellers for chemoprophylaxis worldwide since 1985 in Europe and 1990 in the USA (Schlagenhauf et al 2010), there is a strong likelihood that even rare effects would be able to be detected with reasonable frequency if a causal

relationship existed. Nevertheless, there are relatively few case reports of long term adverse effects given the high level of usage.

35. In a study using cases reported to a Danish adverse event reporting system, Ringqvist et al (2015) described long term effects of mefloquine in 73 subjects who reported mefloquine associated side effects over a 5 year period (1996-2000). 33 subjects reported that nightmares and cognitive dysfunction persisted beyond 9 months. This group of subjects was not randomly selected and there could be alternative explanations for the symptoms other than prolonged neurotoxic effects. The non-specific nature of the reported symptoms means that plausible alternative explanations could include anxiety arising from an acute reaction, use of other medications or exposure to unmeasured stressful life events. Because data were collected retrospectively, there may have been a bias towards recall of symptoms of concern, and it is uncertain when the symptoms first began in relation to taking mefloquine. Duration of symptoms could not be compared with a control group. There was no assessment of other potential causes of the symptoms.

36. There are occasional case reports of psychiatric effects lasting longer than a few months (Ronn et al 1998, unspecified duration; Lysack et al 1998, 12 months). There were three case reports in which, amongst other symptoms, persistent vertigo was reported (Lysack et al 1998, Nevin 2012, Livezey et al 2016) and one in which persistent hearing loss after mefloquine overdosage was reported (Lobel et al 1998). In two cases central vestibular dysfunction was suspected (Nevin 2012, Livezey et al 2016), though magnetic resonance imaging (MRI) was normal in both cases. There is a case report demonstrating damage to various parts of the brain in a person who was given 20 times the therapeutic dose of pamaquine, a historical drug belonging to the 8-aminoquinoline subclass and related most closely to primaquine (Loken and Haymaker 1949).

Biological mechanisms

37. The precise mechanism by which mefloquine might cause damage to the brain or vestibular system is unclear, but several hypotheses have been suggested. These include blockage of calcium channels and induction of toxic reactive oxygen species (Yu et al 2011), membrane channel blockade (Quinn 2015), apoptotic response and oxidative injury (Milatovic et al 2011), liver toxicity and hypervitaminosis A (Mawson 2013), and induction of autophagy (Shin et al 2012).

38. Animal studies of a number of quinoline compounds have investigated a possible central mechanism for dizziness and vertigo. One study demonstrated damage to brainstem nuclei in rats given mefloquine (Dow et al 2006). Rhesus monkeys given lethal and sublethal doses of the 8-aminoquinoline primaquine did not specifically demonstrate degenerative changes in the vestibular nuclei (Schmidt and Schmidt 1951). Primaquine was much less neurotoxic than the historical quinoline compound Plasmocid in rhesus monkeys (Schmidt and Schmidt 1948). While Plasmocid affected multiple brainstem nuclei at lethal doses, the auditory and vestibulo-cerebellar systems were much less affected by subfatal doses. At one quarter the maximum tolerated dose, only scattered degenerating cells were observed in the vestibular nuclei.

39. Other studies have focussed on potential peripheral effects of mefloquine on the vestibulocochlear system. Carrara et al (2008) assessed the effects on auditory function of a standard 3-day oral dose of artesunate combined with mefloquine for treatment of acute uncomplicated falciparum malaria. Among the 93 patients, neither audiometric or the auditory brainstem responses tests showed clinical evidence of auditory toxicity seven days after receiving treatment. In an experimental study, Yu et al (2011) examined the effect of mefloquine on organotypic cultures of the macula of the utricle from rats to determine if mefloquine might be toxic to the vestibular system. Hair cell nuclei in mefloquine-treated utricles showed evidence of apoptosis, which was consistent with earlier studies of inner ear toxicity. However, vestibulotoxicity of mefloquine in humans would depend on many factors, including dose and duration of treatment, uptake of the compound across the blood-brain barrier and individual susceptibility.

40. The occurrence of acute neuropsychiatric reactions in a minority of mefloquine users suggests that individual susceptibility is likely, but no biomarkers or genotypes of susceptibility have yet been confirmed (Nevin and Ritchie 2016). There is no imaging modality which has been able to reliably diagnose damage in the human brain after taking mefloquine.

Limitations of the available epidemiological SMSE

41. Among the difficulties with attributing persistent symptoms to mefloquine is the lack of comparative studies and the non-specific nature of most of the reported symptoms. While there is often a plausible relationship between a patient's initial symptoms and mefloquine exposure, the cause of progression of symptoms over the subsequent periods is difficult to ascertain. Without a comparison group, it is not possible to be sure that symptoms can be attributed to neurotoxicity, especially when these symptoms are common in the general population and overlap with other disorders, including PTSD and depression. In relation to military settings, McCarthy (2015) points out that many reported symptoms are not reasonably distinguishable from normal psychological or physiological reactions to psychological or environmental stressors that are frequently experienced in military environments.

42. Dizziness and vertigo have featured in case reports, but these are highly prevalent symptoms in the general population which can be attributed to a number of different pathological mechanisms, including disorders of the inner ear or labyrinth and general medical, cardiac, neurological, endocrinological, and psychological disorders. A systematic review of balance disorders in the general community (Murdin and Schilder 2014) identified a prevalence of dizziness severe enough to interfere with normal activities in the last month of around 11%. For symptoms of vertigo that interfere with daily activities, lifetime prevalence has been estimated at 3.0 to 7.8%. Two studies estimated 12-month incidence of new onset vertigo attacks at 0.76% and 1.4%.

43. There is no case definition for chronic mefloquine toxicity syndrome and no unique or distinctive group of symptoms has yet been specified (Nevin 2014, McCarthy 2015). Nevin and Leoutsakos (2017) sought to identify a distinct neuropsychiatric syndrome class associated with mefloquine using latent class modelling of US FDA Adverse Event Reporting System data. This technique produced a syndrome defined by a very high probability of symptoms of deliria (82.7%), including confusion and disorientation,

and a moderate probability of other severe psychiatric and neurologic symptoms, including dementia and amnesia (18.6%) and seizures (18.1%). The syndrome was more strongly associated with mefloquine than with other drugs, but was not specific to mefloquine or to antimalarials. This study was not designed to determine the sequence of the symptoms in relation to each other, or the duration of the symptoms.

Summary and conclusions

44. In summary, the attribution of chronic brain injury as a result of having taken mefloquine is postulated on the basis of acute neuropsychiatric symptoms, with some case reports and adverse event reports of persistence of a variety of commonly experienced symptoms, some pathology identified from animal studies and putative biological mechanisms. In order to establish that mefloquine can cause ongoing brain damage, it is necessary to consider whether there is SMSE showing a consistent pathology in human brain tissue that is associated with exposure to mefloquine and an enduring pattern of signs and symptoms, where the pathology, signs and symptoms are not likely to be attributed to any other risk factor.

45. No studies have measured cognitive performance in people who have taken mefloquine and reported ongoing symptoms, so it is not known whether they demonstrate neurocognitive deficits capable of meeting the DSM-5 criteria for a neurocognitive disorder.

46. No brain pathology has been demonstrated in people who have taken mefloquine and reported ongoing symptoms.

47. The three available comparative studies of longer term effects, while retrospective, show overall findings of similar or decreased risk of neuropsychiatric outcomes for mefloquine-prescribed groups compared to control groups.

48. No pattern of symptoms unique to past mefloquine users who report ongoing symptoms has been identified.

49. Therefore, at present there are insufficient data to define a specific chronic toxic encephalopathy which could be causally attributed to taking mefloquine.

50. This conclusion does not imply that symptoms experienced by people who have taken mefloquine are not real. Some people are reporting that they are experiencing a range of symptoms, which may be causing varying levels of distress and disability and which may require treatment.

51. To show that any chronic effects to the brain are due to mefloquine and not some other cause, prospective, controlled studies measuring rates, patterns and duration of symptoms in comparison with a non-exposed group are needed. Other methods which would assist in the confirmation of a specific chronic toxic encephalopathy attributable to mefloquine would include a working case definition in which the frequency, duration and pattern of symptoms is specified, evidence of neurocognitive deficits in comparison to a control group before and after taking mefloquine, and evidence of a specific and consistent pathology in the human brain from imaging and other suitable tests of brain function.

Tafenoquine

52. Tafenoquine belongs to the chemical class of drugs known as quinolines, the same chemical class as mefloquine. On this basis it has been proposed as another possible cause of long term brain injury. Tafenoquine is an 8-aminoquinoline drug, whereas mefloquine is a methanol-quinoline drug (Castelli et al 2010).

53. Tafenoquine has not been approved for use in Australia and its use has been limited to clinical trials. Tafenoquine has been trialled in the shorter term for prophylaxis (up to 6 months) or *Plasmodium vivax* post-exposure prophylaxis.

54. Randomised, controlled trials support the safety and efficacy of tafenoquine for malaria prophylaxis (Novitt-Moreno et al 2017, Leary et al 2009, Hale et al 2003, Lell et al 2000, Nasveld et al 2010) and post-exposure prophylaxis (Rajapakse et al 2015, Elmes et al 2008). One subject taking tafenoquine in one of the Australian Defence Force (ADF) clinical trials (Nasveld et al 2010) reported a severe adverse event (diarrhoea and abdominal pain). Other adverse events were mild and self-limiting, with gastrointestinal effects being the most common. Clinical trials do not report on adverse effects beyond the duration of the trial, so longer term effects of tafenoquine are unknown.

55. Two known side effects of tafenoquine are vortex keratopathy and haemolytic anaemia in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Vortex keratopathy is a benign and reversible condition, and as such unlikely to cause ongoing disability. It was reported in two of the ADF trials, but vision was not impaired in any subject and the condition was fully resolved by one year (Nasveld et al 2010, Kitchener et al 2007). Haemolytic anaemia in people with G6PD deficiency is also usually reversible and subjects were screened for this defect in the clinical trials conducted by the ADF.

56. A study of adverse effects of high dose tafenoquine in rats (Dow et al 2017) did not provide evidence of neurological toxicity, and suggested that, as in humans, dose-limiting toxicities are gastrointestinal disturbances and haemolysis in those with G6PD deficiency, rather than neurological effects.

57. These studies do not identify any evidence that tafenoquine causes long term signs, symptoms or pathology suggestive of chronic neurological damage in humans.

58. At present there are insufficient data to define a specific chronic toxic encephalopathy which could be causally attributed to taking tafenoquine.

Primaquine

59. Primaquine belongs to the chemical class of drugs known as quinolines, the same chemical class as mefloquine. On this basis it has been proposed as another possible cause of long term brain injury. Primaquine is an 8-aminoquinoline drug, whereas mefloquine is a methanol-quinoline drug (Castelli et al 2010).

60. Primaquine was developed in the 1940s and it has been the standard treatment for elimination of the dormant liver stage parasites of *Plasmodium vivax* and *Plasmodium*

ovale for more than 60 years (Recht et al 2014). Primaquine has also been used in addition to the standard treatment of falciparum malaria in areas of low transmission to reduce transmissibility of the treated infection. It has sometimes been used as chemoprophylaxis and in mass treatment campaigns (Recht et al 2014).

61. The long experience with the use of primaquine has provided data on the safety of primaquine, although these reports and trials were not specifically designed to assess long term adverse effects of primaquine on the brain. Gastrointestinal disturbance and haemolysis in those with G6PD deficiency are the main acute toxicities reported.

62. A comprehensive World Health Organisation (WHO) review reported on the safety of 8-aminoquinoline antimalarials, including primaquine (Recht et al 2014). Evidence for the safety of primaquine comes from case reports, clinical studies and observations during mass drug administration. The report confirmed that the most common and serious adverse reaction to this drug is haemolytic anaemia due to G6PD deficiency. There were four case reports of acute psychosis in patients taking primaquine in combination with chloroquine or mefloquine.

63. A Centers for Disease Control and Prevention (CDC) review (Hill et al 2006) likewise reported that neuropsychiatric changes seem to be rare, with only a single case report of depression and psychosis after primaquine use. This case was one of the four cases reported in the WHO review (Schlossberg 1980). A meta-analysis of randomised controlled trials (Kolifarhood et al 2017) concluded that primaquine is a safe and effective drug for malaria prevention, and non-inferior to other chemoprophylactic regimens concerning gastrointestinal and neuropsychiatric side effects.

64. Two clinical trials involving members of the ADF compared the safety and efficacy of primaquine with tafenoquine (Elmes et al 2008, Nasveld et al 2002). The most frequent adverse events reported across both groups were nausea, abdominal distress and diarrhoea. No serious adverse events were reported.

65. Fatal and subfatal doses of primaquine produced lesions in specific areas of the brain of rhesus monkeys, but the lesions were not considered severe and had no functional effect (Schmidt and Schmidt 1951). The authors concluded that "there was little likelihood that significant neuronal injury would result from use of primaquine in doses such as are employed for malaria therapy." The authors found that there was considerable variation in the types of toxic reactions caused by different 8-aminoquinoline compounds. Primaquine was much less toxic than Plasmocid, one of the other candidate 8-aminoquinolines they tested (Schmidt and Schmidt 1948). There was also considerable interspecies differences in toxic effects, with monkeys being much more susceptible to specific neuronal injuries than dogs, rats and mice (Schmidt and Schmidt 1949).

66. High and very high doses of primaquine given to humans in a 1952 clinical trial did not produce any neurotoxic effects, despite doses 16 times higher than the standard dose (Clayman et al 1952). There is a 1949 case report of a fatal overdose of pamaquine, another 8-aminoquinoline compound (Loken and Haymaker 1949). Over 20 times the therapeutic dose caused methaemoglobinaemia, haemoglobinuria, focal changes in the pons and some mild to moderate degenerative changes in parts of the brainstem and cerebral cortex.

67. These studies do not identify any evidence that primaquine causes long term signs, symptoms or pathology suggestive of chronic neurological damage in humans.

68. At present there are insufficient data to define a specific chronic toxic encephalopathy which could be causally attributed to taking primaquine.

PART VII DECISION

69. The Authority declares that it does not propose to make a Statement of Principles concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine, for the purposes of subsection 196B(2) or (3) of the Act. The Authority is of the view that there is insufficient sound medical-scientific evidence that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury. Further, there is insufficient sound medical-scientific evidence that there is a characteristic and persisting pattern of signs and symptoms following exposure to mefloquine, tafenoquine or primaquine that could be determined to be a particular kind of disease of, or injury to, the brain.

Professor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

18 August 2017

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