Chapter 2

The causes of symptoms

Introduction

2.1 The committee received over 100 submissions from veterans suffering from chronic and complex symptoms which they attribute to taking mefloquine and/or tafenoquine over 18 years ago. The Quinism Foundation in the USA has proposed that there is a pattern of symptoms and has suggested the terms 'chronic quinoline encephalopathy' or 'neuropsychiatric quinism'.[1] Others such as the Australian Quinoline Veterans and Families Association (AQVFA) have used the terms 'mefloquine or quinoline poisoning'[2], 'mefloquine toxidrome'[3] or 'acquired brain injury'.[4] The Repatriation Medical Authority (RMA) notes other terminology used including 'chronic mefloquine toxicity syndrome', 'mefloquine intoxication syndrome', and 'chronic mefloquine-induced encephalopathy'.[5]

2.2 The weight of medical evidence presented to the committee in response to these claims is, in summary, that long term problems as a result of taking mefloquine are rare and there is no compelling evidence that tafenoquine causes long term effects. While committee members are not medical experts and can make no medical findings, this chapter provides a summary of the evidence on this issue provided to the committee.

2.3 This chapter contains a brief description of what is being claimed in relation to the medications; the broad response from the medical community; the safety profiles and side effects for mefloquine and tafenoquine; the use of mefloquine in the civilian population; the domestic and international evidence; the Therapeutic Good Administration (TGA) adverse event register; related medical inquiries by the RMA and Specialist Medical Review Council (SMRC); and attempts to explain what is occurring in some sections of the veteran community.

Disagreement over the cause of symptoms

2.4 Disagreement over the cause of symptoms was clearly evident during the inquiry. Associate Professor Harin Karunajeewa succinctly captured the issue:

> The point of controversy lies not in whether or not individuals are suffering from these symptoms, but in whether or not they are causally related to prior antimalarial drug use.[6]

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1 Dr Remington Nevin, *Committee Hansard*, 11 October 2018, p. 2.

2 AQVFA, *Submission 16*, pp. 8, 41.

3 AQVFA, *Submission 16*, p. 8.

4 AQVFA, *Submission 16*, p. 44. Mr Stuart McCarthy, *Submission 94*, p. 5.

5 RMA, *Submission 4*, Attachment 4, p. 53.

6 *Submission 15*, p. 5.

What is being asserted?

2.5 The AQVFA submitted that 'mefloquine poisoning', 'an accumulation of symptoms associated with adverse reactions to mefloquine' is responsible for the current symptoms being experienced by veterans. AQVFA advised that commonly reported symptoms include:

> …headache, tinnitus, dizziness, fatigue, anxiety, depression, sleep disturbances including vivid or lurid dreams, changes in thought and mood, confused thought processes and loss or diminution of working and / or long term memory, heightened feelings of aggression and paranoia. Acute physiological symptoms such as diarrhea, nausea, cutaneous rashes and cardiac arrhythmias…Severe acute adverse reactions include frank psychosis, hallucinations, and seizures. These symptoms represent a toxidrome which is clearly identifiable subsequent to mefloquine exposure...[7]

2.6 The AQVFA claim that 'an increasing body of evidence has established that serious symptoms of central nervous system dysfunction occur far more commonly tha[n] had been previously recognized[,] that had been originally intimated in the safety information associated with the drug and that these could be more prevalent and in military populations than has been previously anticipated'.[8]

2.7 Mr Stuart McCarthy, President of and spokesperson for the AQVFA argued that 'mefloquine is now known to be neurotoxic in some individuals, able to cause lasting or permanent brain damage, with chronic symptoms typically misdiagnosed as PTSD or other psychiatric disorders'.[9] He spoke of 'quinoline poisoning' and categorises symptoms as follows:

- psychiatric disorders including depression, anxiety, bipolar disorder and schizophrenia.
- cognitive impairments including memory and concentration difficulties.
- hearing problems including tinnitus, hearing loss and hyperacuity.
- vestibular disorders including dizziness, vertigo and spatial disorientation.
- neurological disorders including neuropathies, seizures, Parkinson's disease and motor neurone disease (MND).[10]

2.8 The AQVFA refers to work of Dr Remington Nevin[11] who is Executive Director of the Quinism Foundation, a US non-profit charitable organisation

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7 *Submission 16*, pp. 8-9.

8 *Submission 16*, p. 9.

9 *Submission 94*, p. 1. See also *Submission 16*, p. 42. *Submission 16.1*, p. 6; The Quinism Foundation, *Submission 17*, p. 5; Defence Force Welfare Association, *Submission 95*, p. 2.

10 *Submission 94*, p. 5.

11 According to his website, remingtonnevin.com, Dr Nevin 'was the first to publish clinical descriptions of the permanent toxic syndrome of brain and brainstem dysfunction caused by the use of mefloquine'.

established on 1 January 2018 which 'promotes and supports education and research on the family of medical disorders caused by poisoning by quinoline drugs'.[12] Dr Nevin is the only staff member and there is a board of directors consisting of five former US military officers or senior non-commissioned officers. The Foundation relies entirely on private donations.[13] The Quinism Foundation:

> …has proposed the term chronic quinoline encephalopathy, otherwise known as neuropsychiatric quinism, to define the clinical disorder caused by quinoline CNS neurotoxicity. The clinical features of neuropsychiatric quinism reflect the localization of observed neurotoxic injury across the broader quinoline class, with chronic dysfunction in affected areas of the brain and brainstem providing the most parsimonious explanation for the pattern of observed signs and symptoms from the disorder.[14]

2.9 Dr Nevin claims that for a 'sizeable minority of users we see this propensity to neuropsychiatric adverse effects and this risk of permanent disability associated with their use'. He stated that mefloquine and tafenoquine are 'idiosyncratic neurotoxicants at the doses used for prophylaxis' explaining that 'the drug is acting as a toxicant in some users and not in others—idiosyncratic. We don't know the reasons for that'.[15] He argued that it is inherently unsafe to use these drugs in a military environment as it is 'likely that the user will confuse or misattribute side effects from the drug to the stresses of travel, to the effects of crossing time zones and to the effects of stress on deployment'. His theory is that civilian users of mefloquine will stop taking the medication if they experience unpleasant symptoms whereas veterans 'in many cases they were simply ordered to take the drug' and 'never had the opportunity to stop [if they experienced unpleasant side effects]'.[16] Dr Nevin believes that 'veterans are disproportionately represented because in many cases they have been involuntarily intoxicated by these drugs'.[17]

The response of the medical community

2.10 The view of the medical professionals is that this syndrome put forward by Dr Nevin, AQVFA and others is not supported by the available medical evidence. Associate Professor Karunajeewa summarised this alternative theory being put forward:

> In recent years some authors have proposed an alternative theory that mefloquine (and tafenoquine) cause significant neurological toxicity that

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12 *Submission 17*, p. 2. See also Dr Remington Nevin, *Committee Hansard*, 11 October 2018, p. 2.

13 Dr Remington Nevin, *Committee Hansard*, 11 October 2018, p. 2.

14 *Submission 17*, p. 3. See Dr Remington Nevin, *Committee Hansard*, 11 October 2018, pp. 2-3 for further discussion of the theory being put forward.

15 *Committee Hansard*, 11 October 2018, p. 5. See also Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, p. 40.

16 *Committee Hansard*, 11 October 2018, pp. 4-5. See also Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, p. 41.

17 *Committee Hansard*, 11 October 2018, p. 5.

> results in neurological or psychiatric symptoms that can persist for many years after the drugs are ceased or even be permanent. This has variously been described using terms such as 'chronic mefloquine toxicity', 'mefloquine induced chronic CNS syndrome', 'acquired brain injury', and 'mefloquine (or quinoline) toxidrome'. This theory relies heavily on numerous assumptions, especially in extrapolating findings from older, more toxic quinoline drugs to mefloquine/ tafenoquine and from animal and laboratory studies to humans.[18]

2.11 Associate Professor Karunajeewa advised the committee that this should be regarded as a speculative hypothesis unless it can be supported by evidence from human subjects treated with mefloquine.[19] He added that the terminology being used such as 'chronic mefloquine toxicity' and 'mefloquine (or quinoline) toxidrome' are not 'widely used throughout the mainstream medical community, having until now been restricted to a fairly small core of authors with a particular interest and viewpoint on this matter'.[20]

2.12 The view of Associate Professor Karunajeewa was supported by Professor Geoffrey Quail, President, Australian College of Tropical Medicine:

> The theory that mefloquine causes long-term neuropsychiatric problems relates to work done with older drugs which were more toxic, and also from animal studies. It's very difficult to extrapolate from animal studies to humans. It [is] speculative unless supported by evidence from human treatment with mefloquine. Based on well-conducted studies of over 360,000 US military, which compared mefloquine with alternative drugs for malaria prophylaxis, the long-term mefloquine toxicity is quite minor. If it occurs at all, it's really topping up pre-existing neurological or neuropsychological problems. It is extremely rare for it to occur long term in someone who didn't have other problems. Thus in any subject with common psychological complaints—anxiety, depression, post-traumatic stress disorder—it is overwhelmingly likely to have existed due to factors other than mefloquine exposure.[21]

2.13 Professor Dennis Shanks in his personal submission also stated:

> As with all arguments of causation, there are elements of truth contained within the assertions regarding the toxicity of antimalarial drugs. However, the facts do not support the version of events put forward by some veterans which has symptoms developing years after drug administration and this causing current neuropsychiatric symptoms.[22]

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18 *Submission 15*, p. 4.

19 *Submission 15*, p. 4.

20 *Submission 15*, p. 6.

21 *Committee Hansard*, 30 August 2018, p. 42.

22 *Submission 13*, p. 1.

2.14 In looking at this issue, the RMA noted that '[t]here is no case definition for chronic mefloquine toxicity syndrome and no unique or distinctive group of symptoms has yet been specified…'.[23] The RMA concluded:

> The claim that there are persistent symptoms that are due to mefloquine is based on a small number of case reports and adverse event reports of a variety of commonly experienced symptoms in a widely prescribed medication. These same animal and human case reports are cited repeatedly as the basis for the contention of a syndrome resulting from permanent brain injury.[24]

2.15 Professor Nick Saunders AO, Chairperson, RMA responded to questions from the committee regarding the evidence presented by Dr Nevin:

> Doctor Nevin's evidence is based on case reports—case series. Epidemiologists have a hierarchy of evidence, and studies that generate evidence, for medical conditions. We consider, and epidemiological analysis considers, case reports to be the lowest level of evidence—very weak evidence. The sort of evidence that one would use to then properly design an epidemiological study to analyse or test the hypothesis that might come from that. Doctor Nevin is basing his premises and his assertions on the basis of a small number of case reports. It is very weak evidence, whereas there is much stronger evidence from larger studies, cohort studies, studies that have got controls in place, showing that, in fact, these drugs do not have demonstrable long-term neurocognitive ill-effects on the brain.[25]

2.16 Professor James McCarthy, Professor of Tropical Medicine and Infectious Diseases, Royal Brisbane Hospital and QIMR Berghofer Medical Research Institute spoke on the theory being put forward regarding mefloquine:

> Mefloquine is a drug that was discovered in the 1970s. Right at its very discovery, it was realised that it caused particular mental, psychologic and neurologic side effects in a small proportion of people who took it. That's been very clearly recognised by doctors and people involved in prevention and treatment of malaria, and I personally have observed that in patients I've treated with malaria. As well, there is a small proportion of people who take this drug for prophylaxis—that is, once a week—who unequivocally develop neurologic side effects and therefore should cease taking it, and certainly some groups of people are at higher risk of getting these side effects. What is not, in my mind, certain is the relationship between taking mefloquine for a short period of time and having long-term and permanent neuropsychiatric problems that are clearly caused by a short-term exposure to mefloquine. The literature and the scientific community do not believe that there's a strong link between people who've taken it and having long-term consequences. Certainly people have long-term consequences, but

23 RMA, *Submission 4*, Attachment 4, p. 58.

24 RMA, *Submission 4*, p. 8.

25 *Committee Hansard*, 15 October 2018, pp. 2-3.

> whether that's due to the mefloquine or something else is always very hard to figure out.[26]

2.17 When asked to respond to the evidence provided by Dr Nevin, Professor McCarthy responded:

> I suppose, being a doctor and a scientist, I try to return to what the evidence is and what's been published in the medical literature and what has been subjected to peer review. As I said before, the problem is you've got a situation where you've got a relatively common outcome in human populations, more common in soldiers that were deployed, and you've got a relatively low frequency of outcomes, and statistically it is very hard to be certain that there is an association that meets the criteria of being statistically significant. Although I may not be an epidemiologist, all of my work requires that I understand statistics and risk-benefit analysis. My view is in concurrence with the medical literature that there is no statistically significant association of tafenoquine with any of these purported problems—and, with mefloquine, for the long-term ones that I've described, not the short-term ones, it's very difficult to discern a statistically significant association between those things. That's not to say there might be an effect, but, if there is, it's very hard to find from the population data that we have available to us.[27]

2.18 Professor Dennis Shanks, Director, ADF Malaria and Infectious Disease Institute, also responded to the evidence by Dr Nevin:

> …I think that just about everything Remington Nevin said [to the committee] this morning was wrong. To make this short, when he stood up before the USFDA and tried to explain to people who understood drugs why his view of things—and it was the same view—was correct, he quoted two studies. One was a large study looking at 8-Aminoquinolines in monkeys which was done in the 1940s, and the one was a summer-student stem project done at Walter Reed which was never published. It's a poster. It's one-page long. I would be embarrassed trying to hang anything on those two studies. One was done long before mefloquine or tafenoquine were even synthesised, much less tested, and the other was a completely uncontrolled—interesting, but uncontrolled—study. The controlled studies with toxicity have come back with completely different answers. Tafenoquine and mefloquine are not the same drug. They don't have the same risk profile. What Remington Nevin says is wrong.[28]

2.19 At a Canberra hearing Associate Professor Karunajeewa summarised his view:

> In my submission I've done my best to summarise and synthesise the available evidence as I see it regarding neurotoxicity of mefloquine and tafenoquine. To restate my conclusions: for mefloquine I say that if

26 *Committee Hansard*, 11 October 2018, p. 22.

27 *Committee Hansard*, 11 October 2018, p. 26.

28 *Committee Hansard*, 11 October 2018, p. 58.

> permanent or long-term mefloquine toxicity does exist—and I think it's still a big 'if'—then it seems very unlikely that it causes a significant number of additional neurological and psychiatric problems over and above that which ordinarily occurs due to background rates of mental illness in the community. With respect to tafenoquine, my conclusions are, I think, even stronger still, and I say that there is no evidence at all that it causes increased rates of significant neurological or neuropsychiatric problems, whether acute or chronic, when used in conventional doses in humans.[29]

Possible side-effects

2.20 It is important to note that some evidence provided by individuals does not clearly distinguish between mefloquine and tafenoquine. Although they are both quinolines, tafenoquine is 'not structurally related to mefloquine' and is a primaquine[30] analogue.[31]

2.21 Given the numerous individual accounts of various symptoms the committee looked at the possible side effects of mefloquine and tafenoquine as stated in the advice to clinicians and patients as well as the possible duration of any side effects.

Mefloquine

2.22 Overseas, mefloquine was first granted marketing approval in Switzerland in 1984 and as at February 2018 was approved in approximately 27 countries worldwide. Around 40 million patients around the world have been treated with mefloquine since it was first made available. Mefloquine is listed as a malaria treatment option by the World Health Organization (WHO) and US Centres for Disease Control and Prevention (CDC). It is listed as a WHO essential medicine and is recommended in other authoritative guidelines for the prevention of malaria.[32]

2.23 In Australia, mefloquine is registered under the brand name Lariam, receiving regulatory approval and entered on to the Australian Register of Therapeutic Goods (ARTG) on 27 January 1993. It is indicated for malaria treatment and malaria chemoprophylaxis (prevention).[33] The submission and additional information from Roche indicates that mefloquine was approved in Australia on 3 September 1986.[34] Roche notes that this difference in dates:

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29 *Committee Hansard*, 11 October 2018, p. 29.

30 Primaquine is an antimalarial medication used to prevent and treat relapses of malaria. It is given to people as they leave a malarious area to kill any parasites that may be in the body. Defence, *Submission 1*, p. 15. See also Adjunct Professor John Skerritt, Department of Health, *Committee Hansard*, 11 October 2018, p. 40.

31 It is chemically closely related to primaquine. See 60P, *Submission 9*, p. 2; GSK, *Supplementary submission 8.1*, p. 1. See also Defence *Submission 1*, p. 15.

32 Roche, *Submission 12*, p. 2; Mr Svend Peterson, Managing Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 1.

33 Department of Health, *Submission 3*, p. 2.

34 Roche, *Submission 12*, p. 2.

> …reflects the introduction of the *Therapeutic Goods Act 1989* and the requirement for products to be listed on the Australian Register of Therapeutic Goods (ARTG). After the commencement of the legislation, products already approved and on the market were grandfathered into the ARTG. On the 27 January 1993, mefloquine was grandfathered into the ARTG. Mefloquine had indications for treatment and prophylaxis since is original registration in 1986.[35]

2.24 The Department of Health pointed out that as with all medicines there is a balance of benefits and risks for the population that will use them and regulatory approval by the TGA 'is based on an assessment that at a population level the benefits of the medicine exceed the risks'.[36]

2.25 Roche acknowledged that approval of a medication by the regulator does not indicate that the medication is suitable for everyone. Companies therefore work with regulators to develop and update Product Information (PI) and Consumer Medicine Information (CMI) which assist clinicians, pharmacists and patients to select the most appropriate medicine.[37] In the case of mefloquine, Roche advised that:

> …important safety information from patient and clinician reports have been included in PIs and CMIs since the medicine was made available in Australia. This has included information about neuropsychiatric side effects and precautions around use by people with existing mental health conditions. The purpose of this is to allow healthcare professionals to make a considered judgement on whether mefloquine or another antimalarial is most appropriate for a given person.[38]

Safety profile

2.26 The committee was told that long term problems as a result of taking mefloquine are rare.

2.27 The Department of Health noted that the use of mefloquine is contraindicated (i. e. not recommended for use) as follows: Patients with a past history of active depression, a recent history of depression, generalised anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders or convulsions should not be prescribed Lariam prophylactically (to prevent malaria).[39]

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35 Roche, Additional information, received 19 November 2018.

36 *Submission 3*, p. 2.

37 *Submission 12*, p. 3.

38 *Submission 12*, p. 3. Roche noted over the time that mefloquine has been registered with the TGA the product information has been updated 15 times to provide more information to prescribers and consumers about the risks and benefits. Five of these related to information around neuropsychiatric adverse events. Ms Natalie Touzell, Director, Regulatory Affairs Australia-New Zealand, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 7.

39 Department of Health, *Submission 3*, p. 2. See also Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 24.

2.28 The adverse effects section of the Lariam Product Information (PI) notes:

> The rate of adverse events associated with Lariam is published to be similar to that with other antimalarial prophylactic medications. In chemoprophylaxis[40] the safety profile of Lariam adverse events is characterised by a predominance of neuropsychiatric adverse reactions.
>
> Due to the long half-life[41] of Lariam, adverse reactions to Lariam may occur or persist up to several weeks after the last dose. In a small number of patients it has been reports that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine. There have been rare reports of suicidal ideations. No relationship to drug administration has been established.[42]

2.29 Regarding treatment:

> At the doses given for acute malaria, adverse reactions for Lariam may not be distinguishable from symptoms of the disease itself.
>
> Among subjects who received lariam for treatment, the most frequently observed adverse experiences included: dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhoea, skin rash, abdominal pain, fatigue, loss of appetite and tinnitus. Those side effects occurring less frequently included bradycardia, hair loss, emotional problems, pruritis, asthenia, transient emotional disturbances and telogen effluvium (loss of resting hair). Seizures have also been reported.[43]

2.30 In summary Roche advised:

> Based on Roche's evaluation of all available information, including data from post-marketing experience, published literature and other safety-risk management sources, the benefit-risk profile of mefloquine use in the prevention and treatment of malaria remains positive. This is aligned with the views of regulators such as the TGA and bodies such as the WHO and CDC. As a result, it remains available as an option for clinicians and patients to consider when selecting a medicine to prevent or treat the serious condition of malaria.[44]

2.31 At the 8 November 2018 hearing in Canberra, Roche confirmed that the 'benefit-risk profile of mefloquine is well understood and remains positive'.[45]

2.32 The RMA noted:

> Given that mefloquine has been used by more than 35 million travellers for chemoprophylaxis worldwide since 1985 in Europe and since 1990 in the

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40 The use of drugs to prevent disease.

41 Persistence in the bloodstream.

42 Department of Health, *Submission 3*, p. 3.

43 Department of Health, *Submission 3*, p. 3.

44 *Submission 12*, p. 4.

45 Mr Peterson, *Proof Committee Hansard*, 8 November 2018, p. 1.

> USA, it would be expected that even rare effects would be able to be detected with reasonable frequency if a causal relationship existed. Instead, there are only five case reports of people with some long term symptoms (especially vertigo or dizziness), together with reports of persistence of a range of commonly experienced symptoms amongst some of the cases reported to adverse event databases.[46]

2.33 The RMA stated that in relation to the 'acute adverse effects of the drug' which are the effects which occur at the time of taking the drug or soon after it has been discontinued, 'there is undoubtedly evidence that mefloquine is associated with a range of symptoms, some of which can be quite distressing…that evidence has been translated into 16 statements of principles as a causal factor in relation to particular diseases or injuries.'[47] However, the evidence shows that 'these reactions are not experienced by the majority of people who take the drug':

> These are reactions that occur in a minority of people. The evidence shows that the vast majority of those reactions settle over weeks or months, or sometimes symptoms have continued into more than 12 months. So, there are these acute effects. They are uncommon. When they do occur they can be very distressing. In their extreme form, they can have disastrous outcomes in terms of psychotic episodes and the like, but they resolve after taking the drug.[48]

2.34 Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health provided his view on the safety profile of mefloquine:

> Used in patients or individuals who do not suffer from psychiatric disorders, mefloquine, as antimalarials go, is quite a respectably safe medicine—I've taken it myself. Tafenoquine doesn't have as many adverse events in people with psych issues as does mefloquine. But, as antimalarials go, mefloquine definitely has a place.[49]

2.35 This view was supported by Professor Quail:

> Sure, mefloquine, as we've said, has this side effect profile, but it really is reasonably clear of side effects in about 90 per cent of cases. If it's taken, mefloquine is taken at a dose of 25 milligrams per kilogram, which is a standard dose. The incidence of severe neurotoxicity is less than one in 1,500. As I said, in almost every case that clears away unless there's a pre-existing psychiatric problem.[50]

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46 *Submission 4*, p. 9.

47 Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

48 Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

49 *Committee Hansard*, 11 October 2018, p. 40.

50 *Committee Hansard*, 30 August 2018, p. 42.

2.36 Adjunct Professor Skerritt emphasised the need for second or third line drugs due to antimalarial resistance in parts of Asia and Africa and because some people cannot tolerate doxycycline.[51]

2.37 Responding to concerns about whether a public health danger is being missed, Associate Professor Karunajeewa stated:

> The scale of this is that we're talking about 200 million people a year. Most of those people are being treated with some form of quinoline antimalarial of one type or another, and this has been going on for decades—hundreds of tonnes per year. The quinoline antimalarial drugs are probably the most-used drugs in human history, just to keep that in perspective. 'Are we missing something actually causing long-term harm?'…I go back to the evidence that we have. I don't think there's anything particular to suggest that that is the case. We're in the business of trying to limit sickness and death from one of the most serious illnesses that has ever affected humans. It has killed 300 million people over the history of humankind, and we're trying to put a stop to that. We're trying to put a stop to that, and we've had, I think, not insignificant successes over the last 15 years or so. There have been profound advances in the control of malaria which we think have saved about six million lives over the last 15 years. The improvements in malaria control are related to the use of bed nets but also to these new quinoline drugs that we're using for malaria. Six million people we think are alive today who wouldn't be if we hadn't been instituting those measures. We can't just sit around and watch it all happen; we have to try to do something about it, and that involves some risks. Nothing is achieved without risks, but our job is to try to manage those risks and minimise them.[52]

Defence approach

2.38 The potential side-effects of mefloquine were known and taken into consideration by Defence and are reflected in their cautious approach:

> Defence has always acknowledged that mefloquine can cause side effects, including neuropsychiatric problems, while individuals are taking the drug. Our conservative approach is a direct acknowledgement of these potential side effects. Generally, symptoms will disappear when the individual stops taking the drug but they can persist for some time afterwards due to the drug's long half-life of two to four weeks. Defence also acknowledges that neuropsychiatric side effects have been known to continue and become long term in a small number of individuals.[53]

2.39 Defence emphasised to the committee that at the time of the trials in the late 1990s and early 2000s, mefloquine was approved by the TGA, however Defence recognised:

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51 *Committee Hansard*, 11 October 2018, p. 40.

52 *Committee Hansard*, 11 October 2018, pp. 33-34.

53 *Submission 1*, p. 2. See also Defence, *Supplementary submission 1.1*, pp. 22-23.

> …mefloquine should not be taken for malaria prevention by people who have, or have had, a psychiatric condition, seizures, kidney disease or liver disease. For these reasons, Defence health policy requires that ADF members be properly informed of the potential side effects of mefloquine and that the drug only be prescribed by a qualified medical practitioner after the member has been provided information about the drug's side effects.[54]

2.40 Defence indicated that the known possible side-effects are outlined in the patient information:

> Mefloquine is known to cause unusual dreams and can cause psychiatric symptoms in some people, including disturbed sleep, anxiety, paranoia, depression, hallucinations and psychosis. Dizziness and loss of balance have also been reported as side effects from the use of mefloquine. For this reason, the medication is not used in ADF aircrew.[55]

2.41 The committee received a number of submissions from individuals recalling the vivid dreams they experienced while taking mefloquine.[56] This was addressed by Professor McCarthy who explained:

> When you take it, the levels of the drug go up in your blood very quickly and then they go down quite quickly. During that phase of 12 hours or so when the drugs are at high levels in the blood, people very frequently describe how, in the evening after they take their mefloquine, they would have a disturbed night's sleep or vivid dreams. But that is not a dangerous effect, and that's an effect that does disappear. I would always warn somebody that they should expect to have perhaps some disturbances in their sleep the night they take their mefloquine.[57]

2.42 Professor Sandy McFarlane AO, Director of the Centre for Traumatic Stress Studies at the University of Adelaide was asked by Defence to conduct a literature review on the adverse effects of mefloquine. The major findings of this review were:

- there are various theories on how mefloquine might cause neuropsychiatric effects based on its underlying action.
- there are varying conclusions about its potential toxicity.
- these variations are, in part, explained by the differences of the methodology used in the published reports.

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54 *Submission 1*, p. 12

55 *Submission 1*, p. 12.

56 See for example, Name withheld, *Submission 53*, p. 1; Mr Benjamin Fleming, *Submission 72*, p. 2; Name Withheld, *Submission 76*, p. 3; Name withheld, *Submission 97*, p. 1; Name Withheld, *Submission 101*, p. 1.

57 *Committee Hansard*, 11 October 2018, pp. 24-25. See also Associate Professor Harin Karunajeewa, *Committee Hansard*, 11 October 2018, p. 32; Defence, *Supplementary submission 1.1*, p. 22.

- the serious side effects of mefloquine have been known for many years, but continuation of effects after ceasing medication is a concern raised in recent years.
- there is no specific way to diagnose chronic mefloquine effects as many symptoms are shared with other conditions such as PTSD.
- there is no specific treatment except to cease the drug when symptoms develop and to treat the symptoms.
- the literature available at the time of this review does not address some questions, including:
    - Are some individuals pre-disposed to adverse effects?
    - Does mefloquine modify the response to trauma?[58]

Duration of side effects

2.43 Regarding the length of any side effects, the committee was told that they normally resolve after the medication is stopped. Defence indicated:

> Normally side effects, including neuropsychiatric side effects, resolve within days to weeks after stopping mefloquine. Mefloquine has a half-life (persistence in the bloodstream) of two to four weeks, which is longer than other antimalarials, therefore side effects that emerge while taking mefloquine have been reported to persist after cessation of the medication and sometimes for several months.[59]

2.44 Roche provided further detail on how long the medication takes to be eliminated from the body:

> …the half-life of the drug is quite long—it's 21 days—so that allows people not to have to take it daily—hence the weekly dosing regime that I described. That is, of course, an advantage when one looks at compliance and how well people adhere to medicines that have been prescribed to them. So the fact that the drug itself and its metabolites have half-lives of about 21 days means that, after 21 days, half the drug is eliminated from the body. The general understanding is that, in five times the half-life for the drug, it will be eliminated, which would be maximally 100 days. But they would be very low doses at that time, very low concentrations.[60]

2.45 Associate Professor Karunajeewa pointed to data from numerous clinical studies which have consistently found that any mefloquine side effects:

- develop early on in the drug's use;
- are more likely to occur in those with pre-existing psychiatric illnesses;

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58 Defence, *Submission 1*, p. 45; Defence, *Supplementary submission 1.1*, p. 25.

59 *Submission 1*, p. 12.

60 Dr Peter Stewart, Roche, *Proof Committee Hansard*, 8 November 2018, p. 4.

- are dose-related (therefore more likely to occur or be more severe if higher doses are used); and
- generally resolve following cessation of the drug.[61]

2.46 Associate Professor Karunajeewa emphasised that these findings have been reinforced by the clinical experience with many millions of people treated with mefloquine throughout the world.[62]

2.47 Further explanation was provided:

> …mefloquine, like virtually all drugs, can cause toxicity that encompasses a spectrum from none at all on one side, to very severe on the other. The key question then becomes, in practice, how many people taking the drug fall into the "very severe" category with lasting or permanent significant side effects. Is this likely to be very rare or quite common? To answer this question, our best available approach is to draw on the results of carefully constructed studies that apply the best statistical methods to compare the prevalence of these symptoms in humans who have taken these drugs, with a suitable group for comparison (often referred to as a control group).[63]

2.48 Associate Professor Karunajeewa discussed the possible length of side effects with the committee:

> To actually understand whether that does occur or not [that side effects are generally resolved following cessation of the drug] is the difficult process that we need really good evidence for, and I believe that large study of 360,000 is probably the best that we've got. There certainly have been reports, case reports, of people who have had persisting dizziness, persisting problems with ringing in the ears and that sort of thing, but it's still hard to be absolutely sure that it's mefloquine that's the cause of the problem. But, look, I'm perhaps a little bit more sanguine than some people in terms of being absolutely on one side of the barge or the other. I still think it's possible that in some rare, unlucky individuals that they do experience longstanding effects from mefloquine. I still think that's possible. But my reading of the literature and of the accumulated evidence is that, if that does occur, it's highly likely that it's actually quite a rare event.[64]

2.49 He further responded that these rare events are more likely to occur in those who have a pre-existing psychiatric illness.[65]

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61 *Submission 15*, p. 4. See also Professor Geoffrey Quail, President, Australian College of Tropical Medicine, *Committee Hansard*, 30 August 2018, pp. 44-45.

62 *Submission 15*, p. 4.

63 *Submission 15*, p. 8.

64 *Committee Hansard*, 11 October 2018, pp. 32-33.

65 *Committee Hansard*, 11 October 2018, p. 33. See also The Australasian Society for Infectious Diseases, *Submission 6*, p. 2.

International and domestic studies

2.50 The committee was told about the international and domestic studies involving mefloquine. Although the next section is not exhaustive, relevant submissions contain further details.

2.51 Associate Professor Karunajeewa directed the committee to a large and well-designed study published in 2017 of 367 840 US military personnel[66] which compared the incidence of neuropsychiatric diagnoses occurring up to a year following drug exposure in 36 568 individuals who took mefloquine with 331 272 who took an alternative malaria drug such as doxycycline or Malarone.[67] Following analysis of the findings in his submission Associate Professor Karunajeewa concluded:

> Based on these findings, we cannot absolutely with 100% [certainty] disprove the theory that mefloquine causes long-term toxicity in humans. In fact we can never do this - that's just not how science works. However, based on the study's findings, we can say, that if mefloquine did cause long-term toxicity (and that is still a very big "if"), then this is likely to occur as a fairly uncommon event and would only contribute to a very small proportion of the background rates of psychiatric disease in the population.[68]

2.52 Associate Professor Karunjeewa indicated that this US study '[b]y nature of this [the use of appropriate methods] and its very large size, it effectively constitutes the best evidence on this subject we currently have, and probably the best evidence we are ever likely to have'.[69] However, he also pointed to a smaller study conducted by the US CDC in 2016 which invited former Peace Corps volunteers (from 1995 to 2014) to participate in an internet based survey related to malaria prophylaxis and medical diagnosis. Noting the methodological problems (only 11 per cent participation) and recall bias, the overall conclusions were that:

> (1)'Malaria prophylaxis use by Peace Corps Volunteers is safe', (2) 'When excluding those with prior psychiatric illness there were no difference in psychiatric diagnosis rates' in mefloquine users and (3) In those with pre-existing psychiatric diagnoses, 'certain psychiatric diagnoses were more likely among Mefloquine users'. This last point is consistent with existing knowledge regarding risk factors for neuropsychiatric effects of mefloquine and emphasizes the importance of good screening for these contraindications prior to prescribing.[70]

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66 Eick-Cost et al, Neuropsychiatric outcomes after Mefloquine exposure among U.S. military service members, *American Journal of Tropical Medicine and Hygiene* 2017; 96: 159-166. See also Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 25.

67 Atovaquone-proguanil.

68 *Submission 15*, p. 9.

69 *Submission 15*, p. 8; *Committee Hansard*, 11 October 2018, p. 29. See also Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 27.

70 *Submission 15*, p. 9.

2.53 Associate Professor Karunajeewa stated that '[o]verall I think their findings were consistent with and supported by the larger and more rigorous subsequent [2017] study'.[71]

2.54 Responding to a question about taking mefloquine long-term, Professor McCarthy also referred to the study of US Peace Corps volunteers who took mefloquine for years while working in sub-Saharan Africa and that 'the rate of these side effects went down as people took the mefloquine for longer'.[72]

2.55 Associate Professor Karunajeewa emphasised that the results of these studies:

> …are also borne out by the now very extensive clinical experience with mefloquine. Until as recently as 2011, up to 17,000 Australian travelers were being prescribed mefloquine by GPs and travel clinics. As many as 35 million people a year receive the drug (mostly in much higher treatment doses than are used for prophylaxis). This represents the very large 'denominator' of total mefloquine use in the community and suggests that the isolated reports of serious side effects represent an extremely small fraction of the total users.[73]

2.56 Professor McCarthy also spoke about his own research involving mefloquine in small groups in three different doses:

> With the people on the highest dose, I think three or four of the eight people had what I would consider to be unacceptable side effects of the mefloquine when given very high doses to cure their malaria. So, without a doubt, the mefloquine did cause those transient side effects that went away once the mefloquine went out of their system.[74]

2.57 Defence also pointed to a 2006 study[75] which was a retrospective analysis of US military health records between 2002 and 2004 to examine the adverse effects of antimalarials. The study compared numbers of hospitalisations of military personnel who had been prescribed mefloquine and were deployed to active duty in malarial areas with those who had not and resided in Europe or Japan and those who were otherwise deployed. It found that '[m]efloquine users were statistically less likely to be hospitalised (after deployment) with mood disorders, or for any cause, than military personnel who did not receive any antimalarial agents but who were deployed to a war zone'.[76]

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71 *Submission 15*, p. 9. See also Defence, *Supplementary submission 1.1*, p. 21.

72 *Committee Hansard*, 11 October 2018, p. 22.

73 *Submission 15*, pp. 9-10.

74 *Committee Hansard*, 11 October 2018, p. 23.

75 Wells TS, Smith TC, Smith B, Wang LZ, Hansen CJ, Reed RJ, et al. Mefloquine use and hospitlaizations among US service members, 2002-2004, *American Journal of Tropical Medicine and Hygiene 2006*; 74(5): 744-9.

76 *Submission 1*, p. 47.

2.58 Dr Nevin criticised the studies cited, saying they have not been informed by 'methods of modern psychiatric epidemiology'.[77] This was not supported in evidence to the committee.[78] Adjunct Professor Skerritt commented that in general, 'neuropsychiatric tools are used to determine fairly subtle changes…You don't need a neuropsychiatric tool to say you've had severe insomnia or bad dreams or bad depression…so I'm not sure that that's necessarily required if you're looking for a serious adverse event'.[79]

2.59 Dr Peter Stewart, Roche, told the committee that 'mefloquine is the most studied of all the antimalarials' and '[t]here is a very large volume of evidence that has been collected around the safety and efficacy of this drug'.[80] He referred the committee to the most recent publication on the safety of efficacy published in 2017 by the Cochrane Collaboration[81] which is 'one of the most respected, independent, evidence based scientific bodies in the world'.[82] It reviewed a million patients using a variety of information sources including clinical trials, non-clinical trials, hospital records, and health authority records. It found that the 'risk benefit profile is very well understood and very well described and remains positive'.[83] Dr Stewart pointed to some of the findings of the Cochrane Collaboration that 'mefloquine does not have more frequent serious side effects overall than the two commonly used other antimalarials, doxycycline and atovaquone-proguanil [Malarone]'. 'They [the Cochrane Collaboration] did note, as we know, that people taking mefloquine are more likely to have [transient] abnormal dreams, insomnia, anxiety and a depressed mood for the period during travel than those who take doxycycline or atovaquone'.[84]

2.60 Dr Stewart also noted the large volume of clinical research data and real world data collected over 32 years and stated that this body of evidence does not support the hypothesis of brain injury from antimalarial treatment generally or mefloquine specifically.[85] He pointed to one of the conclusions of the Cochrane Collaboration which was:

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77 *Committee Hansard*, 11 October 2018, p. 8.

78 Associate Professor Harin Karunajeewa, *Committee Hansard*, 11 October 2018, p. 33; Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 26.

79 *Committee Hansard*, 11 October 2018, p. 44.

80 *Proof Committee Hansard*, 8 November 2018, p. 3.

81 See https://cidg.cochrane.org/news/cochrane-review-update-mefloquine-preventing-malaria-during-travel-endemic-areas, accessed 19 November 2018. Tickell-Painter M et al, Melfoquine for preventing malaria during travel to endemic areas, Cochrane database of Systemic Reviews, 2017, Issue 10:CD006491; See also, Roche Products Pty Ltd, Answers to questions on notice from 8 November 2018 hearing, received 19 November 2018.

82 *Proof Committee Hansard*, 8 November 2018, p. 3.

83 Dr Stewart, *Proof Committee Hansard*, 8 November 2018, p. 8.

84 *Proof Committee Hansard*, 8 November 2018, p. 4.

85 *Proof Committee Hansard*, 8 November 2018, pp. 8-9.

> We believe it is important that the large retrospective healthcare record analyses did not demonstrate a clear quantitative association between mefloquine use and formal mental health disorders.[86]

Metabolisation

2.61 As the AQVFA points to metabolisation of the drugs as a possible reason for potential adverse reactivity,[87] the committee discussed the metabolisation of mefloquine with Roche which advised that metabolisation occurs through a class of enzymes called the cytochrome P450 enzymes. While there are more than 50 types of cytochrome P450 enzymes, the two most common are CYP3A4 and CYP2D6 and mefloquine is metabolised by CYP3A4. Dr Stewart noted the hypothesis that if a patient has a low level of CYP3A4 then potentially the body might not be able to metabolise mefloquine as well as others or it might not be cleared as rapidly. He explained that all medicines are metabolised by one of these enzymes and it has not been determined that routine use of testing to discover genetic variations in people would improve outcomes. He also pointed to the large body of evidence in relation to mefloquine which does not support the hypothesis that mefloquine causes brain injury[88] or long term mental health disease or conditions.[89] See below for further discussion of metabolisation in relation to tafenoquine.

PTSD

2.62 Professor McFarlane speculated about the role of antimalarials which may modify the risk of developing a range of psychiatric disorders including PTSD.[90] This was addressed by Dr Dow from 60 Degrees Pharmaceuticals:

> It is not disputed by most travel physicians that mefloquine at prophylactic doses statistically increases the risk of the following adverse events relative to doxycycline and atovaquone-proguanil: insomnia, abnormal dreams, anxiety and depression. Professor McFarlane speculates that antimalarial drugs that are "psychotropic" and cause such events in some individuals might increase the risk of rarer and more severe post-deployment psychiatric events, particularly in stressful situations. However, he neglects to mention that, at a population level, the scientific literature does not support such a causal association in practice. In fact, recent reports from reputable U.S. government agencies have demonstrated that (i) deployment and combat experience not antimalarials increases the risk of PTSD and other serious psychiatric events, (ii) mefloquine and atovaquone-proguanil result in a similar increase in the total burden of neuropsychiatric illness during deployment and (iii) the long term risk of serious psychiatric events

86 *Proof Committee Hansard,* 8 November 2018, p. 9.

87 *Submission 16*, pp. 51-52.

88 *Proof Committee Hansard,* 8 November 2018, pp. 8-9.

89 *Proof Committee Hansard,* 8 November 2018, p. 6.

90 *Submission 58,* p. 2.

is not increased for mefloquine relative to other antimalarial prophylactics if prescribing information is followed.[91]

Use by the civilian population

2.63 Defence advised that its use of mefloquine has been conservative compared to its use in other militaries around the world and in the civilian population. It is commonly prescribed in the broader Australian community.[92]

Estimated Australian Civilian Prescription Data[93]

Anti-malarial	2010	2011	2012	2013	2014	2015	2016
Mefloquine	14,149	16,512	13,674	14,030	13,770	12,713	11,457

Source: Australian statistics on medicines/Roche Products Pty Ltd

2.64 Roche advised that 8,810 scripts for mefloquine were issued in Australia in 2017[94] with approximately 40 million patients treated with mefloquine globally since it was made available.[95] Approximately 300,000 Australian patients have been prescribed mefloquine.[96]

2.65 The RMA noted that mefloquine has been used by more than 35 million travellers for chemoprophyaxis worldwide since 1985 in Europe and 1990 in the USA and therefore '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'.[97]

2.66 The committee spoke to Dr Penny Burns, GP representative of the Royal Australian College of General Practitioners to discuss the use of mefloquine in the civilian population. Emphasising that 'malaria is a very serious and deadly disease', she confirmed that 'GPs are still regularly prescribing mefloquine and the '[c]urrent evidence based resources used by many GPs as reference on best management of

91 *Supplementary Submission 9.1*, p. 5.

92 Defence, *Submission 1*, p. 2.

93 See http://www.defence.gov.au/Health/HealthPortal/Malaria/Anti-malarial_medications/Mefloquine/, accessed 4 July 2018.

94 *Submission 12*, p. 10.

95 *Submission 12*, p. 6. Mr Svend Peterson, Managing Director Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 1.

96 Dr Stewart, Medical Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 3.

97 Australian Government, 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, pp. 10-11.

patients, including therapeutic guidelines up to date, still include mefloquine as an option for malarial prophylaxis'.[98] Dr Burns spoke about her personal experience:

> …I've seen a lot of patients prescribed mefloquine with minimal percentage, in my experience, having had side effects. I've probably only seen about three people with side effects from mefloquine that have been impacted over that period of time.[99]

Tafenoquine

Potential to assist the region

2.67 It was noted that the approval of tafenoquine would be the first new medicine for the prevention of relapse of P. vivax malaria in more than 60 years, addressing the need for a single dose, effective medicine.[100] Evidence noted the potential public health value of tafenoquine for the Asia Pacific region.[101] The Asia Pacific Leaders Malaria Alliance reported:

> As expressed during the recent Malaria World Congress in Melbourne (1-5 July 2018) by world experts on P. vivax, the promise of Tafenoquine as a single dose radical cure is revolutionary. Not only will Tafenoquine improve patient adherence by reducing a current standard regimen from 14 days, but will also reduce the risks of resistance, because of its single-dose formulation as a radical cure. This is particularly relevant in settings where regular follow-up with patients is a challenge due to poor geographic accessibility to public health services.[102]

2.68 It also advised that:

> In addition, Tafenoquine as a preventive treatment is crucial from a public health perspective to mitigate the risk of malaria spreading beyond borders, as well as to reduce the number of imported malaria cases, which could reverse efforts to eliminate malaria. What is more, Tafenoquine as a prophylaxis could support efforts to prevent transmission from asymptomatic carriers.[103]

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98 *Committee Hansard*, 11 October 2018, p. 15.

99 *Committee Hansard*, 11 October 2018, p. 15.

100 See Medicines for Malaria Venture, 'GSK submits US regulatory application for single-dose tafenoquine for Plasmodium vivax malaria', M*edia Release*, 28 November 2017. Note: For radical cure, primaquine needs to be administered daily over 2 weeks but there can be poor compliance which can lead to a 3 to 4 fold reduction in efficacy. See MMV, *Submission 10*, p. 3. See also GSK, *Supplementary submission 8.1*, p.1; Australasian Society for Infectious Diseases, *Submission 6*, p. 1. See also Geoffrey S. Dow et al, Tafenoquine is not neurotoxic following supertherapeutic dosing in rates, *Travel Medicine and Infectious Disease*, 17 (2017) 28-34, see Introduction.

101 See for example Mr Karl Herz, Managing Director, Biocelect Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 17.

102 *Submission 5*, p. 1.

103 *Submission 5*, p. 1.

2.69 Professor McCarthy also supported the approval of tafenoquine:

> I think it's a really useful drug and will protect lots of people from catching malaria—as long as we've got adequate mechanisms in place to give surveillance for these unusual side effects, which are of uncertain relationship to tafenoquine. Certainly if I was to go to one of these malaria areas I would be wanting to have tafenoquine available. I think it will be a fantastic drug for the prevention of malaria, if we can continue to monitor for the unusual outcomes.[104]

2.70 Mr David Herd, Director, Market Access and Communications and Government Affairs, GlaxoSmithKline Australia Pty Ltd emphasised the importance of the radical cure[105] treatment as a 'critical step towards the effective elimination of P. vivax malaria globally'.[106] GSK spoke about their work with Medicines for Malaria Venture (MMV)[107] to address the 'very significant unmet medical need in malaria-endemic countries for an alternative treatment to the current standard of care, which you have to give for 14 days'.[108]

2.71 Responding to concerns raised by Dr Nevin about the safety of tafenoquine, and the effect in poorer countries[109] Professor McCarthy responded:

> It's obviously morally really important that we don't relegate drugs as 'second class' so, therefore, they can be tested or deployed in populations where they will never be accepted in Australia. But you've got to remember that these drugs have been approved for use in the US on US citizens, so I don't believe that we can do any better than that. As long as we've got a robust process in place for surveillance after licensing these drugs, I think, to turn it on its head, it would be unethical and immoral to deprive the people who are most at risk of malaria of getting a new drug that's going to be the first prophylactic drug available for many years. I think that you could turn that around and say that it would be inappropriate to deny them access to this drug.[110]

2.72 At the time of the ADF trials tafenoquine was not registered in Australia. However, in July 2018 it was approved by the US FDA for malaria radical cure

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104 *Committee Hansard*. 11 October 2018, p. 26.

105 Prevention of relapse, or eradication.

106 *Proof Committee Hansard*, 8 November 2018, pp. 10, 15.

107 MMV works closely with the World Health Organization, and is funded by donors including the governments of Australia, Ireland, Japan, the Netherlands, Norway, Switzerland, the UK and the USA; the Bill and Melinda Gates Foundation and the Wellcome Trust. MMV, *Submission 10*, p. 2.

108 Dr Webster, *Proof Committee Hansard*, 8 November 2018, p. 12.

109 See *Committee Hansard*, 11 October 2018, p. 9.

110 *Committee Hansard*, 11 October 2018, pp. 27-28.

(prevention of relapse)[111] of liver-stage infections under the trade name Krintafel.[112] On 8 August 2018 it was approved by the US FDA for malaria prevention under the trade name Arakoda.[113] In September 2018 it was also approved by the Australian TGA for prevention under the trade name Kodatef[114] and radical cure under the trade name Kozenis.[115]

2.73 Dr Geoffrey Dow, CEO and Chairman, 60 Degrees Pharmaceuticals explained the relationships between GSK, 60 Degrees Pharmaceuticals and Biocelect in relation to tafenoquine in evidence to the committee.[116]

Safety profile

2.74 The committee was told that there is no compelling evidence that tafenoquine causes long term adverse effects.

2.75 Dr Dow addressed the assertions made by some groups:

> Activist groups such as the Quinism Foundation, in common cause with some veterans' groups, (hereafter referred to as the 'anti-tafenoquine activist community') bluntly assert that all quinoline antimalarials are neurotoxic. This is false. Primaquine…is an 8-aminoquinoline. It is activated in the body to form unknown oxidative intermediates that confer an indirect antimalarial effect on hepatic stages without causing neurologic deficits….In contrast, mefloquine is a 4-aminoalcohol with a side chain and confers both a potent and direct effect only on blood stage malaria parasites, while inducing an increased rate of some specific neuropsychiatric events relative to the standard of care in travelers. Since tafenoquine is an 8-aminoquinoline analog of primaquine, and is not structurally related to

111 For a more detailed explanation of radical cure see Mr David Herd, Director, Market Access and Communications and Government Affairs, GlaxoSmithKline Australia Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 10.

112 US FDA approved single-dose 300mg tafenoquine for the radical sure of P. vivax malaria. This was sponsored by GSK and MMV.

113 It provides effective protection against both the major types of malaria (P. vivax and P. falciparum) killing the parasites in the blood and the liver. This was sponsored by 60 Degrees Pharmaceuticals. Dr Geoff Dow, Chief Executive Officer and Chief Scientific Officer, 60 Degrees Pharmaceuticals, *Proof Committee Hansard*, 8 November 2018, p. 17. See Also Mr Mark Reid, *Submission 71*, p. 9.

114 Sponsor Biocelect. Dr Dow, 60 Degrees Pharmaceuticals, *Proof Committee Hansard*, 8 November 2018, p. 17

115 Sponsor, GSK. See Defence, *Supplementary Submission 1.1*, pp. 4-5.

116 See *Proof Committee Hansard*, 8 November 2018, p. 20. Note: Biocelect have been helping 60 Degrees Pharmaceuticals with the commercialisation of tafenoquine since 2013. This assistance was provided by the consulting company Biointelect Pty Ltd of which Mr Herz, Managing Director of Biocelect, is a director, employee and one of the owners. Biocelect Pty Ltd licenced tafenoquine from 60 Degrees Pharmaceuticals under a Supply and Distribution Agreement executed 22 September 2016 for Australia, NZ, PNG and various Pacific Islands. See Biocelect, additional information, received 19 November 2018.

> mefloquine, there is no reason, a priori, to expect it to exhibit the same adverse event profile as mefloquine.[117]

2.76 Biocelect also addressed the claims:

> We are aware of a small group of veterans and their supporters who attribute their mental health issues to having been given Tafenoquine in trials conducted within the Australian Defence Force during their deployment in East Timor. We wholeheartedly sympathise with these veterans and while we recognize and appreciate that they have served our country, based on the evidence available we do not attribute these mental health issues experienced by the veterans to Tafenoquine….We believe that this position has been confirmed by the recent approval for Tafenoquine as a treatment (radical cure) for malaria by the U.S. Food and Drug Administration (FDA) and the recent recommendation by the U.S. FDA expert Advisory Committee for the approval of Tafenoquine for the prevention of malaria. This recent FDA approval for treatment and FDA expert Advisory Committee recommendation, for approval by the FDA for prevention, was conducted by highly qualified scientific and medical experts based on their review of the scientific evidence.[118]

2.77 GSK emphasised to the committee that they take safety very seriously. 'We have been fully transparent with all of the safety data that we've gathered across all of the studies that were done—not just the ones done more recently—that are relevant to a radical cure. They have been evaluated very thoroughly by the regulators'.[119] GSK advised that they will continue to review the safety profile as tafenoquine is rolled out in the US and working with WHO when it is available for radical cure in endemic countries.[120]

2.78 GSK advised that the full report of safety data was submitted to the FDA and TGA for review. GSK added 'there is no evidence that tafenoquine concentrates at toxic levels in the brain causing permanent brain injury'.[121] GSK advised that 13 clinical trials were submitted to US and Australian regulatory authorities involving more than 800 patients.[122] GSK noted that the FDA and its Antimicrobial Drugs Advisory Committee were aware of the concerns raised by ADF veterans.[123] Dr Nevin

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117 *Submission 9*, p. 2. See also Biocelect, *Submission 11*, p. 2; Jonathan Berman et al, Tafenoquine and primaquine do not exhibit clinical neurologic signs associated with central nervous system lesions in the same manner as earlier 8-animoquinolines, *Malaria Journal*, (2018) 17:407.

118 *Submission 11*, p. 2.

119 Dr Webster, GSK, *Proof* Committee Hansard, 8 November 2018, p. 14.

120 Dr Webster, GSK, *Proof Committee Hansard*, 8 November 2018, p. 15.

121 *Supplementary submission 8.1*, p. 1.

122 *Submission 8*, p. 3.

123 *Supplementary submission 8.1*, p. 3.

confirmed that he was the only submittor to the FDA against approval of tafenoquine.[124]

2.79 MMV, a product development partnership in the field of antimalarial drug research and development, reported:

> …it should be noted that no serious neurological or psychiatric adverse events (AEs) were noted in the clinical efficacy & safety studies that investigated the single 300mg tafenoquine treatment dose (GSK-MMV clinical trials program for TQ), and no subjects withdrew from the studies or discontinued treatment due to central nervous system (CNS) AEs. All CNS events seen in these studies were mild to moderate in severity and were self-limiting.
>
> …
>
> We therefore conclude that in the >800 subjects who have received a total single-dose of 300mg TQ, no serious CNS events have been reported and the observed events have been mild to moderate and self-limiting. Therefore, the single 300 mg TQ dose + [chloroquine] CQ for radical cure of P. vivax malaria is anticipated to have a low risk of significant CNS effects in patients without an active or past history of serious psychiatric disorders.[125]

2.80 The Australasian Society for Infectious Diseases said that the extensive experience with the structurally similar primaquine is reassuring:

> In more than 36 million exposures, there has only been 1 report of neurotoxicity in a 55 year old man who developed depression and psychosis after the 2nd dose of primaquine which resolved within 24 hours on stopping the drug.[126]

2.81 Dr Dow noted that the US prescribing information for Arakoda includes a contraindication for those with psychotic illness and explained this as precautionary because three clinical trial participants with an undisclosed history of psychosis experienced psychotic events at doses which were not the approved dose.[127]

2.82 MMV provided information on non-clinical animal studies which do not suggest a signal for CNS toxicity with tafenoquine.[128] MMV concluded:

> We believe its use will transform case-management of P. vivax infection, improve compliance, help achieve improved rates of radical cure and

124 *Committee Hansard*, 11 October 2018, p. 4.

125 *Submission 10*, pp. 4-5.

126 *Submission 6*, pp. 2-3. See also 60P, *Submission 9*, p. 2; Dr Webster, GSK, *Proof Committee Hansard*, 8 November 2018, p. 12.

127 60 Degrees Pharmaceuticals, *Supplementary Submission 9.1*, p. 4.

128 *Submission 10*, p. 4.

> contribute to achieving both the Sustainable Development Goals and malaria elimination targets set by WHO.[129]

2.83 Professor McCarthy spoke about his clinical trials using small groups of people. He reported that in the case of tafenoquine, '[a]ll of the subjects who were given tafenoquine had no neurologic side effects at all'.[130]

2.84 Dr Dow confirmed that during its review of tafenoquine, the US FDA included specialists from their division of psychiatry as well as the pharmacovigilance and epidemiology areas to review the data.[131] He also outlined the additional work undertaken in an attempt to address the concerns of some advocates.[132]

2.85 The Department of Health took the committee through the approval process for drugs which tafenoquine has just been through and the ongoing safety monitoring of drugs.[133] Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health, confirmed that experts within the TGA include medical doctors, toxicologists and pharmaceutical chemists. He also advised that the TGA sought external advice 'from an advisory committee of doctors, community representatives, epidemiologists, statisticians'.[134]

2.86 Adjunct Professor Tim Greenaway, Chief Medical Adviser, Health Products Regulation, Department of Health, pointed out that there is much more data available than just the ADF trial involving tafenoquine. He pointed to a review of 22 trials of tafenoquine where 'the safety profile of tafenoquine was very, very good and the risk-benefit analysis was favourable' and this was considered by Australia's Advisory Committee on Medicines (ACM)[135] and the US FDA independently.[136]

2.87 The US FDA and TGA approval processes included an audit of the Defence studies involving tafenoquine:

> The U.S. FDA, with TGA observing, audited study records for Study 033 and 049. The auditor, commented…that the level of oversight by ADF

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129 *Submission 10*, p. 4.

130 *Committee Hansard*, 11 October 2018, p. 23.

131 *Proof Committee Hansard*, 8 November 2018, p. 19. See Also Mr Mark Reid, *Supplementary Submission 71.3*, p. 3.

132 *Proof Committee Hansard*, 8 November 2018, p. 21. GSK also outlined the steps they have taken to address concerns, see Answers to questions taken on notice at 8 November 2018 hearing in Canberra, received 21 November 2018.

133 Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health, *Committee Hansard*, 11 October 2018, pp. 35, 37.

134 *Committee Hansard*, 11 October 2018, p. 37. Dr Dow also spoke of the wide range of specialists accumulating and analysing medical data, *Proof Committee Hansard*, 8 November 2018, p. 19.

135 Providing independent medical and scientific advice to the Minister for Health and the TGA.

136 *Committee Hansard*, 11 October 2018, p. 37; Adjunct Professor Skerritt, *Committee Hansard*, 11 October 2018, p. 42.

> medical officers, in particular Lieutenant Colonel Peter Nasveld, [of soldiers] receiving tafenoquine and mefloquine in these studies was of a very high standard.[137]

2.88 Dr Dow stressed:

> The 'bottom line up front' of the testimony contained herein, is that scientific studies in animals and humans do not suggest that tafenoquine is neurotoxic. Furthermore, the suggestion by advocacy organizations that a causal relationship exists between tafenoquine administration and anecdotal reports of adverse events on social media 15+ years later is not supported by the facts. The U.S. FDA has concluded in regulatory briefing documents that tafenoquine is effective and reasonably safe.[138]

Animal studies

2.89 Professor McCarthy responded to the view put forward by Dr Nevin that tafenoquine had not been tested on monkeys:[139]

> There are good reasons not to do studies on monkeys. I'm sure you're aware of the, obviously, ethical issue about doing studies on monkeys. In the drug-development community, which I'm very closely involved in, we would require two non-human mammal species to be tested. Monkey studies are almost never done these days because of all of the problems that you'd be well aware of. I don't believe it would be appropriate to do a monkey study with tafenoquine when we've got clear evidence from some of the other species, and we've got good guidelines from the USFDA about what studies need to be done for licensing a drug. The USFDA, as you know, recently licensed tafenoquine for both prophylaxis of malaria and clearing the liver of malaria parasites. That was done based upon all the scientific information available to the FDA.[140]

2.90 Professor McCarthy spoke further about the findings in rat studies:

> Going back to some of the rat studies that were done, if you give a rat a really high dose of mefloquine, that rat looks very dizzy and doesn't do well neurologically. You can't replicate that when you give tafenoquine to the rat. To me, that says that we've got good information that the neurotoxicity of tafenoquine is much lower than mefloquine.[141]

Long term study

2.91 Dr Dow from 60 Degrees Pharmaceuticals advised that prior to marketing approval in the US, 60P and its partners 'committed to conducting a long-term study in

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137 Mr Mark Reid, *Submission 71*, p. 11. See also 60 Degrees Pharmaceuticals, *Submission 9.1*, pp. 3-4; Defence, *Supplementary Submission 1.1*, p. 5.

138 *Submission 9*, p. 1.

139 See *Committee Hansard*, 11 October 2018, p. 3.

140 *Committee Hansard*, 11 October 2018, p. 27. See also GSK, *Supplementary submission 8.1*, p. 2.

141 *Committee Hansard*, 11 October 2018, p. 27.

which the safety and tolerability of the drug is being evaluated following 12 months exposure (current safety database is six months)'. Dr Dow provided further information:

> This study will take several years and is being conducted at considerable expense. This study includes, as secondary endpoints, specific and validated neuropsychiatric assessments to monitor those events which were elevated in incidence in the ADF Timor deployment (general psychiatric events, insomnia and motion sickness/dizziness). Since we attribute the higher incidence of such effects to the operational environment, not tafenoquine, we expect a similarly low incidence of psychiatric events to be reported in the placebo and tafenoquine arms of this study. More details of the study can be found at www.clinicaltrials.gov (reference number NCT03320174). Additional studies in pediatric subjects and travelers are being planned with regulatory input from FDA.[142]

Defence view

2.92 Regarding possible side effects Defence advised:

> Tafenoquine has not been shown to have any serious neuropsychiatric side effects, including in the long term. Like primaquine, the main concern regarding tafenoquine relates to people who are deficient in the G6PD enzyme. In those people, tafenoquine can cause red blood cell problems, potentially leading to anaemia.[143]

2.93 Defence added:

> Defence acknowledges that mild and moderate neuropsychiatric side effects have been reported in individuals participating in tafenoquine studies, including in Defence studies. These include vertigo, sleepiness, abnormal dreams, dizziness and insomia.
>
> Defence is not aware of any clear evidence that tafenoquine produces serious neuropsychiatric side effects, including in the long term.[144]

G6PD deficiency

2.94 GSK advised that tafenoquine is contraindicated in the following: G6PD deficiency (see below); pregnancy; breastfeeding an infant who is G6PD-deficient or if the G6PD status of the infant is unknown; and patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of the formulation. These contraindications have been fully reviewed by the US FDA and TGA and appropriate labelling describing the warnings and precautions has been agreed.[145]

2.95 Tafenoquine and primaquine share a key safety concern which is the potential to cause hemolysis (destruction of red blood cells) in individuals with a hereditary

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142 *Supplementary Submission 9.2*, p. 1.

143 *Submission 1*, pp. 2-3.

144 *Submission 1*, p. 17.

145 *Supplementary submission 16.1*, p. 2.

disorder, deficiency of Glucose-6-Phosphate-Dehydrogenase (G6PD) enzyme. Individuals must be tested for this deficiency before receiving either of these drugs.[146]

2.96 All ADF members are checked for this deficiency before being administered such medications.[147] The committee discussed with 60 Degrees Pharmaceuticals the test that could be made available in developing countries in the context of a sponsored aid program to undertake the G6PD testing.[148]

Vortex keratopathy

2.97 Some ADF trial participants experienced the benign, reversible eye condition vortex keratopathy (small deposits in the cornea) while taking tafenoquine.[149] This is covered in further detail in Chapter 3.

Metabolisation

2.98 The AQVFA calls for 'CYP450 pharmacogenomic profiling' to be implemented for current ADF members and veterans involved in the trials contending that of those experiencing long term adverse health effects and volunteering the information, 92 per cent were poor or intermediate metabolisers of the CYP2D6 enzyme.[150]

2.99 In relation to the claims that the absence or poor functioning of an enzyme called CYP2D6 has implications for the efficacy and safety of tafenoquine, Defence responded:

> While the CYP2D6 metaboliser status of individuals may be significant in terms of the effectiveness of the medication, it has no known relationship to adverse events. If anything, failure to generate active metabolites would be expected to stop/limit adverse events.[151]

2.100 GSK also responded to these claims:

> The Committee has been advised in other submissions to this Senate Inquiry that tafenoquine requires activation by the CYP 2D6 enzyme to be effective (as is the case for primaquine), and two studies in mice are referenced in support of this. Clinical trials of tafenoquine for radical cure

146 GSK, *Submission 8*, p. 2; Defence, *Submission 1*, p. 15. See also Australasian Society for Infectious Diseases, *Submission 6*, p. 2; Dr Webster, GSK, *Proof Committee Hansard*, 8 November 2018, p. 12; Dr Dow and Mr Herz, *Proof Committee Hansard*, 8 November 2018, p. 22.

147 Defence, 'Response to Fairfax reporting on the use of tafenoquine in the ADF', *Media release*, 2 May 2016.

148 *Proof Committee Hansard*, 8 November 2018, p. 23.

149 Defence, *Submission 1*, pp. 2-3; Defence, *Supplementary submission 1.1*, pp. 10, 14.

150 *Submission 16*, pp. 6, 52-54. See also Mr Stuart McCarthy, *Submission 94*, p. 4. Note: Cytochrome P450 enzymes are essential for the metabolism of many medications. CYP2D6 is one of the CYP450 enzymes.

151 *Submission 1*, p. 21. See also Professor Dennis Shanks, Director, ADF MIDI, *Committee Hansard*, 11 October 2018, p. 57.

> of P. vivax malaria show no difference in efficacy resulting from CYP 2D6 metabolizer status (extensive, intermediate or poor) [St Jean 2016]. The results of the mice studies are likely accounted for by differences in substrate metabolism and tissue expression between the CYP2D orthologues (mouse and human) [Miksys 2005, Scheer 2012]. The Committee has also been advised in Submission 16[152] that CYP alleles have been linked to treatment failure for antimalarials, which is documented in the case of primaquine, however, GSK has found no evidence that this is the case for tafenoquine.[153]

2.101 AVM Tracy Smart AM, Commander Joint Health, Defence, added that the US FDA and TGA did not recommend that CYP2D6 enzyme testing be conducted before administering tafenoquine.[154]

TGA database of adverse events

2.102 The TGA is Australia's regulatory authority for therapeutic goods, including prescription medications. As it is not possible to know all potential adverse events of a medicine before it is approved for use, the TGA monitors adverse events (such as side effects) related to medicines to safeguard the health of the Australian community. Most adverse events reports are made by sponsors such as pharmaceutical companies or medical device suppliers, others by state and territory health department, hospitals, health professionals and consumers.[155]

Mefloquine

2.103 Roche advised that following registration, 'sponsors such as Roche are required[156] to collect and evaluate safety information about the product continuously, in order to report serious adverse reactions and significant safety issues to the TGA, identify any changes to the benefit-risk balance of the product and to take action where necessary'.[157]

2.104 The Department of Health advised that the TGA receives adverse event reports associated with medicines and medical devices which come from a wide variety of sources including members of the public, general practitioners, nurses, other health professionals and the therapeutic goods industry. It maintains a public database of suspected adverse events. The Department of Health indicated at the 11 October

152 AQVFA.

153 *Supplementary Submission 8.1*, p. 2. See also 60 Degrees Pharmaceuticals, *Submission 9.2*, Presentation of Clinical Safety, p. 81.

154 *Committee Hansard*, 11 October 2018, p. 57.

155 See www.tga.gov.au, accessed 13 November 2018.

156 A legal requirement.

157 *Submission 12*, p. 3.

2018 hearing that for the period January 1971 (when the adverse event database started) to 20 June 2018, 242 adverse events were received.[158] It noted:

> The most commonly-reported events are neuropsychiatric (depression 55 reports, dizziness 53, anxiety 51, headache 29, nightmare 28, insomnia 24, agitation 22) and gastrointestinal (nausea 52 reports, abdominal pain 19, diarrhoea 17). This is in keeping with the known adverse effect profile of the drug.
>
> In that…period there were 11 reports of suicidal ideation, and 4 reports of completed suicide, with no other reports of fatalities. The database does not contain any reports describing adverse events arising from the use of mefloquine in a clinical trial. The four cases of suicide reported in the database contained insufficient information to determine cause-and-effect.[159]

2.105 In relation to the TGA database of suspected adverse events, the Department of Health emphasised:

> It is important to emphasise that the search results cannot be used to determine the incidence of an adverse event (that is, how often the adverse event has occurred in patients taking a particular medicine), or the likelihood of a patient experiencing that reaction, as they do not include information on the total number of patients who have taken the medication or the total number of adverse events occurring (because reporting of adverse events is not mandatory, other than for industry sponsors). As a result the search results cannot be used to make accurate numerical comparisons between adverse events associated with different medicines.[160]

2.106 Adjunct Professor Skerritt emphasised that the adverse reports received up until the last few years were largely related to the short term impacts of the drug or the 'immediate psychological and psychiatric adverse events'. This resulted in the warnings being updated.[161]

2.107 Roche confirmed to the committee that there are robust mechanisms in place to capture and act on adverse event reports and that the risk benefit profile of mefloquine remains positive:

> We are very, very confident that the mechanisms in place to capture, record and analyse adverse events associated with all our medicines, including mefloquine, are very robust. It's not only what we as a company do.

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158 Adjunct Professor Skerritt, *Proof Committee Hansard*, 11 October 2018, p. 36. Note: the submission from the Department of Health refers to the database containing 242 adverse reports for mefloquine submitted from 1993 to 2018. See *Submission 3*, p. 4. The committee understands the reference to 1993 in the submission is incorrect.

159 *Submission 3*, p. 4.

160 *Submission 3*, p. 4. See also Adjunct Professor Skerritt and Adjunct Professor Greenaway, *Committee Hansard*, 11 October 2018, p. 39.

161 *Committee Hansard*, 11 October 2018, pp. 41, 44.

> Just to illustrate this to you, in my medical department in Australia alone, there is a department of drug safety of 20 professional people, whose role it is to monitor, review, follow up and discuss with people who have reported adverse events, to ensure that we understand things fully. This happens in every single country around the world.
>
> Globally, Roche has a drug safety department that specifically looks at this daily for all of our medicines. We very closely monitor the safety profile of all of our medicines. Our safety department produces documents called PBRERs, or periodic benefit-risk evaluation reports. They run to hundreds of pages. The most recent one was completed on 17 April 2018, and it essentially concluded that there was no new information: 'The risk-benefit profile of mefloquine remains positive and favours its use in the approved indications and adheres to the prescribing information.'[162]

Tafenoquine

2.108 Chapter 3 details the adverse events reported during the tafenoquine trials involving ADF members. Following the trials, Defence noted:

> An administrative error by TGA allowed entry of adverse events to the database subsequent to the study period. This was unusual as this would normally only be possible for a registered medication on the market in Australia. The remaining 26 of the 32 total entries relating to the use of tafenoquine have been entered into the database since 2016, some 15 years after the study. 18 of these were entered in a ten day period following a social media campaign in early in 2017. The entries related to tafenoquine have since been removed from the online [Database of Adverse Event Notifications] DAEN by the TGA.[163]

2.109 Defence emphasised:

> There is no way to establish definitive links between the symptoms recorded in the anonymous entries made to the DAEN since 2016 and tafenoquine use. Indeed, there could be many other causes for these symptoms. As such this is does not constitute clear evidence of long term tafenoquine-related effects.[164]

2.110 60P advised that these more recent reports were examined and 'in all instances but one, contemporaneous accounts of adverse events could not be verified as actually having occurred'. 60P noted that 'GSK reached broadly the same conclusion as did the FDA in an independent audit of ADF records'.[165] Biocelect provided further detail:

> For events alleged to have occurred during or after 2017, it is not scientifically plausible based on the available evidence that Tafenoquine could have been a causative factor. It is implausible for Tafenoquine to cause long term psychiatric events if (i) there is no drug in the patient's

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162 Dr Stewart, *Proof Committee Hansard*, 8 November 2018, p. 7.

163 *Submission 1*, pp. 17-18. See also Annex C.

164 *Submission 1*, p. 18. See also Defence, *Supplementary submission 1.1*, p. 23.

165 *Submission 9*, pp. 3-4.

> system when the events occur and (ii) it does not cause meaningful increases in the risk of psychiatric adverse events compared to placebo over the shorter term following administration of drug when drug levels are at their highest. In other words you would need an initial psychiatric event to plausibly claim a later psychiatric event was related. Therefore, with the greatest respect to the veterans affected, their adverse experiences cannot, in 60P's view, be reasonably attributed to Tafenoquine. Biocelect supports the position of 60P in this matter.[166]

2.111 GSK reported that it has followed up with those who have recently reported adverse events. The recent reports 'prompted a thorough evaluation by GSK of all available clinical data and literature. To date it has not been possible to make a connection between the mild to moderate side effects reported during the ADF study and any permanent, serious long-term effects with onset after completion of the study'.[167]

2.112 Biocelect emphasised that it takes seriously its 'commitment to the TGA to collect further safety information and provide it to the regulators in a timely manner for their analysis'.[168]

Labelling

2.113 Adjunct Professor Skerritt told the committee that with new drugs such as tafenoquine, a black triangle is placed on the patient leaflet which is to make sure health professionals and consumers are encouraged to report adverse events.[169]

Related medical inquiries

2.114 The AQVFA is calling for a single Statement of Principles (SOP) covering the condition they term 'quinoline poisoning' to inform decisions made regarding support available for veterans.[170] The AQVFA points out that without a single SOP for 'quinoline poisoning' veterans have to lodge multiple claims which is an administrative challenge to those who are unwell.[171] Administrative barriers are addressed in more detail in Chapter 4.

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166 *Submission 11*, p. 3. See also 60 Degrees Pharmaceuticals, *Submission 9*, p. 3. Note: the 60P submission reference to 2007 refers to the adverse events made to the TGA in 2017 or later which were reported to have occurred many years after the drugs were taken with the earliest such onset being 2007 (see case 2 in Appendix A to Briefing Document for the Antimicrobial Drugs Advisory Committee, p. 139, available in *Submission 9*, Attachment 1)

167 Mr Herd, *Proof Committee Hansard*, 8 November 2018, pp. 10, 13.

168 Mr Herz, *Proof Committee Hansard* 8 November 2018, p. 17.

169 *Committee Hansard*, 11 October 2018, pp. 41, 42; Dr Carolyn Tucek-Szabo, Head, Regulatory Affairs, Australasia, GSK Australia, *Proof Committee Hansard*, 8 November 2018, p. 15. See also: https://www.tga.gov.au/black-triangle-scheme, accessed 29 October 2018.

170 *Submission 16*, pp. 40-42.

171 *Submission 16*, pp. 41- 42. Associate Professor Quinn, *Proof Committee Hansard*, 5 November 2018, p. 42.

2.115 Serving and ex-serving ADF members can claim compensation at any time for conditions they believe are related to their service. For DVA to accept liability for compensation there has to be a causal link determined between the person's service and their medical conditions. Under the *Veterans' Entitlements Act 1986* (VEA) and the *Military Rehabilitation and Compensation Act 2004* (MRCA) the potential link between a medical condition and service is assessed using SOPs.[172]

2.116 The main function of the Repatriation Medical Authority (RMA) is to determine SOPs for the purposes of the VEA and the MCRA. SOPs determined by the RMA are legislative instruments and apply to decisions about liability for injuries, diseases and deaths made under both the VEA and the MCRA.[173]

2.117 The RMA clarified that SOPs are made for diseases or injuries, not for exposures:

> If an exposure can be causally related to a disease or injury then it can become a factor within a statement of principles, but we do not make statements of principles relating to exposures to drugs, toxins or those sorts of things.[174]

2.118 The RMA stressed that the VEA is 'beneficial legislation' 'and is intended to be generous'.[175] This point was further emphasised by Professor Nick Saunders, Chairperson, RMA, who stated 'we take a very generous view of the evidence when we write the statements of principles'.[176]

RMA

2.119 The claim that taking mefloquine or tafenoquine causes chemically-acquired brain injury has been raised with the RMA.

2.120 The RMA received a request dated 6 February 2017 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 in order to find out whether SOPs may be determined concerning the claimed condition. This was agreed by the Authority on

172 DVA Information Paper: Mefloquine, p. 3. Note: SOPs are legal instruments, based on sound medical-scientific evidence (SMSE) which state the factors that must exist for a particular disease, injury or death to the linked causally to prior service. See RMA, *Submission 4*, Attachment 1, p. 4.

173 See http://www.rma.gov.au/sops/, accessed 27 June 2018. Note: the RMA determines SOPs at two standards of proof: reasonable hypothesis, where the SMSE has to indicate or point to a reasonable hypothesis of a causal association between the factor and the disease; and balance of probability, where the SMSE has to show that it is more probable than not that the factor is causally related to the disease. RMA, *Submission 4*, Attachment 1, p. 5.

174 Professor Saunders, Chairperson, RMA, *Committee Hansard*, 15 October 2018, p. 1.

175 RMA, *Submission 4*, Attachment 1, p. 4.

176 *Committee Hansard*, 15 October 2018, p. 8.

7 February 2017 and an investigation notice placed in the Commonwealth of Australia Gazette on 14 February 2017.[177]

2.121 On 18 August 2017, the RMA declared 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 [Veterans' Entitlements Act 1986]'.[178] It noted:

> 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.[179]

2.122 The RMA provided further detail for this finding in its submission:

> The hypothesis that mefloquine causes permanent brain damage is based on proposed causal mechanisms and pathology identified in high dose animal studies mostly conducted shortly after World War II. There is no direct evidence that it causes permanent brain damage in humans given therapeutic doses.
>
> The claim that there are persistent symptoms that are due to mefloquine is based on a small number of case reports and adverse event reports of a variety of commonly experienced symptoms in a widely prescribed medication. These same animal studies and human case reports are cited repeatedly as the basis for the contention of a syndrome resulting from permanent brain injury.
>
> Animal studies and case reports are considered "hypothesis generating", since the associations they suggest need to be evaluated in well-conducted comparative studies in humans. Human studies of this type are considered higher quality evidence. Because of the lack of supporting evidence from such studies, the RMA found that the evidence was not persuasive when critical appraisal of the total body of SMSE [sound medical-scientific evidence] was taken into account.[180]

177 Australian Government, 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, p. 3.

178 Australian Government, Repatriation Medical Authority, Declaration under subsection 196B(6) of the *Veterans' Entitlements Act 1986*, 18 August 2017.

179 Australian Government, 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, p. 3. See also Defence, *Supplementary submission 1.1*, pp. 24-25.

180 *Submission 4*, p. 8. See also Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

2.123 Professor Saunders told the committee that for a chronic brain injury to be caused by a particular agent, damage to the brain needs to be demonstrated. While this can be done through imaging of the brain and other tests in relation to sniffing solvents or lead poisoning for example:

> There is no evidence of that in terms of the quinoline class of drugs—there is no evidence of that in relationship to mefloquine or tafenoquine. Nobody has been able to demonstrate in humans that there are imaging abnormalities or other evidence of structural abnormality of the brain. The only evidence that we have for structural changes relates to animal experiments. Also, I think there was one case where a massive overdose of a drug was taken, which killed the person, and autopsy evidence showed that there was damage of the brain. I think the person took twenty-fold times the prescribed dose. So, we have no evidence that is sufficient to allow us to define a particular condition, be that in terms of the constellation of symptoms and signs that might be present, or indeed other evidence of structural abnormality.[181]

2.124 The RMA emphasised the lack of evidence of harm despite widespread and long term use of mefloquine and the inclusion of mefloquine by the WHO in its Model List of Essential Medicines.[182]

2.125 Professor Saunders summarised that with the millions of doses of mefloquine worldwide:

> One would have thought that even a rare adverse effect causing chronic brain injury would have become evident given the scope of the usage of this particular agent. There has been no defined syndrome or clinical entity that one could recognise as chronic brain injury from the civilian use of this drug.[183]

2.126 Mr Paul Murdoch, Registrar, RMA advised that when individuals attempt to link conditions to eligible service, it needs to be on the basis of a diagnosed disease or injury, not symptom by symptom. Therefore getting a clear diagnosis is key as a diagnosed injury or disease 'can then be matched very quickly to a statement of principle, [which] is the key from a compensation point of view'.[184] Professor Saunders further explained that:

> Although a range of symptoms have been reported following the use of these drugs, the timing of these symptoms, their duration and severity, and the set of individual symptoms which could define a condition have not really been established.[185]

2.127 Professor Saunders continued his explanation:

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181 *Committee Hansard*, 15 October 2018, p. 2.

182 *Submission 4*, p. 9.

183 *Committee Hansard*, 15 October 2018, p. 3.

184 *Committee Hansard*, 15 October 2018, p. 5.

185 *Committee Hansard*, 15 October 2018, p. 2.

> In 1994 the government of the day introduced this current system, which, really, I think, has served the veteran community very well, because the government felt that one would have greater transparency and greater equity if decisions were based on sound scientific medical evidence. So passionate opinion does not trump objective evidence in the system we have at the moment. The fact that somebody has been given a drug and now they are claiming to have a chronic brain injury from that drug is not sufficient in the system we have today. Indeed, it would undermine the system if one were to carve out exemptions to the system as a whole.[186]

SMRC review

2.128 The AQVFA noted that a review of the RMA's decision was underway at the time of lodging their submission.[187] In November 2017 the Specialist Medical Review Council[188] gave notice that it had been asked under section 196Y of the VEA to review the decision of the RMA which should be finalised before the end of 2018.[189] The RMA indicated that the review was requested by the AQVFA.[190]

2.129 On 17 September 2018 the SMRC announced that it had completed its review and affirmed the RMA's decision not to make a SOP for 'chemically acquired brain injury'.[191]

2.130 Professor Saunders spoke about the composition of the RMA and the SMRC:

> The council's composition is different from ours in terms of the people who do the assessment. In our case the RMA is made up of five medical academics, or epidemiological academics, who have their own specialties but, as well as that, have a broad general experience. When this decision was reviewed by the Specialist Medical Review Council, their committee was an expert committee; it contained people who understood epidemiology but also were drawn from pharmacology, neurology, mental health and neuropsychology. These were expert people. They considered the same evidence that we considered, and drew the same conclusions that we drew.[192]

2.131 Professor Saunders answered assertions[193] about the evidence being relied upon:

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186 *Committee Hansard*, 15 October 2018, p. 5.

187 *Submission 16*, p. 42.

188 An independent statutory body, established by the VEA, responsible to the Minister for Veterans' Affairs.

189 DVA, *Submission 2*, p. 8.

190 Mr Paul Murdoch, Registrar, RMA, *Committee Hansard*, 15 October 2018, p. 3.

191 Commonwealth of Australia Gazette, Specialist Medical Review Council Declarations, Request for Review Declaration no. 34, 17 September 2018. See also Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

192 *Committee Hansard*, 15 October 2018, p. 3.

193 See Dr Remington Nevin, *Committee Hansard*, 11 October 2018, pp. 7-9.

> …the evidence that we place highest reliance on—sound, epidemiological evidence—is not being driven by the pharmaceutical industry or the malarial specialists. These are people who are interested in population based studies and who look at the evidence in an impartial way.[194]

Inclusion of mefloquine and tafenoquine in SOPs

2.132 The RMA has included mefloquine and tafenoquine, either by name or in more general terms, as a potential causal factor in the SOPs for a total of 16 conditions – 15 for mefloquine and six for tafenoquine where there was a least a reasonable hypothesis that the relevant condition can occur.[195] The RMA notes that 'the wording of the mefloquine- or tefenoquine-related factors in these SOPs requires a close temporal link between the taking of the drug and the onset of the condition…reflecting the well-accepted evidence that these agents can have acute neuropsychiatric effects'.[196]

2.133 The RMA told the committee that they 'are confident that we have included mefloquine or tafenoquine in statements of principle for all diseases or injuries which could be linked to taking these drugs based upon sound medical scientific evidence that meets standard epidemiological criteria when examining things for causation'.[197]

2.134 Acknowledging the chronic and complex symptoms being presented to the committee, Professor Saunders mentioned the SOP concerning 'chronic multisymptom illness'[198] determined in 2014:

> We have a statement of principle on an illness called chronic multisymptom illness. This arose out of an inquiry that we conducted in relation to Gulf War syndrome. Although this did not satisfy the Gulf War advocate group that was presenting to us, it became quite clear to us that there were a significant number of veterans who had quite debilitating symptoms that fitted into particular patterns of illness, but this wasn't related just to serving in the Gulf War. In fact, it was related more broadly to deployment into hazardous environments. So we wrote a statement of principle called 'Chronic multisymptom illness'. That statement of principle is available today for those people who were deployed to, say, East Timor, took antimalarial drugs and now have debilitating symptoms that are broad-ranging.[199]

2.135 Professor Saunders again emphasised that the RMA takes a very generous view of evidence when they write the SOPs.[200] Therefore in his view the key for many

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194 *Committee Hansard*, 15 October 2018, p. 7.

195 DVA *Submission 2*, p. 7. See also RMA, *Submission 4*, Attachment 2.

196 RMA, *Submission 4*, p. 6.

197 *Committee Hansard*, 15 October 2018, pp. 1-2.

198 See Statement of Principles concerning chronic multisymptom illness No. 55 of 2014.

199 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 5.

200 *Committee Hansard*, 15 October 2018, p. 8.

veterans is getting assistance from an advocate for example to establish a causal link between their service and their health today.[201]

Review processes and ongoing monitoring

2.136 The RMA specifically searches for 'new evidence in relation to factors that have a particular association with the veteran community'.[202] The RMA regularly reviews the evidence through a comprehensive evidence-gathering process, using standard scientific methods and recognised epidemiological criteria.[203] It reviews 'the entire literature that is available on the large public databases in the English language'.[204] Each SOP is reviewed at least every ten years, with an aim of reviewing them more frequently.[205] RMA experts can identify new evidence from their fields, and SOP reviews can be initiated through the authority's own motion.[206] Individuals outside the RMA can also request reviews, as was the case for the recent reviews completed by the RMA and Specialist Medication Review Council.[207] The committee also understands that consultation between the RMA and a range of stakeholder organisations including Joint Health Command (JHC) in Defence, DVA, and the RSL occurs regularly on a range of topics relating to the health of veterans.[208]

2.137 The JHC seeks to ensure the health preparedness of ADF members by developing evidence-based health policy. Among other things, it is responsible for 'participating in research to inform and improve health policy, programs and services', 'developing strategic health policy and programs' and 'reviewing and assuring health policy, programs and services to drive continuous improvement'.[209] ADF clinical and medical policy is developed with clinical medical input.[210] Defence also undertakes and supports a range of research activities, including through the Mental Health Research and Evaluation section.[211]

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201 *Committee Hansard*, 15 October 2018, p. 5.

202 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 1.

203 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 1.

204 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 3.

205 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 4.

206 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 4; Mr Murdoch, *Committee Hansard*, 15 October 2018, p. 4.

207 Mr Murdoch, *Committee Hansard*, 15 October 2018, p. 3.

208 See http://www.rma.gov.au/consultation/, (accessed 30 November 2018).

209 Australian Government, Joint Health Command, *Annual Review 2016–17*, 2017, p. 4.

210 Australian Government, Defence, 'Directorate of Military Medicine', http://www.defence.gov.au/Health/SHC/militaryMedicine.asp, (accessed 29 November 2018).

211 Australian Government, Defence, 'Mental Health Research and Evaluation (MHR&E)', http://www.defence.gov.au/Health/DMH/ResearchSurveillancePlan.asp, (accessed 29 November 2018).

Searching for an explanation

2.138 As the concerns expressed by individuals appear to be manifested in military and not civilian populations, the committee discussed possible explanations for this with witnesses. Mr Mark Reid indicated that in his view:

> I contend that these soldiers raising concerns about chemically acquired brain injury resulting from use of tafenoquine have PTSD. The PTSD has arisen more than 16 years after taking tafenoquine and mefloquine, but the PTSD is not related to these anti-malarial drugs.[212]

2.139 Professor Graham Brown, Australian College of Tropical Medicine posited:

> I was explaining this to a layperson. For example, let's say, you were trying a new flu vaccine in New South Wales two months ago. You did a three-month review, and people had nightmares and couldn't sleep and were anxious and depressed. You'd say, 'That's the flu vaccine.' Perhaps it was, but the fact that they were firefighters fighting bushfires with people dying could surely have contributed to the symptoms. We couldn't say, 'It's not the flu vaccine,' but most of us would think it's highly unlikely. That's the sort of example. It's a coincidence of things and trying to work out the underlying cause. So, I would say that that's the importance of controlled trial evidence that we look at. Many of the symptoms reported are found in other conditions. I'm also aware of certain unproved hypotheses about what might cause these problems, and I think it's important to start with the evidence based information and separate this away from ideas or options or hypotheses, which are terribly important in science but they need to be proved and not confused with opinion.[213]

2.140 Professor Shanks pointed out the many potential contributors to a veteran's current health:

> Trying to assign any single cause to various post-military, veteran's illnesses does not accurately reflect the many potential contributors to a soldier's mental and physical health.[214]

2.141 When asked his view on the issues raised with the committee, Professor Shanks responded:

> It's multifactorial…Mental illness is a broad category and a very frequent one, but trying to blame a drug 20 years after the fact, when it's long, long been cleared, isn't plausible. That isn't how drugs work.[215]

2.142 Associate Professor Karunajeewa also emphasised the difficulty of attributing causality to taking a drug nearly 20 years ago:

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212 *Submission 71*, p. 5.

213 *Committee Hansard*, 30 August 2018, p. 44.

214 Professor Shanks, *Submission 13*, p. 2.

215 *Committee Hansard*, 11 October 2018, p. 58.

> I suppose the first thing to say is that we want to avoid at all costs being at all dismissive or belittling about their experiences and their symptoms, and they should be regarded as real. Essentially the difficulty comes down to the fact that a lot of the symptoms and a lot of the illnesses being described, unfortunately, as you know, are highly prevalent in the general Australian community. For example, I think the statistics are that two or three million Australians are out there suffering from depression, and a similar number have anxiety. The most common cause of death now in young people under the age of 44 is suicide. So this mental health crisis that we have in the country is obviously highly prevalent. There are an awful lot of other people out there who haven't taken mefloquine, of course, who are dealing with very, very similar problems. So the difficulty comes in ascribing causality when you have conditions and symptoms that are very, very common throughout the general community. So actually ascribing causality to something that happened 20 years ago becomes very difficult.[216]

2.143 Vice Admiral David Johnston AO, VCDF, acknowledged the challenges of dealing with PTSD:

> There are many other possible causes of the symptoms that these people are suffering. Indeed, many admit that they have been diagnosed with PTSD but are frustrated that the treatment does not seem to be working. The challenge for some people with PTSD to recover is a known problem, but it doesn't mean that the diagnosis is wrong. Even if it were possible to connect the use of mefloquine with these symptoms, it's unlikely to alter the individual's treatment or management.[217]

2.144 AVM Tracy Smart put forward that:

> It's very hard to distinguish or diagnose what could be the problem of someone who develops a health problem many years after an event. We've heard today that there is some evidence—and certainly there have been some reports—that people can get long-term effects from mefloquine. There are no reports that someone can take the drug, get some symptoms, stop the drug, have the symptoms stop and then get symptoms a long way down the track. There is no evidence to suggest that. That's not been recorded in the literature. You've also got to look at someone who is this many years down the track; what other events have occurred in their life, including on deployment, in terms of both traumatic events and the stressors in deployment, because there are many: away from home, poor living conditions—all of these things can contribute to having health problems.
>
> I think this is one of the main problems we have got here: what is the cause of this problem? The overwhelming evidence suggests that, in the majority of cases, it is not the antimalarials. As some of the presenters today have

216 *Committee Hansard*, 11 October 2018, p. 30.

217 *Committee Hansard*, 11 October 2018, p. 46. See also Defence, *Supplementary submission 1.1*, p. 27.

> said, it's rare or very rare at best to see long-term symptoms of mefloquine.[218]

2.145 AVM Smart continued:

> Being exposed over a military career over a life to a number of stressors can cause neuropsychiatric problems, can cause psychiatric problems or can cause brain injury. Things like traumatic brain injury, which you've heard about—a number of things can cause acquired brain injury down the track. The important thing is that I can't tell you sitting here that someone has or hasn't got a particular diagnosis. That is something that a doctor needs to do one-on-one with the individual, looking at their symptoms. When did they come on and when did they finish? That's what a diagnosis is all about. I would say, though, that some of the people who've written to us through our malaria email address have really told us they are suffering from severe problems similar to the ones in the submission[s]. When we look back at their documents, some of those have continued to deploy many time[s] after Timor, including to the Middle East. To then say this condition was caused by this drug we took at that time is very problematic.[219]

Influence of social media

2.146 Many witnesses referenced social media as the catalyst for bringing them together. An individual listing 32 symptoms[220] reported the following:

> I read an article published by Stuart McCarthy in December 2015. After reading this article I realised that everything I had experienced, physically and mentally, were very real. For the first time in 11 years there was a diagnoses to 'fit' my medical situation.[221]

2.147 Many others also referred to Mr Stuart McCarthy and his facebook page as did a number of confidential submissions. A few of those that are public are listed below:

> I came across a Facebook group started by fellow veterans, namely Stuart McCarthy, who was also suffering. This was a God send for me. I was not alone and was not the only one with these symptoms.[222]

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218 *Committee Hansard*, 11 October 2018, p. 54.

219 *Committee Hansard*, 11 October 2018, pp. 54-55. See also Defence, *Supplementary submission 1.1*, pp. 23-24.

220 Loss of sight/visual disturbances; Encephalitis; Swelling of the brain; Demyelination; Chronic diarrhoea, Irritable Bowel Syndrome (IBS); Body Rashes; Migraines; Photosensitivity; Chronic infections caused by Low Immunity; Allergies; Suicidal; PTSD; Chronic fatigue; Major Depression/Withdrawal; Fibromyalgia; Chemical sensitivities; Low immunity; Weight gain (BMI over 30); Memory loss; Chronic reflux; Aggressive Explosive Anger; Impatient; Overwhelmed; Psoriasis; Hearing loss (not noise related); Auto-immune (blood); Herpes simplex (Compromised Immunity); Vertigo; Daily Nausea; Light headedness; Tinnitus. Name withheld, *Submission 67*, pp. 2-3.

221 Name withheld, *Submission 67*, p. 3.

222 Mr Colin Brock, *Submission 69*, p. 2.

> …in February, 2018 I became aware of Retired Major Stuart McCarthy, who has been of great comfort and assistance to my family.[223]
>
> Well several years ago information started to appear from fellow Vets, especially on Facebook. We started talking and finally telling each other what had happened, how we felt etc.[224]
>
> For almost twenty years I felt isolated and alone with my 'creeping madness' until I stumbled across a Facebook group for soldiers who had suffered from Mefloquine poisoning. There in front of me were men and women detailing strikingly similar symptoms that I had experienced.[225]

2.148 Mr David Madsen also listed a number of diagnoses[226] and referred to the facebook page of Mr Stuart McCarthy:

> I [knew] nothing about [mefloquine] toxicity or any potential side effects prior to and after all of this until [I] saw Major McCarthy's Face book page after being invited by an old army Friend.
>
> Over time I have started to see the GLARING similarities between where I am at and what many studies are showing now.[227]

Conclusion

2.149 The committee was very concerned to hear the stories from individual veterans and their families outlining their health and other challenges. Though there may be disagreement between them and the medical professionals on the cause or causes of their health conditions there was no disagreement that their physical and mental symptoms are real and that they require assistance. This is the focus of Chapter 4.

223 Mr Syd Carter, *Submission 108*, p. 3.

224 Name withheld, *Submission 75*, p. 3.

225 Name withheld, *Submission 61*, p. 6.

226 Mr David Madsen, *Submission 91*, p. 1.

227 Mr David Madsen, *Submission 91*, p. 2.