Specialist Medical Review Council

Declaration and Reasons for Decisions

Section 196W
Veterans' Entitlements Act 1986

Re: Decision of the Repatriation Medical Authority not to make Statements of Principles for "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine".

Request for Review Declaration No. 34

1. In relation to the decision of the Repatriation Medical Authority (RMA) not to make Statements of Principles for **"chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine"** the Council under s.196W(5)(b) of the VEA,

   DECLARES that it **was not satisfied** on the balance of probabilities that "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine" is a particular kind of injury or disease within the meaning of the VEA and accordingly the sound medical-scientific evidence available to the RMA is **insufficient** to justify the making of Statements of Principles in respect of **"chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine"**.

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REASONS FOR DECISIONS

Introduction

1. The Specialist Medical Review Council (the Council) is an independent statutory body established by the VEA. In general terms, upon receipt of a valid application the Council is to review as relevant:

   – the contents of Statement/s of Principles in respect of a particular kind of injury, disease or death; or

   – a decision of the Repatriation Medical Authority (RMA) not to determine, not to amend, Statement/s of Principles in respect of a particular kind of injury, disease or death.

2. In conducting a review, the Council must review all of the information (and only that information) that was available to the RMA when it made the decision under review. This is information, which was actually used by the RMA as opposed to information, which was generally available but not accessed by the RMA. A list of the information that was available to the RMA is listed in **B1 of Appendix B**.

3. Fundamental to Statement of Principles (SoPs), and so to a Council review, is the concept of sound medical-scientific evidence (SMSE), as that term is defined in section 5AB (2) of the VEA.[1]

[1] The SMSE is a subset of the available information. It comprises those articles which the Council considers:

a) are relevant to the matters within the proposed scope of review, and

b) satisfy the definition in the VEA of 'sound medical-scientific evidence'.

Sound medical-scientific evidence is defined in section 5AB(2) of the VEA as follows:

"Information about a particular kind of injury, disease or death is taken to be sound medical-scientific evidence if:

a) the information:

(i) is consistent with material relating to medical-science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or

(ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

b) in the case of information about how that kind of injury, disease or death may be caused – meets the applicable criteria for assessing causation currently applied in the field of epidemiology."

The latter requirement is held to mean 'appropriate to be taken into account by epidemiologists'.

4. The SMSE relevant to this application (the relevant SMSE) is listed in **B1 of Appendix B**.

5. The information to which the Applicants referred, being information, which was not available to the RMA at the relevant times, and so was not considered by the Council in reaching its review decision is listed in **B2 Appendix B.**

6. **Appendix A** sets out further details regarding the composition of the Council for this review and the legislation relating to the making of SoPs.

Scope of this review

7. The Specialist Medical Review Council (SMRC) received an application seeking review of the decision of the RMA not to create SoPs for "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine" contending that there was SMSE on which the RMA could have relied to create SoPs.

8. The Council wrote to the Applicant and to the Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) advising its decision on the proposed scope of the review and inviting comment. No comments were received on the proposed scope of the review and therefore the Council decided that it would have particular regard to whether there was SMSE on which the RMA could have relied to determine that:

   – exposure to mefloquine, tafenoquine or primaquine causes "chronic brain injury".

     and

   – 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.

9. If the Council was positively satisfied in respect of both of the above points, it would further be required to consider whether there was sufficient SMSE before the RMA on which to determine Statements of Principles for "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine".

Methodology (the Available Information)

10. The RMA provided the SMRC with the list of papers at B1 **of Appendix B** that it advised were available to it when it last investigated the questions under review. Conclusions were based

on an overall evaluation of the papers by the Council. Papers referenced in these reasons are those that the Council considered were most relevant to the issues before it.

Written and oral submissions

11. The Council took into account the submissions made to it, both written and in oral form.

Applicants' Submissions

12. On 9 February 2018 the Quinoline Veterans and Families Association (QVFA) provided a written submission to the SMRC, prepared for it by the Quinism Foundation. In it, the Applicant contended that "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine" is synonymous with a condition the Applicant referred to as chronic quinoline encephalopathy, or neuropsychiatric quinism. The Applicant submitted that this is a medical condition caused by poisoning of the brain by quinolines, including mefloquine, tafenoquine, and primaquine, with symptoms including sleep disturbance, anxiety, paranoia, personality change, dissociation, depression, suicidal ideation, cognitive dysfunction, disequilibrium, dizziness, vertigo, paresthesias, auditory and visual disturbances, and other effects that reflect dysfunction localized to areas of the limbic system and brainstem known to be affected by quinoline neurotoxicity.

13. The Applicant referred to papers by Nevin (2012, 2014, 2015), Nevin and Ritchie (2015), and Nevin and Leoutsakos (2017) in support of contentions that there is "a characteristic and persisting pattern of neuropsychiatric symptoms that occur following exposure to mefloquine, tafenoquine, or primaquine", and that this, "meets the statutory definition of disease".

14. The Applicant contended that the RMA made a number of errors in its interpretation of this literature.

15. On 14 June 2018, A/Prof Jane Quinn, representing the QVFA, provided an oral submission to the SMRC. She contended that the acute affects for the quinolone drugs are well documented and that the literature supports a 'toxidrome' which has a symptomatic relationship with mefloquine which is clearly documented in clinical case

reports in both the civilian and military domains. She submitted that existing SoPs for tinnitus sensorial hearing loss indicate permanent neurological injuries which are present at a cellular level. A/Prof Quinn submitted that "permanent neurocognitive deficits are a clear sign of neurological damage" and added that "cognitive problems are maintained for months and years after the drugs are withdrawn". She contended that "long-term neurocognitive deficits really impact people".

16. A/Prof Quinn stated that the best evidence in support of her contentions can be found in papers published since 2012, in particular those by Nevin, Ritchie, Ringqvist and Livezey, which set out a large number of individual case reports. She also referred to the Database of Adverse Event Reports as a source of evidence for the type of long-term cognitive effects which she had described.

17. In relation to the issue of Acquired Brain Injury, A/Prof Quinn submitted that there are two 'states'. The first relates to 'core neurological effects, sensory and cognitive' and the second to 'neuropsychological problems secondary to neurological damage'. She cited 'alcohol, cannaboids, opioids, solvents, and lead' as 'examples' of this.

Commissions' Submissions

18. The Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) made a written submission to the Council received on 1 February 2018 and an oral submission on 14 June 2018. The Commissions did not make specific contentions about the medical science in its submissions.

RMA Reasons

19. In its investigation, gazetted on 14 February 2017 and concluded on 18 August 2017, the RMA determined that, "there is insufficient sound medical-scientific evidence (SMSE) that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury." Further, the RMA considered that there is insufficient SMSE 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. The RMA set out its reasons in statement published on its website.

20. In its reasons the RMA said that it investigated whether SMSE existed for an association between exposure to mefloquine, tafenoquine or primaquine and "chronic brain injury". The RMA performed a literature search for material published between 1996 and the time of the review using search terms that included the drug names and the terms "adverse events", "poisoning", "toxicity", "psychotic disorders", ""neuropsychiatric", "mental disorders", and/or "brain injury". Evidence submitted to the RMA, literature cited within articles, literature from internet searches and reference textbooks were also included in the available literature.

21. The RMA reviewed the available literature for evidence of damage to human brain tissue following exposure to any of the named drugs and/or evidence for a characteristic and persisting pattern of signs and symptoms which could be considered a disease of, or injury to, the brain. The RMA considered results from animal studies with caution due to interspecies differences in drug toxicities and the higher drug concentrations typically used in animal studies.

22. The RMA said that it noted that the named drugs are known to have adverse effects which are recognised in existing SoPs, including acute neuropsychiatric effects. The RMA noted that there were few reports of prolonged and persistent symptoms following exposure. All such reports were either case reports or adverse event reports. The RMA noted that the absence of a control or comparison group in these types of studies limits the conclusions that can be made. The RMA also noted that a comparison group is important for this particular investigation since the nominated symptoms following exposure occur frequently in the general population. No human studies showed changes in cognitive performance or brain pathology following exposure to the named drugs. Some pathology was identified in animals exposed to high doses of mefloquine. Putative biological mechanisms have been proposed for mefloquine, but no experimental evidence was found to support these hypotheses.

23. The RMA concluded that there was insufficient SMSE to show that chemically-acquired brain injury can develop following exposure to mefloquine, tafenoquine or primaquine. It also concluded that there was insufficient SMSE for a characteristic and

persisting pattern of signs and symptoms following exposure to these drugs that could be considered a particular kind of brain injury or disease.

Background

Definitions of Disease or Injury

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

Disease means:

- *any physical or mental ailment, disorder, defect or morbid condition (whether of sudden onset or gradual development); or*
- *the recurrence of such an ailment, disorder, defect or morbid condition;*

but does not include:

- *the aggravation of such an ailment, disorder, defect or morbid condition; or*
- *a temporary departure from:*
- *the normal physiological state; or*
- *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 disease; or*
- *the aggravation of a physical or mental injury.*

25. The question of what constitutes a disease or injury for the purposes of determining a SoP under the Act is to be determined by the ordinary meaning of those words. While reference and regard may be had to ordinary dictionary definitions, medical dictionaries, and expert knowledge, ultimately, determining whether a condition is a disease as defined, the Council must conclude on the balance of probabilities whether or not the claimed condition is a 'disease' or 'injury' as used and understood in its ordinary meaning.

26. Being familiar with the ordinary English meanings of the terms that are used in section 5D, the Council considered whether “chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine” is a disease or injury. In doing so, it had regard to its expert medical knowledge and internationally agreed concepts.

27. A disease is a disorder (a disturbance or departure —e.g., of an organ or body system—from normal balance or healthy function).

28. An injury is generally identified where an individual has suffered something that can be described as a sudden and ascertainable or dramatic physiological change or disturbance of the normal physiological state. The suddenness of the change can be relevant to distinguishing a physiological change from the progression of an underlying disease.

29. In epidemiology, accurate diagnosis of a disease requires a case definition. A case definition is a set of criteria that must be fulfilled in order to identify a person as representing a case of a particular disease.

30. A case definition may be based on geographic, clinical, laboratory, or combined criteria or on a scoring system with points for each criterion that matches the features of the disease. In deciding whether to include or exclude cases in an epidemiological study, a case definition must be highly reliable.

Council's decisions on the relevant SMSE

31. The Council considered that the SMSE to be assessed in the review should comprise information:

    - that was available to the RMA at the relevant times;
        i. which was sent by the RMA to the Council under section 196K of the VEA;
        ii. which was considered by the Council to be SMSE as defined in section 5AB(2) of the VEA being information which:
    - epidemiologists would consider appropriate to take into account; and

- in the Council's view 'touches on' (is relevant to) matters within the scope of review.

32. The Council's final decision on the SMSE for the review was that it should comprise the information referenced in these Reasons.

33. Information, which the RMA advised was not available to it at the relevant times, was not taken into account by the Council for the purposes of the review, as it could only be considered as 'new information'.

Council's Evaluation of the SMSE

34. When evaluating the SMSE, the Council focussed on information relevant to the scope of the review and the list at **B1 of Appendix B.**

35. In forming its decisions on the SMSE, the Council brought to bear its scientific expertise and judgement. The Bradford Hill criteria, the NHMRC levels of evidence,[2] and other tools or criteria appropriate to be taken into account by epidemiologists were applied to the articles under review.

36. For ease of reference, the Bradford Hill criteria (noting that these are not exhaustive) are:

    - strength of association
    - consistency across investigation
    - specificity of the association
    - temporal relationship of the association
    - biological gradient
    - biological plausibility
    - coherence
    - experiment
    - analogy

[2] NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Available from https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf

37. The Council noted that these criteria are not necessary conditions of a cause and effect relationship. They act to provide some circumstantial evidence of such a relationship.

38. When considering the scientific literature The Council took into account methodological limitations or flaws which impact on the validity and conclusions which can be drawn from the available body of published research. Of particular relevance are limitations in statistical power, failure to control for confounding variables (e.g concurrent use of other drugs), sampling / selection / response biases, inadequate drug exposure assessment methods, deficiencies in psychometric test procedures, and inadequate follow-up periods following drug cessation.

39. The Council considered that while **animal studies** may sometimes support the biological plausibility of an association, the results from animal studies may not be generalisable to humans due in part to the extremely high doses of drug typically used. At best animal studies may be used as initial research to generate hypotheses, which may indicate a need for further studies on human subjects or to demonstrate possible biological mechanisms. For this reason, the Council focussed on studies that involved human subjects rather than animals.

40. The Council ordered papers by study type in reference to the levels of evidence recommended by the NHMRC. The order was from highest quality (meta-analysis or systematic review) to lowest quality (case series).

Definition of Chemically-acquired brain injury

41. In relation to the issue of the definition of, and terms used as synonyms for, Acquired Brain Injury (**ABI**) and Chemically-Acquired Brain Injury (**CABI**), the Council noted the following:

    - in the scientific literature, definitions of ABI vary considerably. However, it is generally accepted that ABI:

i. is an umbrella term which encompasses injuries and conditions of varying aetiology occurring after birth which result in brain damage; and

ii. carries a significant risk of a deterioration in cognitive, physical, emotional or independent functioning;

- in the available information for this review, ABI and CABI have not been clearly defined nor consistently applied, and various terms have been used. Of note are the following:

  i. the RMA did not provide a case definition for CABI and different terminology (e.g., chronic brain injury; chronic toxic encephalopathy) was used in the RMA's Statement of Reasons;

  ii. the submission by the Quinism Foundation considered CABI synonymous with "*chronic quinolone encephalopathy or neuropsychiatric quinism*" without providing specific descriptions or definition of the condition; and

  iii. the submission by the Commissions referred to "*particular disease, injury or death related to exposure to particular anti-malarial drugs and manifesting as a discrete form of chronic neurotoxicity*";

- in the most widely used classification system for psychiatric disorders, the DSM-5[3], there is no specific reference to or diagnostic criteria for ABI/CABI. However, a number of generally accepted ABIs in which the primary deficit relates to cognitive impairment are referred to in the diagnostic criteria for "Mild and Major Neurocognitive Disorders". "Substance/medication use" is specified as one of the aetiological subtypes.

42. This review was not an attempt to resolve issues relating to the definition of, and synonyms for, CABI/ABI. However, the Council has adopted the following definition of

[3] Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), (2013) *American Psychiatric Association*. Available from https://www.psychiatry.org/psychiatrists/practice/dsm

CABI for the purpose of assessing whether, on the balance of probabilities, CABI is caused by mefloquine, tafenoquine or primaquine:

Objective/scientific evidence of symptoms/changes in keeping with damage or injury to brain tissue as a direct consequence of, and specific to, use/exposure to mefloquine, tafenoquine or primaquine. These symptoms/changes are not better explained by the following: other psychiatric/medical conditions; a premorbid condition and/or non-specific symptoms which are common in general population (non-clinical) samples.

43. The following are considered supportive, although not essential, in establishing, mefloquine, tafenoquine and primaquine as an CABI risk factor:

- evidence of a dose-response relationship;
- evidence of brain injury/impairment on objective measures, including quantified clinical assessment, neuroimaging and standardised neuropsychological assessment;
- evidence of chronicity (i.e. persistence of symptoms/changes following cessation of drug exposure); and
- evidence of functional effects (at the body, person or functional level), particularly if chronic and/or severe.

44. The Council did not consider acute psychiatric disorders (e.g. anxiety, psychosis) or neurological symptoms (seizures), which have been found to resolve following drug cessation, to be sufficient for the diagnosis of ABI. The Council noted that some elements of these disorders are covered by existing SoPs (see paragraphs 50 and 51).

45. The Council noted that the term 'neuropsychiatric' outcomes/events was used in a number of studies. This generally included various emotional and physical symptoms which are not specific to/diagnostic of ABI.

46. The Council noted that in some of the studies the outcomes were self-reported and non-specific, with symptoms such as headache, sleep disturbance and dizziness. These symptoms, which are common in the general population, as well as in a range of medical and psychiatric conditions, are insufficient for a diagnosis of ABI.

47. The Council expressed concern about the use of the diagnosis Posttraumatic Stress Disorder (PTSD) in some of the studies, noting that the term may be referring to putative trauma-induced mental health symptoms rather the tightly defined entity of PTSD (classified as Disorder 309.81 in DSM-5).

Council's Conclusions on the Relevant SMSE

48. In reaching a decision about the **existence or otherwise of a particular kind of disease, injury or death**, the Council must consider and evaluate all of the SMSE and ultimately conclude on the balance of probabilities whether or not the identified condition meets the definition of an injury or disease as defined in the Act.

49. From the information that was available to the RMA at the relevant time, the Council considered all studies important to the scope of this review. In considering the matters within the scope of the review the Council closely analysed these studies, both individually and collectively, taking into consideration both quantitative and qualitative evidence.

50. The Council noted that mefloquine is currently included as a factor in SoPs for 15 conditions: acquired cataract, anxiety disorder, bipolar disorder, depressive disorder, epileptic seizure, heart block, myasthenia gravis, peripheral neuropathy, psoriasis, schizophrenia, sensorinueural hearing loss, suicide and attempted suicide, tinnitus, toxic retinopathy and trigeminal neuropathy. Twelve of these SoPs include "mefloquine" or "quinine and quinine derivatives" or "synthetic antimalarial drugs (e.g. quinacrine, hydroxychloroquine, chloroquine, primaquine, mefloquine)" as a drug in a specified list of drugs. The SoPs for suicide and attempted suicide specifically refer to taking mefloquine or chloroquine within six months before onset, and the SoPs for acquired cataract and toxic retinopathy list antimalarial agents and quinoline based drug as factors, respectively. For myasthenia gravis and schizophrenia mefloquine is not a factor for the onset of the condition, but is a factor for clinical worsening only.

51. The Council noted that tafenoquine and primaquine are currently included as factors in SoPs for the six conditions: acquired cataract, epileptic seizure, methaemoglobinaemia, psoriasis, sensorinueural hearing loss and tinnitus. Both tafenoquine and primaquine are included in the SoPs for epileptic seizure due to "antimalarials (including chloroquine, primaquine)" being included on the Specified List of drugs, with the onset of the condition required to be within 24 hours of drug dosing.

52. In reviewing the SMSE the Council considered the best evidence according to the hierarchy of study type. The SMSE contained a number of case studies which the Council acknowledged may be relevant to the generation of hypotheses but which do not fall within the NHMRC levels of evidence.

53. The following sections consider each of the proposed medications separately.

Mefloquine

54. The Council reviewed a number of papers[1-29] that reported mefloquine use in humans, where brain injury, central vestibular disorders or other neurological disorders were reported as outcomes. Among these papers were multiple reviews,[3, 9, 11, 14-18, 20, 22, 25, 30] which did not fit within the NHRMC levels of evidence. Two reviews[11, 16] were published as book chapters, one[30] as a standalone report and one[17] as an opinion piece. The Council noted that many of the source papers in the reviews were included in the SMSE.

55. The Council reviewed in vitro and animal studies[31-36] and concluded that they provided little evidence which related to ABI in humans. One study provided evidence that mefloquine can cross the blood-brain barrier in mice.[32]

Evidence from population studies

56. Two studies of neuropsychiatric outcomes in randomized control trials (RCTs) had conflicting results using the same measurement tool. Results from a 13-week RCT in 203 US military personnel stationed in Hawaii[1] found no significant changes during mefloquine use in a dizziness index on the Environmental Symptoms Questionnaire

(ESQ) for depression, anger, tension, fatigue, confusion and vigor as measured on the Profile of Mood States Questionnaire (POMS), compared to pre-drug baseline values. In contrast an RCT in non-immune travellers from the Netherlands[26] compared shortened POMS results before and after less than 1 month of travel for 58 mefloquine users and 61 people using atovaquone plus chloroguanide. The authors concluded that scores for depression, fatigue and vigor and overall mood disturbance on the POMS deteriorated significantly more during travel for the mefloquine group compared to the atovaquone plus cholorquanide group. This study also briefly assessed the effects of each of the drug regimens on three standardised tests of motor and cognitive functioning which were selected from a computerised test battery developed in the 1980s to assess the effects of exposure to neurotoxins, the Neurobehavioural Evaluation System (NES). The period between baseline and follow-up testing was fairly short (around 4 to 8 weeks). Both groups demonstrated a slight deterioration on a continuous performance task (assessing reaction times and accuracy over time) and improvements on two tests assessing eye-hand coordination and visuomotor processing speed. The two groups did not differ on any of the NES measures. The Council considered that these findings do not support a specific association between mefloquine and cognitive impairment on standardised testing.

57. Two studies reported results from RCTs involving mefloquine conducted within Australian Army personnel.[6, 10] Neuropsychiatric adverse events attributed to mefloquine were reported in less than 1.5% of the 153 participants during 6 months of prophylaxis, with mild vertigo the most frequent condition.[10] In the larger trial[6] where 1,157 individuals commenced mefloquine prophylaxis, there were 62 withdrawals from the study due to neuropsychiatric conditions (including sleep disturbance, anxiety, irritation, depression, hallucinations, confusion and balance problems) with three being classified as serious adverse events. Pre-existing medical conditions (auditory hallucinations and epilepsy) were identified in two individuals. The third individual experienced depression, episodic anxiety, mild paranoia, short-term memory loss and suicidal ideation and continued to deteriorate after cessation

of mefloquine. No further information about the medical diagnosis or long-term follow up of this individual was reported.

58. The case-control study of 564 travellers reported by van Riemsdijk et al[27] included 111 cases who contacted an insurance alarm centre during travel for diagnosed psychiatric symptoms and 453 controls who contacted an insurance alarm centre for non-psychiatric medical reasons. An elevated occurrence of psychiatric events during travel among females was reported which was statistically significant. There was a slightly increased risk in males that was not statistically significant. The most frequent events were depression, anxiety, panic attack, psychosis and insomnia. Delayed onset of symptoms which may have occurred after travel was not considered and the duration of long-term outcomes of the psychiatric events was not reported. The study did not address the issue of cognitive impairment or other possible indications of ABI.

59. Ringqvist et al[21] conducted a case control study assessing acute and long-term outcomes in 73 patients who reported adverse events to the Danish National Drug Authority. Measurement tools were the self-report symptoms checklist-90-revised (SCL-90_R) and SF-36 questionnaire with an average time of 988 days (270 – 2010 days) between onset of adverse event and completing questionnaire. There was some evidence that mefloquine may have long-term mental health effects using the SF-36 questionnaire. The Council noted that the SF-36 questionnaire does not directly address cognitive or neurological symptoms of relevance to ABI, and that no standardised neurocognitive tests were administered. Other areas of concern were that the control group of Danish 'norms' was only matched on age and sex, and not travel history or other potentially confounding factors experienced by the mefloquine group, and that other life events may have occurred in the extended duration between adverse event and survey completion which could confound the results.

60. The odds of developing first-time diagnosis of any anxiety or stress-related disorder or psychosis within 540 days of mefloquine use was significantly reduced (odds ratio (OR) = 0.71, 95% CI 0.56 – 0.90) compared to non-users of antimalarials in a nested case-control study of UK residents.[24] Increases in the BMI-smoking adjusted odds of

psychosis (OR = 2.17, 95% CI 0.85 – 5.99) were noted, along with decreases in odds of phobia (OR = 0.73, 95% CI 0.40 – 1.34) and panic attack (OR = 0.68, 95% CI 0.39 – 1.17). None of these sub-group analyses was statistically significant. A significant reduction in the adjusted odds of anxiety (OR = 0.60, 95% CI 0.43 – 0.83) was reported for mefloquine users.

61. Two large cohort studies[4, 29] in US military personnel showed little consistent evidence of increased risk of medically-diagnosed neuropsychiatric outcomes or hospitalisations for mental disorders, nervous system conditions or ill-defined conditions (including insomnia, hallucinations, convulsions and vertigo) following use of mefloquine. The numbers of personnel using mefloquine covered by these studies were 36,538[4] and 8,858.[29] Given the numbers involved here, the occurrence of CABI, if indeed it was a complication of mefloquine, might well have been evident, but it was not.

62. The cohort study reported by Japers et al[5] in 73 Dutch military personnel using mefloquine for prophylaxis documented adverse events in 13% of individuals either one month and/or three months after start of prophylaxis. No detail was provided for the type of event, although at least one of the events related to dizziness and coordination disorders which resolved with a reduction in drug dose.

63. A pooled analysis of data from 19,850 patients treated with mefloquine for malaria found that acute serious neuropsychiatric adverse events (headaches, dizziness, rigors, ataxia, sleep disturbance, tremor and palpitations) were rare (7.55/10,000).[7] All these patients had malaria parasitaemia and it is unclear that these symptoms are attributable only to mefloquine.

64. A statistical analysis of 12,478 records from the FDA Adverse Event Reporting System described a neuropsychiatric syndrome which was positively associated with use of mefloquine.[19] The syndrome had very high probability (82.7%) of deliria and moderate probability of depressed mood disorders and disturbances (31.8%) and psychiatric

disorders NEC[4] (31.4%). Other psychiatric and neurological symptoms occurred at lower probability including dementia and amnestic conditions (18.6%), seizures (18.1%) and communication disorders and disturbances (18.2%). A total of 933 records listing mefloquine were included and compared to 3,949 for doxycycline and 450 for atovaquone-proguanil. Although the absolute numbers where high, the comparison between mefloquine and doxycycline prophylaxis had low statistical power and potential bias due to 99.2% (3,919) of doxycycline records being excluded for not stating prophylaxis as the drug indication, compared to 65.5% (639) for mefloquine. The Council also noted that this study included all adverse event reports where antimalarial drugs were used irrespective of whether the drug was suspect or not.

65. A review of population-based studies by Schlagenhauf et al[22] found mixed results for increased incidence of neuropsychiatric adverse events following mefloquine use compared to other antimalarial drugs. The authors highlight the difficulty in defining the role of antimalarial drugs in neuropsychiatric adverse events due to the presence of other potentially confounding factors including travel.

66. A review by Nevin and Ritchie[11] used data predominantly from case studies to outline the challenges of diagnosing brain injury caused by mefloquine in the absence of biomarkers. The authors note that brain imaging often returns normal results but specialist testing sometimes results in a diagnosis of central vestibular disorder.

Case Studies in humans

67. A case report from Livezey et al[8] of chronic neuropsychiatric symptomology consistent with migraines, motion sickness or a central vestibulopathy documents the persistence of symptoms four and a half years after mefloquine exposure in a 32-year-old male who continued mefloquine prophylaxis for four months after onset of symptoms and did not seek medical assistance for four years. This case study did not

[4] Not elsewhere classified

include standardised cognitive testing or neuroimaging findings. PTSD and possibly also heavy use of alcohol at the time of mefloquine use were confounding factors.

68. Nevin[12] reported the case of a 24-year-old male with chronic symptoms lasting in excess of 10 months with a suspected diagnosis of somatoform disorder. Symptoms developed soon after the first dose of mefloquine prophylaxis and worsened with additional doses of the drug. Findings of neuroimaging (MRI/CT brain scans) were normal. No standardised cognitive testing was conducted.

69. Nevin[16] reported a case of a 33-year-old soldier who developed severe anxiety, paranoia, hallucinations, dizziness and photophobia two days after the third weekly dose of mefloquine with no prior prodromal symptoms. Following a diagnosis of PTSD his psychiatric symptoms improved while physical symptoms of vertigo, disequilibrium, photophobia and accommodative dysfunction became more prominent. Vestibular injury was diagnosed following documented nystagmus, six months after mefloquine exposure. No standardised cognitive testing or neuroimaging results were reported.

70. Weinke et al[28] conducted a risk analysis of adverse neuropsychiatric effects of mefloquine use in Germany and found the incidence to be very low (1 in 2,000 users). They also outlined case reports from 12 patients with neuropsychiatric side effects after therapeutic or prophylactic use of mefloquine. A variety of severe adverse effects including acute psychosis, hallucinations and seizures with convulsions were reported with all patients fully recovering within 10 days without sequelae. No standardised cognitive testing or neuroimaging results were reported.

Summary of evidence – mefloquine

71. Three of the population studies[19, 21, 27] considered reported an association between mefloquine use and increased occurrence of neuropsychiatric events (which are not a sufficient condition for diagnosis of ABI). All three had methodological weaknesses and none demonstrated causality or chronicity of diagnosed conditions. With the exception of one study[27] standardised neurocognitive testing was not undertaken.

72. The remaining SMSE arising from population studies showed little or no association between mefloquine use and increased occurrence of neuropsychiatric events. Many of these studies did not present any evidence of diagnosed conditions that would be consistent with ABI. The Council noted some studies[1, 23, 26] measured adverse events using neuropsychiatric outcome measures related to mood. It is not clear how outcomes of such measures relate to ABI or other neurological disorders. Standardised neurocognitive testing was not undertaken in any of the studies.

73. The Council concluded that there was insufficient SMSE documenting the development of ABI following use of mefloquine.

Tafenoquine

74. The Council reviewed a number of papers[3, 10, 37-44] that reported adverse events following use of tafenoquine. One animal study[45] was also reviewed. Since tafenoquine was not licensed by the FDA until 2018 the majority of studies were clinical trials[10, 37, 39-44] with two reviews[3, 38]. Several of the studies[10, 39, 41, 43-45] received funding from, or had lead authors working for, companies who have a financial interest in the registration of tafenoquine.

75. Nasveld et al[10] reported an RCT comparing tafenoquine (n=492) to mefloquine (n=162) for prophylaxis over 26 weeks in Australian soldiers. The authors found no significant difference in the incidence or nature of treatment-related adverse events between tafenoquine and mefloquine groups. There were no drug-related severe adverse events in the tafenoquine group involving neuropsychiatric symptoms. One person withdrew from the study due to depression which was graded as moderate. In total 2.0%, 1.2%, 0.6% and 0.6% of participants in the tafenoquine group reported vertigo, abnormal dreaming, headache and insomnia which were suspected as being drug related, with all cases categorised by a physician as mild or moderate.

76. Results from three clinical trials which were placebo-controlled[40, 41, 44] showed no statistical difference between rates of headache,[40, 41, 44] vertigo[44] or dizziness[41]

between the tafenoquine study groups and placebo. None of these studies reported any serious neuropsychiatric adverse events associated with tafenoquine.

77. Walsh et al[43] investigated tafenoquine for prevention of relapse after *Plasmodium vivax* infection in 35 Thai patients. The only neurological adverse event found was mild, transient headache which occurred in a minority of patients.

78. Nasveld et al[42] and Elmes et al[39] compared tafenoquine to primaquine for post-exposure prophylaxis in Australian soldiers and reported headache as the only neurological adverse event. In the majority of cases the severity of headache was classified as mild.

79. Bruechner et al[37] reported a dosing study conducted in healthy male volunteers. Some participants reported headache and/or being lightheaded/dizzy after taking tafenoquine, but the rates of these events were no different to that observed in the placebo group.

80. Two reviews[3, 38] were considered with neither reporting any neuropsychiatric side effects following use of tafenoquine.

81. Dow et al[45] reported no observable neurological changes in rat behaviour or brains following a single super-therapeutic dose of tafenoquine.

Summary of evidence – tafenoquine

82. The SMSE for tafenoquine was limited with studies only reporting headache or dizziness, and no subsequent medical assessment or standardised neurocognitive testing.

83. The Council concluded that there was insufficient SMSE documenting the development of ABI following use of tafenoquine.

Primaquine

84. Primaquine can be used for causal prophylaxis, terminal prophylaxis when leaving an area with malaria transmission, radical cure after vivax or ovale malaria, or as a gametocytocidal agent to prevent *P. falciparum* transmission. The last three of these

uses usually result in primaquine being administered with, or shortly after, other antimalarial drugs making it difficult to assign potential adverse events to the use of primaquine alone. Only two studies[46, 47] within the SMSE report results for primaquine use alone.

85. Kolifarhood et al[47] conducted a systematic review and meta-analysis of seven studies that investigated primaquine use for prophylaxis, one of which[42] the Council reviewed independently. Clinical side effects were self-reported by the participants or their supervisor in all studies except one where side effects were evaluated by physicians. The period of observation (prophylaxis plus follow-up) varied from 14 weeks to 37 months. The incident risk ratio comparing primaquine to placebo showed no significant difference in neuropsychiatric adverse effects. A similar result was obtained when primaquine was compared to other study drugs including mefloquine, doxycycline, proguanil and atovaquone/proguanil.

86. Clayman et al[46] reported on the toxicity of primaquine but no neuropsychiatric outcomes were described.

87. Recht et al[30] analysed a total of 1,429 individual case reports, describing 4,560 reactions, submitted to the Uppsala Monitoring Centre between 1969 and 30 July 2012 in which primaquine was suspected of being a causative or possible interacting factor. The authors noted reporting bias by year, country and individual reporter, and highlighted that adverse event reports can only originate in locations where systems exist to report such events. The large majority (89%, 4,062) of reactions were reported from Thailand with 96.6% (3,925) of these reported in 1997-98. The USA and Australia reported the next highest numbers of reactions with 216 and 102, respectively. Other drugs were implicated as possible contributors in several reports, particularly reports from Thailand where artesunate and mefloquine were listed as possible causes. A total of 14 deaths were attributed to primaquine, none of which involved neuropsychiatric symptoms. Nervous system disorders were reported in 1,518 reactions including dizziness (838), headache (657) and anoxic seizure (1). Psychiatric disorders appeared in 510 reactions with 260 references to agitation and

125 to confused state. There were three reports of psychosis, with two from the US reporting concomitant use of mefloquine, and one from Malaysia reporting concomitant use of chloroquine with quinine.

88. A review by Recht et al[30] noted that neuropsychiatric effects had been reported after administration of primaquine. In one case report, a 55-year-old man with malaria developed depression and psychosis after the second dose of primaquine (following treatment with chloroquine), with symptoms disappearing within 24 hours of discontinuing primaquine. An unspecified number of cases of vertigo, psychomotor agitation and transitory neurological problems were reported following mass administration of chloroquine and primaquine in Nicaragua in 1973-1983.

Summary of evidence – primaquine

89. The population studies for primaquine showed no association between using primaquine and neuropsychiatric adverse events. Case studies and adverse event reports demonstrate some neuropsychiatric conditions, however reporting bias was identified and often, other drugs were listed as possible causes.

90. The Council concluded that there was insufficient SMSE documenting the development of ABI following use of primaquine.

The council's conclusions on whether there should be statements of principles for "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine"

91. The Council concluded, **on the balance of probabilities**, that the **evidence does not** support that there is a disease or injury as defined in the Act described as "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine"

92. After reviewing the SMSE the Council noted that there were few human studies assessing either the acute or the long-term effects on cognitive functioning using standardised neuropsychological tests. This merits specific comment for a number of reasons. First, both the applicant's written and oral submissions made specific reference to "cognitive dysfunction" and "neurocognitive deficits" as sequelae of mefloquine, tafenoquine and primaquine use which the applicant contended are

evidence of an ABI. However, the SMSE provided little evidence of the presence and magnitude of such dysfunction or deficits. Secondly, there is a large inventory of standardised neurocognitive tests which are regarded as reliable and valid measures of brain function/dysfunction with established normal performance ranges. Evidence of cognitive impairment on standardised neuropsychological tests is usually an important and objective indication of ABI as evidenced by the DSM-5 criteria for a neurocognitive disorder. Thirdly, neurotoxic substances which are accepted risk factors for ABI are usually supported by studies which have used standardised neurocognitive tests and/or compelling pathological or autopsy data but neither was present in the SMSE. The Council noted a lack of reports of neuroimaging findings in available research on mefloquine, tafenoquine and primaquine.

93. The Council considered that the absence of established agreement on terminology to define CABI, particularly related to chronicity, has made the evaluation and the comparison of the SMSE difficult.

94. The Council noted that many of the symptoms reported following use of mefloquine, tafenoquine or primaquine were non-specific and that these symptoms are common in the population and overlap with other health conditions. Self-report of such generalised symptoms cannot be considered specific evidence of ABI in the absence of additional medical investigation including neuropsychological testing.

95. The Council acknowledges the concerns of the applicant and other veterans, particularly where they are suffering from unexplained health symptoms which can sometimes be troubling or debilitating and can have significant impacts on their lives. Reference to other SoPs, as noted in paragraphs [49] and [50] above, may provide an avenue for assistance.

96. Having decided that “chemically-acquired brain injury caused by mefloquine, tafenonquine or primaquine” is not a particular kind of disease or illness, the Council has no power under the Act to determine a SoP.

Council's Analysis of the New Information

97. As mentioned above, in conducting a review, the Council is unable to (and so did not) consider information which was not available to (not before) the RMA at the relevant times. However, having formed the view that there was nothing in the pool of information which pointed to the relevant association, and being mindful of the Applicant's comments, the Council considered whether in its view there was a basis for recommending to the RMA that it (the RMA) undertake a new investigation.

98. The Council has neither the capacity nor the jurisdiction to perform an investigative function, including undertaking a comprehensive literature search. However, by reason of the Councillors' specialist expertise in this kind of injury, disease or death, the Council was aware of some new information (listed at **B2 Appendix B**) which it considered on a preliminary basis.

99. The Council considered the new information to determine whether, in the Council's view, it warranted the Council making any directions or recommendations to the RMA.

100. In the Council's view any such direction or recommendation should only be made by the Council if it formed the view that the new information comprised SMSE as defined in section 5AB(2) of the VEA being information which:

- was information epidemiologists would consider appropriate to take into account; and
- in the Council's view, 'touched on' (was relevant to) the contended factor; and could potentially satisfy the reasonable hypothesis and/or balance of probabilities tests (as appropriate; see paragraphs [108] below for the relevant associations).

101. Two papers (Dow and Schmidt) describe animal studies relating to possible toxicity from mefloquine and aminoquinolines, but the outcomes should not be extrapolated to the occurrence of CABI in humans. The other papers did not include CABI as an outcome.

102. The Council considered that the new papers referred to it did not in its view warrant the Council making any recommendations to the RMA for a new investigation.

DECISION

103. The Council made the declarations summarised in paragraph 1 above.

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Specialist Medical Review Council

Declaration and Reasons for Decisions

Section 196W
Veterans' Entitlements Act 1986

Re: Decision of the Repatriation Medical Authority not to make Statements of Principles for "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine".

Request for Review Declaration No. 34

APPENDICES

APPENDIX A: THE CONSTITUTED COUNCIL AND LEGISLATIVE FRAMEWORK OF THE REVIEW

APPENDIX B:

- APPENDIX B1: MATERIAL BEFORE THE RMA
- APPENDIX B2: NEW MATERIAL WHICH WAS NOT BEFORE THE RMA

APPENDIX A: THE CONSTITUTED COUNCIL AND LEGISLATIVE FRAMEWORK OF THE REVIEW

The Specialist Medical Review Council

104. The composition of each Review Council changes from review to review depending on the issues relevant to the particular Statement/s of Principles under review. When a review is undertaken, three to five Councillors selected by the Convener constitute the Council.

105. The Minister must appoint one of the Councillors to be the Convener. If the Council does not include the Convener, the Convener must appoint one of the Councillors selected for the review to preside at all meetings as Presiding Councillor.

106. **Professor Charles Guest** was the Presiding Councillor for this review. Professor Guest is Chief Health Officer of Victoria, with academic affiliations at the University of Melbourne, Monash University and the Australian National University.

107. The other members of the Council were:

- **Dr Yun Hwang**. Dr Hwang is a neurologist in private practice in NSW with a specialist interest in cognitive disorders.

- **Dr Pauline Langeluddecke**. Dr Langeluddecke is a clinical psychologist in private practice who has considerable clinical experience in the neuropsychological assessment of acquired brain injury.

- **Dr Nicole Jones.** Dr Jones is a combined track teaching and research academic at UNSW Sydney, with specific expertise in neuropharmacology. Her research aims to better understand processes involved in brain injury in order to find new ways to protect the brain against injuries.

- **Associate Professor Jonathan Phillips**. Associate Professor Jonathan Phillips is a clinical and forensic psychiatrist. He was a former convenor of the SMRC.

The Legislation

108. The legislative scheme for the making of Statements of Principles is set out in Parts XIA and XIB of the VEA. Statements of Principles operate as templates. They are determined by the RMA, and set out those criteria (conditions or exposures), known as factors, that must as a minimum exist before it can be said that an injury, disease or death can be connected with service, on either or both of the two statutory tests, the reasonable hypothesis test [5] and the balance of probabilities test. [6] Statements of Principles are ultimately applied by decision-makers in determining individual claims for benefits under the VEA and the *Military Rehabilitation and Compensation Act 2004* (the MRCA). [7]

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5 The reasonable hypothesis test is set out in section 196B(2) of the VEA which provides;

> If the Authority is of the view that there is sound medical-scientific evidence that indicates that a particular kind of injury, disease or death can be related to:
>
> (a) operational service rendered by veterans; or
>
> (b) peacekeeping service rendered by members of Peacekeeping Forces; or
>
> (c) hazardous service rendered by members of the Forces; or
>
> (caa) British nuclear test defence service rendered by members of the Forces; or
>
> (ca) warlike or non-warlike service rendered by members;
>
> the Authority must determine a Statement of Principles in respect of that kind of injury, disease or death setting out:
>
> (d) the factors that must as a minimum exist; and
>
> (e) which of those factors must be related to service rendered by a person;
>
> before it can be said that a reasonable hypothesis has been raised connecting an injury, disease or death of that kind with the circumstances of that service.

6 The balance of probabilities test is set out in section 196B(3) of the VEA which provides:

> If the Authority is of the view that on the sound medical-scientific evidence available it is more probable than not that a particular kind of injury, disease or death can be related to:
>
> (a) eligible war service (other than operational service) rendered by veterans; or
>
> (b) defence service (other than hazardous service and British nuclear test defence service) rendered by members of the Forces; or
>
> (ba) peacetime service rendered by members;
>
> the Authority must determine a Statement of Principles in respect of that kind of injury, disease or death setting out:
>
> (c) the factors that must exist; and
>
> (d) which of those factors must be related to service rendered by a person;
>
> before it can be said that, on the balance of probabilities, an injury, disease or death of that kind is connected with the circumstances of that service.

7 See sections 120, 120A and 120B of the VEA and sections 335, 338 and 339 of the MRCA.

APPENDIX B:

TABLE 1 MATERIAL BEFORE THE RMA

CHEMICALLY-AQUIRED BRAIN INJURY

RMA ID Number	Reference List for #RMA424-1424-1424-1 as at 2 August 20172 August 20172 August 2017

77128	Adshead Surg Lt S (2014). Clinical research. The adverse effects of mefloquine in deployed military personnel. J R Nav Med Serv, 100(3): 232-7.
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60390	American Psychiatric Association (2017). Safety monitoring of medicinal products: Guidelines for setting up and running a pharmacovigilance centre. . Retrieved 14 April 2011, from http://apps.who.int/medicinedocs/en/d/Jh2934e/
80805	Ashley EA, Recht J, White NJ (2014). Primaquine: the risks and the benefits. Malar J, 13: 418.
80934	Australian Government - Australian Institute of Health and Welfare (2007). Disability in Australia: acquired brain injury. AIHW Bulletin, Bulletin 55. .
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77692	Beckley JT, Woodward JJ (2013). Volatile solvents as drugs of abuse: focus on the cortico-mesolimbic circuitry. Neuropsychopharmacol, 38: 2555-67.
81267	Boudreau E, Schuster B, Sanchez J, et al (1993). Tolerability of prophylactic Lariam regimens. Tropical medicine and parasitology, 44(3): 257-265.
16206	Brueckner RP, Lasseter KC, Lin ET, et al (1998). First-time-in humans safety and pharmacokinetics of WR238605, a new antimalarial. Am J Trop Med Hyg, 58(5): 645-49.
75192	Carrara VI, Phyo AP, Nwee P, et al (2008). Auditory assessment of patients with acute uncomplicated Plasmodium falciparum malaria treated with three-day mefloquine-artesunate on the north-western border of Thailand. Malar J, 233: .
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APPENDIX A

Information received in relation to investigation 424-1 concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine as at 2 August 2017

1. Submissions

1.1 [redacted] – email submission concerning information for the RMA review of SOPs related to adverse effects of mefloquine - 4 January 2016 (1690R);

1.2 RMA medical researcher discussion paper - evaluation of articles concerning mefloquine toxicity syndrome - February 2016 (16269R);

1.3 Repatriation Commission & Military Rehabilitation and Compensation Commission (Mr Simon Lewis PSM) - request for investigation of acquired brain injury and anti-malarial drugs - 6 February 2017 (17823R);

1.4 [redacted] - submission - chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine - 15 February 2017 (172294R);

1.5 [redacted] - submission and letter - chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine - 10 May 2017 (172498R & 172499R);

1.6 [redacted] - submission - chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine -10 May 2017 (172559R);

1.7 [redacted] - submission - chemically-acquired brain injury - 16 May 2017 (172535R);

1.8 [redacted] - submission - chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine - 18 May 2017 (172543R);

1.9 [redacted] - submission - chemically acquired brain injury - 18 May 2017 (172557R);

1.10 [redacted] Submission - chemically acquired brain injury - 19 May 2017 (172550R);

1.11 [redacted]

B2 NEW MATERIAL WHICH WAS NOT BEFORE THE RMA

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