Submission to the Senate Inquiry 'Investigation into the use of the quinoline antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force.'

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This submission is made on behalf of the Australian Quinoline Veterans and Families Association by Associate Professor Jane Quinn (BSc Hons, PhD), Charles Sturt University.

Background to the author

Associate Professor Quinn is a published neuroscientist specialising in toxic exposures in both animals and humans with 25 years research experience in this field. In addition to her scientific credentials, she is an advocate for civilian travellers and military veterans exposed to quinoline antimalarials. She is a founder member of the United Kingdom branch of the International Mefloquine Veterans Alliance, and a UK Defence Force mefloquine veteran's suicide survivor. She has worked in a number of international jurisdictions globally for the since 2006 to highlight the issues faced by those who have experienced significant health impacts subsequent to taking quinoline antimalarials, particularly mefloquine, for travel or military service. As well as her international work, she has represented Australian veterans at both a State and Federal level, and through QVFA partnership of the Association of Defence Service Organisations (ADSO). She is currently the Scientific Advisor to the Australian Quinoline Veterans and Families Association (QVFA), a veteran's organisation representing current and ex-serving ADF members, and their families, who have experienced significant health impacts after taking mefloquine and / or tafenoquine for military service.

This submission will consider evidence relating to three of the Terms of Reference of this Senate Inquiry and the following information will be presented in relation to these ToRs:

Prelude

This submission will consider evidence in relation to a number of the terms of reference of this inquiry. In response to that evidence, the following recommendations will be made:

Recommendations:

A number of recommendations will be made in relation to these ToRs, specifically:

i. **That a formal apology is issued by the ADF to the veterans and their families involved in AMI clinical trials of mefloquine and tafenoquine, and;**

ii. **That appropriate clinical review and follow-up is implemented immediately to determine the long term impacts of exposure to mefloquine and tafenoquine in this cohort.**

iii. **That appropriate compensation is offered, without impact or diminution to their current entitlements and benefits, to those veterans and their families found to have suffered long term adverse health impacts from having participated in these trials.**

iv. **That tafenoquine is not adopted for use by the Australian military for the same reasons that mefloquine is relegated to a drug of last resort, that the risk of neuropsychiatric adverse events in military veterans is high and that this is an <u>unacceptable risk</u> for this population.**

v. **That all the original ADF AMI antimalarial trial data is reanalysed by an independent third party to determine the actual incidence of reported adverse events in these studies and that this data reported in the scientific literature.**

vi. **That a formal retraction of 'safety' is issued in relation to the published articles to set the historical record straight on the interpretation of the aforementioned trial data.**

vii. **That a follow-up for female ADF members exposed to quinoline antimalarials in AMI trials is initiated immediately and appropriate compensation offered where long term health impacts are identified.**

viii. **That female ADF members and veterans are not exposed to mefloquine or tafenoquine for malarial prophylaxis and that safer alternatives must be preferentially administered for this group.**

ix. **That an SOP be established for chemically acquired brain injust, quinolone poisoning or similar, to facilitate claims and compensation for veterans and their families exposed to these drugs during ADF clinical trials or general military service.**

x. **That all ADF veterans exposed to the quinolone antimalarials mefloquine and tafenoquine during their ADF service, regardless of operational status of exposure, be awarded a DVA Gold Card in recognition of their service to this country and potential impact on their health.**

xi. **That ADF veterans are precluded by law from being engaged as subjects in clinical trials;**

xii. **That all AMI and other clinical trial records are immediately incorporated into each veteran's main medical record and those additional documents made available to veterans immediately;**

xiii. **That the Government and ADF formally recognize the role played by ADF veterans in advancing our understanding of both the science and treatment of tropical diseases, including malarial, by their role in ADF-sponsored clinical trials, and that this is clearly acknowledged as a significant service to the organization and the wider medical community.**

xiv. **That a Royal Commission be established into the use of ADF members in clinical trials, institutional links with the pharmaceutical sector, and treatment of clinical trials veterans both during their service and post-exit.**

xv. **That CYP450 pharmacogenomic profiling be implemented immediately for current ADF members, and all veterans involved in the AMI mefloquine and tafenoquine trials to determine their risk of adverse events related to these and other pharmacological agents.**

xvi. **That a policy of immediate and complete adverse event reporting to the Therapeutic Goods Administration database is applied to all ADF medical**

practitioners, to ensure that AE reporting is both comprehensive and independently registered.

xvii. That longitudinal data analyses be carried out to determine the risk of long term health impacts from exposure to quinoline antimalarials in ADF veterans, including potential secondary impacts on their children.

xviii. That a working group be established encompassing veterans advocates experienced in the effects of quinoline toxicity with appropriate, independent advisers sourced from the military mental health community, family services, occupational health practitioners, brain injury rehabilitation specialists, neurologists, psychologists, cognitive and behavioural experts and psychiatrists, to establish a recommended assessment and treatment program for those affected by mefloquine and tafenoquine during their military service.

xix. That this advisory panel be appropriately resourced to deliver a national outreach and rehabilitation program for quinoline veterans and families in Australia.

xx. That a program of research is funded to better understand and identify veterans experiencing long term health issues related to quinoline exposure during their ADF service.

Section 1. Introduction - the quinoline antimalarials mefloquine and tafenoquine and their use in the Australian Defence Force

Mefloquine (trade name Lariam®) is an effective anti-malarial and is used worldwide for both malaria treatment and prophylaxis. Despite its undoubted therapeutic properties, it suffers from a variable incidence of neurological and neuropsychiatric side effects that are known to cause both transient and lasting central nervous system dysfunction (Ritchie, Block et al. 2013, Nevin 2015, Livezey, Oliver et al. 2016). Due to its relative ease of administration, a weekly rather than daily oral dose, it was widely utilised by military and volunteer service organisations after its introduction in the 1980's, due to a relative ease of ensuing compliance with prophylactic regimes for members when working in malarial zones. Despite its efficacy, it of mefloquine in military populations has become an area of increasing controversy due to the reported incidence of adverse events and lack of appropriate prescribing and adverse event reporting protocols (Gogtay and Ferner 2015, Quinn 2016).

Section 2. Mefloquine poisoning – a toxidrome of clinical symptoms

The mefloquine toxidrome, an accumulation of symptoms associated with adverse reactions to mefloquine, present a relatively well defined toxic profile. This toxidrome has been described in detail in a number of publications over the past 20 years including those of Nevin (2015) (Nevin 2015), Ringqvist et al, (2015) (Ringqvist, Bech et al. 2015) and others (Boudreau, Schuster et al. 1993, Rendi-Wagner, Noedl et al. 2002, Adshead 2014). Commonly reported symptoms acutely associated with mefloquine ingestion 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 (Ringqvist, Bech et al. 2015). Severe acute adverse reactions include frank psychosis, hallucinations, and seizures. These symptoms represent a toxidrome which is clearly identifiable subsequent to mefloquine exposure (Nevin and Leoutsakos 2017).

Recently, is has become apparent and accepted, that some of the neuropsychiatric symptoms can persist well past discontinuation of the drug, in some cases lasting for many years. Reports in the medical literature have documented cases in service members, perhaps the most comprehensive example being a recent case study in an a serving member of the US military that identified long-term cognitive dysfunction, headaches, mood disturbances and vestibular dysfunction subsequent to mefloquine ingestion for military service (Livezey, Oliver et al. 2016). Thus, despite early claims of safety (1983), an increasing body of evidence has established that serious symptoms of central nervous system dysfunction occur far more commonly that 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 had been previously anticipated (Adshead 2014).

In response to increasing numbers of adverse events reports, and to acknowledge the potential for lasting adverse reactions occurring during or after use of mefloquine for malarial prophylaxis, in 2013 the US drug regulator, the Food and Drug Administration (FDA), required that the mefloquine product label include a boxed warning stating that *"[m]efloquine may cause neuropsychiatric adverse reactions that can persist after mefloquine has been discontinued*" and added the following warning concerning psychiatric adverse reactions:

> *"Psychiatric symptoms ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior can occur with mefloquine use. Symptoms*

> *may occur early in the course of mefloquine use. In some cases, these symptoms have been reported to continue for months or years after mefloquine has been stopped. Cases of suicidal ideation and suicide have been reported"(Agency 2013)*

Subsequent to the advent of the FDA black box warning, a review of patients presenting for neuropsychiatric in-patient treatment, who had taken mefloquine, identified that 77% of patients presented within symptoms within the first three weeks of exposure, with the remaining individuals reporting onset between one month and two months post initiation of drug exposure. This study was the first to indicate that onset of neuropsychiatric symptoms was not necessarily coincident with the primary stage of drug exposure, as had previously been suggested, and that in some cases onset was significantly after first exposure. In this population, a high percentage of adverse events overall were identified as persisting well after initial ingestion of the drug (Table 1: depression 44%, anxiety 55%), particularly with cognitive dysfunction and altered dream states were reported as persisting beyond 3 years post exposure were reported in 20.9% and 33.3% of patients examined (Ringqvist, Bech et al. 2015). This evidence clearly suggested that long term neuropsychiatric sequelae could present in a proportion of individuals who had been exposed to normal levels of mefloquine for malarial prophylaxis (e.g. without excessive dosing or accidental overdose).

More recently, certain symptoms experienced commonly during the early phases of drug exposure, have now been suggested as "prodromal", or a clinical early warning, of more serious or lasting drug toxicity (Nevin 2012, Remington 2012). To acknowledge this risk the current Australian safety leaflet stating that if common symptoms of an adverse reaction are experienced, such as changes in mood, anxiety or altered dream or sleep states that "*[i]n*

*these cases, the drug **must** be discontinued".*

In light of this evidence, insomnia has specifically been included recently (2018) in the manufacturers patient safety leaflets to acknowledge the importance of altered sleep states as a warning of potentially more serious and lasting sequelae. It is these prodromal adverse events that are suggested to make mefloquine particularly unsuitable for use in military populations due to the difficulty in identification of adverse reactions compared to the normal behavioral responses to a high stress combat environment.

Section 3. Tafenoquine, a new quinoline antimalarial

Tafenoquine is an 8-aminoquinoline antimalarial medication, which although not identical, belongs to the same class of drugs as mefloquine (Peters 1999, Shanks, Oloo et al. 2001). Some of the earliest clinical trials of tafenoquine for malarial prophylaxis and radical cure studies undertaken by the Australian Army Malaria Institute utilizing Australian Defence Force (ADF) members on active service in East Timor and Bougainville (Nasveld 2002, Nasveld, Kitchener et al. 2002, Nasveld and Kitchener 2005, Charles, Miller et al. 2007, Edstein, Nasveld et al. 2007, Kitchener, Nasveld et al. 2007, Elmes, Nasveld et al. 2008, Nasveld, Edstein et al. 2010). AMI is a government-funded research arm of the ADF that has a specific remit to develop and deliver research outcomes related to control of eradication of tropical infectious diseases for the Australian military, a remit which has engaged this organization in a large number of clinical trials utilizing ADF veterans to investigate preventatives and treatments for tropical infectious diseases ranging from clinical drug trials in collaboration with the US Defence agencies and pharmaceutical companies such as GlaxoSmithKline (Rieckmann, Cheng et al. 2015).

Table 1. Reported incidence of adverse events by symptom extracted from published large cohort studies of military members and civilian travellers exposed to mefloquine for malarial prophylaxis. Figures are identified to one decimal place where reported in the original publication. Study design is identified at first appearance. Data does not include withdrawals, where reported. Where two denominators were present for a single presentation (e.g. pruritus + 'other skin') these values were combined. Where original data was not represented as a %, these were calculated from the original data. Data extracted from clinical trial reports undertaken by the Army Malaria Institute, Australia, are identified in **bold.** AU: Australia, UK: United Kingdom; US: United States of America, N/R, not reported. Studies with pharmaceutical involvement are identified with an #.

Symptom	Reported Cases %	Dates of study	Study design / Reference
Gastrointestinal dysfunction	58 #	1998 - 2001	Randomised, double blind, four arm trial – civilian travellers (Schlagenhauf 2003)
	57	1996 - 2000	Retrospective case series – civilian travellers (Ringqvist, Bech et al. 2015)
	51 #	**2000 - 2001**	**Comparative, randomised, double blinded active control study – AU military (Nasveld, Edstein et al. 2010)**
	41	2000	Open label prospective study – civilian travellers (Rendi-Wagner, Noedl et al. 2002)
	27 #	N/R	Randomised, double blinded controlled trial – US military (Boudreau, Schuster et al. 1993)
	19 #	1999	Randomised, double-blind controlled trial – civilian travellers (Overbosch 2001)
	18	2013	Open label prospective study – UK military (Adshead 2014)
	15.2 #	1985 -1991	Prospective, randomised, double blinded dose-ranging active control study – African nationals (Steffen, Heusser et al. 1990)
	10	2005 - 2006	Retrospective self-reported comparative review – Peace Corp members (Korhonen, Peterson et al. 2007)
	9.7	1997	Retrospective, cross-sectional study – civilian travellers (Lobel, Baker et al. 2001)
	8.1	2012 – 2013	Prospective, open label two arm cohort study – UK military (Terrell, Forde et al. 2015)
	2	2002 - 2003	Prospective, open label cohort study – Japanese military (Fujii, Kaku et al. 2007)
Dizziness	57	1985 – 1991	(Ringqvist, Bech et al. 2015)
	9 #		(Overbosch, Schilthuis et al. 2001)
	7.6 #		Prospective comparative study – civilian travellers (Steffen, Fuchs et al. 1993)
	7.1		(Fujii, Kaku et al. 2007)
	6 #		(Boudreau, Schuster et al. 1993)
	6		(Terrell, Forde et al. 2015)
	1 #		(Nasveld, Edstein et al. 2010)

Table 1 continued. Symptom	**Reported Cases %**	**Dates of study**	**Study design / Reference**
Nausea	82 57.5 # **16** 14 # **13 #** 12.3 # 8 # 2.2	**2001 - 2002**	(Rendi-Wagner, Noedl et al. 2002) (Schlagenhauf 2003) **Prospective, open label, two arm cross-sectional study – AU military (Kitchener, Nasveld et al. 2005)** (Boudreau, Schuster et al. 1993) (Nasveld, Edstein et al. 2010) (Steffen, Heusser et al. 1990) (Overbosch, Schilthuis et al. 2001) (Fujii, Kaku et al. 2007)
Visual disturbances	49 3 # 2.2 # 1.7		(Ringqvist, Bech et al. 2015) (Overbosch, Schilthuis et al. 2001) (Steffen, Heusser et al. 1990) (Terrell, Forde et al. 2015)
Vertigo / vestibular dysfunction	96 38 10 # **5 #**		(Rendi-Wagner, Noedl et al. 2002) (Ringqvist, Bech et al. 2015) (Hessen-Soderman, Bergenius et al. 1995) Prospective, open label single cohort study – civilian non-travellers (Nasveld, Edstein et al. 2010)
Tinnitus	18 0.4		(Ringqvist, Bech et al. 2015) (Fujii, Kaku et al. 2007)
Headache	73 36 22 # **14** **12 #** 10 # 7 # 6.2 # 6.0 1.3		(Rendi-Wagner, Noedl et al. 2002) (Ringqvist, Bech et al. 2015) (Boudreau, Schuster et al. 1993) (Kitchener, Nasveld et al. 2005) (Nasveld, Edstein et al. 2010) (Hessen-Soderman, Bergenius et al. 1995) (Overbosch, Schilthuis et al. 2001) (Steffen, Heusser et al. 1990) (Terrell, Forde et al. 2015) (Fujii, Kaku et al. 2007)

Table 1 continued. Symptom	**Reported Cases %**	**Dates of study**	**Reference**
Fatigue	49 **21** **4 #** 3.7 3.0		(Ringqvist, Bech et al. 2015) (Kitchener, Nasveld et al. 2005) (Nasveld, Edstein et al. 2010) (Fujii, Kaku et al. 2007) (Terrell, Forde et al. 2015)
Peripheral neuropathy / numbness	30		(Ringqvist, Bech et al. 2015)
Neuropsychological adverse events without specific symptom classification	77 # 65 7.8		(Schlagenhauf 2003) (Korhonen, Peterson et al. 2007) (Lobel, Baker et al. 2001)
Visual / auditory hallucinations	22 10		(Rendi-Wagner, Noedl et al. 2002) (Ringqvist, Bech et al. 2015)
Depression	44 18 16.9 # 10 # 4 # 1.8 # **<1 #**		(Ringqvist, Bech et al. 2015) (Rendi-Wagner, Noedl et al. 2002) (Boudreau, Schuster et al. 1993) (Hessen-Soderman, Bergenius et al. 1995) (Overbosch, Schilthuis et al. 2001) (Steffen, Heusser et al. 1990) (Nasveld, Edstein et al. 2010)
Anxiety	55 10 # 5 4 # 0.5		(Ringqvist, Bech et al. 2015) (Hessen-Soderman, Bergenius et al. 1995) (Rendi-Wagner, Noedl et al. 2002) (Overbosch, Schilthuis et al. 2001) (Fujii, Kaku et al. 2007)
Anger / aggression / irritability	14.3 #		(Boudreau, Schuster et al. 1993)
Psychosis	<0.001 #		(Steffen, Fuchs et al. 1993)

Table 1 continued. **Symptom**	**Reported Cases %**	**Dates of study**	**Reference**
Cognitive dysfunction / confusion	59 5 # 5 10 # 0.3		(Ringqvist, Bech et al. 2015) (Boudreau, Schuster et al. 1993) (Rendi-Wagner, Noedl et al. 2002) (Hessen-Soderman, Bergenius et al. 1995) (Fujii, Kaku et al. 2007)
Paranoia / delusion	51		(Ringqvist, Bech et al. 2015)
Mania	5.5		(Ringqvist, Bech et al. 2015)
Sleep disturbance	59 38 32 **31** 25 # 13 # 9.4 4.2 # **2 #** 2.7		(Ringqvist, Bech et al. 2015) (Adshead 2014) (Rendi-Wagner, Noedl et al. 2002) (Kitchener, Nasveld et al. 2005) (Boudreau, Schuster et al. 1993) (Overbosch, Schilthuis et al. 2001) (Terrell, Forde et al. 2015) (Steffen, Fuchs et al. 1993) (Nasveld, Edstein et al. 2010) (Fujii, Kaku et al. 2007)
Nightmares / vivid dreams	59 39 14 # 7.7 7 # 2.2 1 #		(Ringqvist, Bech et al. 2015) (Adshead 2014) (Overbosch, Schilthuis et al. 2001) (Terrell, Forde et al. 2015) (Boudreau, Schuster et al. 1993) (Fujii, Kaku et al. 2007) (Nasveld, Edstein et al. 2010)

Table 1 continued. **Symptom**	**Reported Cases %**	**Dates of study**	**Reference**
Dermal irritation / rash	36 36 # **21 #** 9.9 # 5.5 # 5 5 2.3		(Ringqvist, Bech et al. 2015) (Schlagenhauf 2003) (Nasveld, Edstein et al. 2010) (Steffen, Fuchs et al. 1993) (Steffen, Heusser et al. 1990) (Fujii, Kaku et al. 2007) (Korhonen, Peterson et al. 2007) (Terrell, Forde et al. 2015)
Cardiac arrhythmias	42 31 2 0.8 <1%		(Ringqvist, Bech et al. 2015) (Rendi-Wagner, Noedl et al. 2002) (Hale, Owusu-Agyei et al. 2003) (Fujii, Kaku et al. 2007) (Terrell, Forde et al. 2015)

In Australia, approval for registration was awarded to tafenoquine on 1 February 2018 by the Therapeutic Goods Administration (TGA) specifically for use of tafenoquine as a single dose for treatment of active malaria infection, and only in persons over 16 years of age, and under specialized clinical supervision (TGA 2018). Safety, efficacy and pharmacokinetic trials are currently being undertaken by GlaxoSmithKline, the drug manufacturer, in collaboration with the Medicines for Malaria Venture (MMV), to determine these parameters in children between 6 months and 15 years of age (Study ID TAF113577)(GSK 2015).

Prior to 2018, tafenoquine was not registered for clinical use in humans in any jurisdiction globally and use of this drug has been restricted to clinical trials. These include a number of studies undertaken by the Army Malaria Institute utilizing Australian Defence Force members (Nasveld 2002, Nasveld, Kitchener et al. 2002, Nasveld and Kitchener 2005, Charles, Miller et al. 2007, Edstein, Nasveld et al. 2007, Kitchener, Nasveld et al. 2007, Elmes, Nasveld et al. 2008, Nasveld, Edstein et al. 2010). The AMI is a government-funded research arm of the Australian Defence Force which has a specific remit to develop and deliver research outcomes related to control of eradication of tropical infectious diseases for the Australian military (Rieckmann, Cheng et al. 2015).

Section 4. Response to the Inquiry Terms of Reference:

(a) identifying and reporting adverse drug reactions from quinoline anti-malarial drugs among ADF personnel, and;

(b) the nature and extent of any adverse health effects of those who have taken mefloquine/tafenoquine on serving and former ADF personnel;

Section 4.1. Clinical trials of quinolone antimalarials in military organisations – institutional failure of adverse event reporting and identified limitations to self-reporting of AE's in military subjects

Antimalarial medications are of key importance in the Australian military setting due to the high rates of deployment to malarious zone within South East Asia and the South Pacific. That troops require protection from exposure to, and infection by the malaria parasite is not a point of debate, however, suitable oversight of methodologies employed from a veteran safety standpoint has perhaps been relegated to of secondary importance behind the need to provide operational forces with protection against malaria in a largely non-immune population. In this section, the evidence of under-reporting of adverse events in ADF AMI administered clinical trials, and the follow-on effects of this lack of documented health information on the ability of veterans to currently attribute their health issues to drug trial exposures will be discussed.

The impact of the AMI antimalarial drug trials on international use of mefloquine, and future use of tafenqouine, cannot be underestimated. Some of the most widely cited evidence of safety for mefloquine in military users has come from the clinical trials carried out in the early 2000's in East Timor using Australian Defence Force (ADF) personnel (Kitchener, Nasveld et al. 2005, Charles, Blomgren et al. 2007, Nasveld, Edstein et al. 2010). It is this

close relationship between the military organisation, its research arm and commercial entities involved that has raised ethical issues around the informed consent process in this trials (McCarthy 2015). The close interdependency between the two organisations, ADF and AMI, as well as strong international links between the AMI and other international military organisations has presented a significant dual loyalty from which ADF veterans became the subjugated parties. This dual loyalty, and the status of ADF veterans as vulnerable trial subjects likely contributed to the poor adverse event reporting associated with these trials, the evidence for which will be discussed further in this submission.

In order to fully understand the extend of these conflicts of interest it is necessary to examine the circumstance, and outcomes of several clinical trials undertaken by the Army Malaria Institute in the late 1990's and early 2000's. These trials examined the efficacy and safety of a number of antimalarials, including the registered drug mefloquine and the unregistered drug tafenoquine and were undertaken using ADF personnel engaged in active 'war-like' deployments (Edstein, Walsh et al. 2001, Nasveld, Kitchener et al. 2002, Kitchener, Nasveld et al. 2005, Nasveld and Kitchener 2005, Charles, Miller et al. 2007, Edstein, Nasveld et al. 2007, Kitchener, Nasveld et al. 2007, Elmes, Nasveld et al. 2008, Nasveld, Edstein et al. 2010). In these studies, mefloquine and tafenoquine were examined both for their efficacy against the malaria parasite, and for their safety in the ADF members taking them. That safety testing was an inherent part of the trial protocols was surprising given that mefloquine was already registered for use in humans for malarial prophylaxis in Australia and other countries.

One of the first randomised, double-blinded phase 3 studies to be undertaken with tafenoquine and mefloquine was carried out by the Army Malarial Institute using ADF

service members deployed to East Timor between 1999 and 2001. This study reported that although tafenoquine elicited more gastrointestinal side effects than mefloquine, the neuropsychiatric adverse event profile of the two drug was not significantly different in magnitude (Charles, Miller et al. 2007, Edstein, Nasveld et al. 2007, Nasveld, Edstein et al. 2010). Specifically, in the 2000-2001 study undertaken by Nasveld and colleagues (published in 2010), 13.0% of tafenoquine and 14.2% of mefloquine subjects experienced a drug related neuropsychiatric adverse event, with vertigo (tafenoquine, 22.0%; mefloquine, 8.0%), fatigue (tafenoquine, 12.0%; mefloquine, 6.0%), abnormal dreams (tafenoquine, 7.0%; mefloquine, 2.0%), and dizziness being the most commonly reported side effects (tafenoquine, 5.0%; mefloquine, 2.0%, Table 1). Mefloquine was already known to cause sever neuropsychiatric side effects and cardiac arrhythmias in a proportion of people it, a fact that had been recognised by the World Health Organisation 1983, well prior to the advent of these trials (Bulletin 1983), yet a conclusion that melfoquine was well tolerated in non-immune adults was a key finding of these trials (Kitchener, Nasveld et al. 2005). The authors reported that there was no significant difference between the two treatment groups, nor flagged the incidence of neuropsychiatric side effects as potential point of concern, despite more than a two-fold greater percentage of affected individuals in the tafenoquine treatment arm compared to the mefloquine treatment group (Nasveld, Edstein et al. 2010).

What is perhaps most surprising is that, despite a clearly reported neuropsychiatric adverse event profile, no adverse events reports for any neuropsychiatric side effects ***for either drug*** were reported to the Australian Therapeutics Administration at the time of the trials (RightToKnow 2018, RightToKnow 2018). In a second trial involving mefloquine, 30 individuals are reported has having been withdrawn from the mefloquine treatment arm due to adverse events yet these numbers also appear to be unreported to the Australian regulatory

drug agency (ADHREC minutes 548-7-45, Report and amendments to mefloquine trial. ADMEC Protocol 249/01, p13) (Kitchener, Nasveld et al. 2005), in addition to those 9 subjects receiving mefloquine in the mefloquine / tafenqoquine trial, and 39 subjects in the tafenoquine group (Nasveld, Edstein et al. 2010) who did not continue with their original designated drug. A significant discrepancy is also apparent between the two ADF clinical trials conducted using mefloquine as the comparator during the East Timor conflict, with the first pharmaceutical and USMAADA-funded trial undertaken by Nasveld and colleagues reporting lower incidences of neuropsychiatric adverse events than his colleague Kitchener for essentially the same subject cohorts (Table 2) (Kitchener, Nasveld et al. 2005, Nasveld, Edstein et al. 2010).

In addition to those discrepancies in neuropsychiatric adverse event reporting, other incongruities exist in the published data compared to the reported adverse events for the 2010 East Timor trial. By far the most prevalent side effect reported in the AMI mefloquine / tafenoquine comparator trial was that of vortex keratopathy (93.2%, 69/74 veterans) (Nasveld, Edstein et al. 2010). In direct contradiction to this published evidence, only 5 adverse events reports were lodged with the Therapeutic Goods Administration (TGA) at the time, all under the identifier ‘visual impairment’(RightToKnow 2018). Together this information suggests that visual anomalies *were* identified by the investigators at the time of the trial, a statement in stark contrast to the data presented in their 2010 paper where no visual impairment was reported (Nasveld, Edstein et al. 2010). Together, this suggests that adverse events related to these trial were clearly under-reported, both in the journal articles reporting the trial outcomes and to the appropriate regulatory bodies governing use of the experimental drug within these trials.

Table 2. Comparison of published adverse event data from two Army Malaria Institute administered clinical trials undertaken in East Timor between 2000 and 2002, comparing of mefloquine for malarial prophylaxis. Where adverse event values were reported from both trials, fold differences are identified in brackets.

DRUG EXPOSURE: MEFLOQUINE	*Nasveld et. al., published 2010*	*Kitchener et. al., published 2005*
Design	Prospective, randomized, double blinded, two-arm, active control	Prospective, open label, two-arm cross-sectional, active control
Date of trial	2000 – 2001	2001 – 2002
Location	East Timor	East Timor
No. taking mefloquine	162	1157
Method of AE collection	Structured interview	Questionnaire and structured interview
GI dysfunction	51%	N/R
Dizziness	1%	N/R
Nausea	3%	N/R
Headache	**12%**	**14% (1.16)**
Fatigue	**3%**	**21% (7)**
Depression	<1%	N/R
Sleep disturbance	**2%**	**31% (15.5)**
Abnormal dreams	3%	NR
Hallucinations	NR	1 individual
Seizures	NR	1 individual
Rash / dermal irritation	21	NR

The rationale for the Kitchener et al (2005) mefloquine / doxycycline comparator study was that compliance with doxycycline had been poor during an international peace-keeping operation in 1999, due to the requirement to take the drug daily and with food, and that a weekly regimen would be more effective in increasing compliance. This trial was reported to 'build upon' their previous study examining the efficacy of mefloquine in a military setting, as a conclusion that mefloquine had been 'well tolerated' had been provisionally reported in conference abstract in the American Journal of Hygiene and Tropical Medicine (Nasveld 2002), the full data from which was only published in 2010, 5 years after the publication of results from the study it was reported to build on. This delay was pivotal in establishing a false safety profile for mefloquine for military use on a global scale.

One of the key outcomes of this study was the reported finding that '*mefloquine was generally well tolerated by Australian soldiers'* using the evidence that 94% of those questioned at the end of deployment would take the drug again (Kitchener, Nasveld et al. 2005). Despite reporting a significant number of prodromal and neuropsychiatric side effects, although limited in definition, their findings did fully support this statement (Table 1 – e.g. sleep disturbance 31% (Kitchener, Nasveld et al. 2005), 32% (Rendi-Wagner, Noedl et al. 2002), 38% (Adshead 2014), 25% (Boudreau, Schuster et al. 1993). Similar results can be seen for 'headache', 'nausea' and 'fatigue' (Table 1). The fact that no detailed adverse event data was published from this trial also leaves an open question as to why the authors did not follow up their report despite suggesting in the text that they would do so.

What is perhaps most important is that the cumulative, long term effect of the lack of appropriate adverse event reporting associated within these trials prevented appropriate

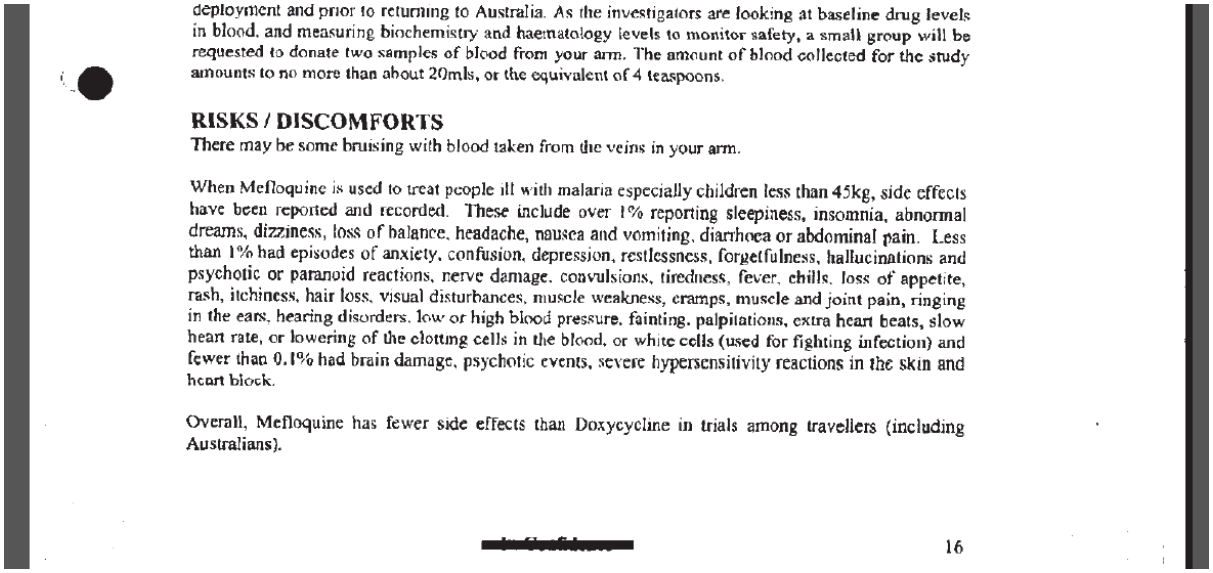
follow-up care for these individuals involved in them for more than two decades.

Section 4.2. International comparison of adverse event reporting for mefloquine in trials undertaken with military members of civilian patients / participants

A comparison between adverse event profiles reported in the AMI trials that utilised ADF members as trial subjects, and those presented both other investigators utilising both military and civilian populations is worthy of discussion. Published adverse events data was extracted from a selection of clinical trials involving mefloquine either as the primary drug of interest, or as a comparator, and data tabulated for comparison (Table 1) to compare presentation rates and range of adverse event data presented across trial cohorts. Data was presented either as the figure reported in the original article or a % value extrapolated from individual patient numbers and the total number of treatment participants. This analysis clearly shows a range of incidence of the various AE categories reported across a number of clinical trials, yet even within this variation Nasveld (2010) report some of the lowest AE %'s comparative to all other trials examined. Potential reasons for this discrepancy in reporting will now be discussed.

One possible reason for the low incidence of neuropsychiatric side effects reported by AMI investigators in the early 2000's, compared to other studies coincident and later investigating similar outcomes, could be the nature of the investigative tool used to measure them. In the Nasveld mefloquine / tafenoquine comparator trial (Nasveld, Edstein et al. 2010), participants were asked the non-leading question by a senior medical officer: "Do you feel differently in any way since starting the new treatment?" Certainly this is likely to be partly the interpretation of the very high levels of neuropsychiatric adverse event reporting observed in other military studies using mefloquine where knowledge of neuropsychiatric side effects

associated with this drug was well known (Adshead 2014). The limited information presented in the patient participation information for this trial is also likely to have played a role in this misrepresentation as the first statement implies that adverse events are related to use of mefloquine for treatment of malaria patients <45kg (see Figure 1), which would be applicable to few or none of the subject cohort (ADMEC minutes 45-7-45 Enclosure 1, (RightToKnow 2016)). In particular, the last sentence: 'Overall, mefloquine has fewer side effects than doxycycline in trials amongst travellers (including Australians)', is simply misleading and could well have led to underreporting of adverse events by negative implication.



deployment and prior to returning to Australia. As the investigators are looking at baseline drug levels in blood, and measuring biochemistry and haematology levels to monitor safety, a small group will be requested to donate two samples of blood from your arm. The amount of blood collected for the study amounts to no more than about 20mls, or the equivalent of 4 teaspoons.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm.

When Mefloquine is used to treat people ill with malaria especially children less than 45kg, side effects have been reported and recorded. These include over 1% reporting sleepiness, insomnia, abnormal dreams, dizziness, loss of balance, headache, nausea and vomiting, diarrhoea or abdominal pain. Less than 1% had episodes of anxiety, confusion, depression, restlessness, forgetfulness, hallucinations and psychotic or paranoid reactions, nerve damage, convulsions, tiredness, fever, chills, loss of appetite, rash, itchiness, hair loss, visual disturbances, muscle weakness, cramps, muscle and joint pain, ringing in the ears, hearing disorders, low or high blood pressure, fainting, palpitations, extra heart beats, slow heart rate, or lowering of the clotting cells in the blood, or white cells (used for fighting infection) and fewer than 0.1% had brain damage, psychotic events, severe hypersensitivity reactions in the skin and heart block.

Overall, Mefloquine has fewer side effects than Doxycycline in trials among travellers (including Australians).

[redacted]

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Figure 1. Exert of consent form indicating side effects likely to be experienced by ADF veterans taking mefloquine for a doxycycline / mefloquine comparator trial during deployment to East Timor (Kitchener, Nasveld et al. 2005, RightToKnow 2016). Taken from clinical trial protocol v1.6.

Perhaps the most striking contrast in AE reporting comes from the Kitchener (2005) mefloquine / doxycycline study and the Nasveld study (2010) it reports to build on. Although data from the mefloquine / doxycycline 2001-2002 trial is reported in their publication as incomplete: the authors stating in their 2005 paper that '**Section 4.3. Concluding remarks**

The importance of the information presented above is that the conclusions that were drawn from this the Nasveld (2010) and Kitchener (2005) studies that mefloquine was 'generally well-tolerated' in a military setting, was used as the rationale for use of mefloquine in military organisations world-wide for more than two decades. The under-reporting of adverse events within these AMI trials, in conjunction with a systemic failure of reporting to the local regulatory authorities, entrenched a perception of safety for use of mefloquine in a military setting that was simply unsupported by any tangible evidence. This perception of safety, and lack of documentation of neuropsychiatric adverse events in the trial cohorts, in combination with the lack of follow-up for these trial participants has meant that their subsequent health issues have gone unrecognised and unreported for several decades. That tafenoquine exerted similar neuropsychiatric adverse events to mefloquine was not appropriately acknowledged as a risk profile for this drug. The long-term sequelae of these events are still being keenly felt my military members and their families globally today.

Section 5. GSK adverse event reporting for tafenoquine for FDA product registration – identification of neuropsychiatric side effect profile

The most recent evidence of causality related to adverse events for the tafenqouine comes from recent documents submitted to the FDA in the US as part of GSK's product registration process. As indicated previously, the lack of adverse event reporting at the time of the Nasveld-led AMI trials had given the implicit impression that tafenoquine did not exert neuropsychiatric side effects of similar magnitude to those know to be associated with mefloquine, and therefore that there was a good safety profile associated with this drug.

When information began to come to light in 2015 that ADF members who had been involved in the trials were experiencing significant long term health effects, in some cases very similar to those experienced by travellers and military veterans who had been given mefloquine for malarial prophylaxis, the QVFA made contact with GSK initially in Australia and then at their Head Office in the UK, to raise awareness of these issues. GSK recommended those veterans who were experiencing significant long term health effects that they believed to be related to exposure to tafenqouine to submit adverse event reports either directly to them or via the TGA adverse event reporting system in Australia. A number of veterans did so which then allowed GSK to review this data, corroborate it with their trial records, and for GSK to determine whether there was a likelihood of causality between exposure and adverse events.

After undertaking this review, GSK concluded that a number of these adverse events could causally be related to exposure to tafenoquine as part of the AMI trials, and these were then required to be reported to the FDA as part of their new drug registration submission. Although it is not possible to individually identify which reports relate to the ADF veterans in this submission, information relating to neuropsychiatric adverse events are clearly discussed.

The following excerpts are taken from the GSK Advisory Committee Briefing Document presented to the FDA regarding registration of tafenoquine succinate tablets (300mg) for Plasmodium vivax malaria radical cure on 12th July 2018, p26-27 (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM612875.pdf):

p26-27: '**Reports from subjects in previous TQ studies**

Reports from subjects in previous TQ studies Starting in 2016, reports of psychiatric disorders have been received from a total of 18 subjects out of the >1500 individuals who received TQ in studies (mostly for prophylaxis) conducted with the Australian Defense Force (ADF) (Study SB252263/033, Study SB252263/046, and Study SB252263/049), which were conducted >15 years ago. The self-reported medical histories contained in these more recent reports from former ADF study participants describe more CNS events than were reported at the time of the study, including anger outbursts, confusional state, and hallucinations. These reports provided only limited medical information, and were not medically confirmed. The majority of soldiers making reports were exposed to triggers for post-traumatic stress syndrome, the symptoms of which are similar to those included in the reports. These aspects taken together make evaluation more challenging and mean that a firm conclusion cannot be drawn although a role for tafenoquine cannot be excluded. Whilethere may be reasons why symptoms were under-reported at the time, the rate for CNS effects was nonetheless higher in the ADF study SB252263/033 compared to study SB252263/057, which studied the same TQ dosing regimen (200mg x 3 loading dose, then 200mg weekly for 6months) but in healthy volunteers including non-deployed military personnel. The absence of an untreated control group in Study SB252263/033 poses difficulties in interpretation of this datacompared to background rates of CNS events in a military population. Literature suggest that thereis a substantial background rate of depression (~12%, Brignone, 2017;

Fanning, 2013; Ilgen, 2010 O'Toole, 2015; Ramsawh, 2014) and anxiety disorders (~10%, Brignone, 2017; Fanning, 2013; Ilgen, 2010; McFarlane, 2011; O'Toole, 2015) in military populations.

To date, due to limitations in the data available and the inability to perform an accurate and non-confounded retrospective analysis, e.g. recruitment/selection and recall bias, it has not been possible to make a connection between mild to moderate side effects reported during Study SB252263/033, and any permanent serious long-term effects with onset after completion of the study. ***It is therefore possible that the deployed ADF soldiers represented a higher risk population***. (emphasis added)

CNS Safety Conclusion: In the >800 subjects who have received a total 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 + CQ for radical cure of P.vivaxmalaria is anticipated to have a low risk of significant CNS effects in patients without an active or past history of serious psychiatric disorders. ***Adopting a conservative approach and given the totality of both clinical data and the scientific literature, the proposed labelling for 300 mg single dose TQ currently under review by the FDA indicates that caution is advised when administering TQ to patients with a current or past history of serious psychiatric disorder. The intention is for the safety of tafenoquine to be monitored carefully post-registration***.' (emphasis added)

p94: ‘7.4.2. Other safety considerations.

The 300mg single dose TQ was associated with a number of ***transient and reversible CNS events (insomnia, anxiety, abnormal dreams, headache, dizziness, somnolence)***. These events are also reported for other antimalarials. None of the events resulted in withdrawal from the study or treatmentdiscontinuation. The risk of CNS effects is judged to be low in subjects without a history of serious psychiatric disorders. Caution is advised when administering TQto patients with a history of, or current, serious psychiatric disorders.’

The conclusions drawn above are both contradictory and misleading. GSK have not proven CNS adverse events to be ‘transient and reverseable’. The reporting of adverse event profiles from ADF members included in this report indicate that in a proportion of exposed individuals tafenoquine will cause long term neuropsychiatric side effects. Although GSK also state no ‘serious’ CNS adverse events were reported in any of the clinical trials, the definition of ‘serious’ in this context indicates long-term hospitalisation, permanent disability or death’. Despite this, there have clearly have been reports of both mild and moderate CNS sequelae causally related to tafenoquine sufficient for them to be reported as part of the registration process *and* for safety wording to be included in the patient safety information to preclude use of this drug in persons with a known history of psychiatric disorder.

Section 5.1. Concluding remarks

The safety contraindications for tafenoquine will be is *identical* to the labelling required for mefloquine, a drug now acknowledged to have a significant and use-limiting neuropsychiatric adverse event profile. The strength of this comparison should not be overlooked when considering the suitability of tafenoquine for use in military populations particularly as the manufacturers themselves identify that military members are likely to represent a high risk population for this drug.

Section 5.2. Recommendations:

- **That a formal apology is issued by the ADF to the veterans and their families involved in AMI clinical trials of mefloquine and tafenoquine, and;**
- **That appropriate clinical review and follow-up is implemented immediately to determine the long term impacts of exposure to mefloquine and tafenoquine in this cohort.**
- **That appropriate compensation is offered, without impact or diminution to their current entitlements and benefits, to those veterans and their families found to have suffered long term adverse health impacts from having participated in these trials.**
- **That tafenoquine is not adopted for use by the Australian military for the same reasons that mefloquine is relegated to a drug of last resort, that the risk of neuropsychiatric adverse events in military veterans is high and that this is an unacceptable risk for this population.**

Section 6. *Response to Inquiry Terms of Reference:*

(d) a comparison of international evidence/literature available on the impact of quinoline anti-malarials

A comprehensive literature review of all available clinical involving mefloquine and tafenoquine trials is a time-consuming process and somewhat out with the remit of this submission. However, a targeted review of published case studies was undertaken noting the occurrence and type of adverse events reported were a primary treatment population was identified (i.e. meta-analyses were not included). Other studies reported in the scientific literature will now be considered looking at the safety of mefloquine specifically. Adverse event profiles will be considered between these studies and those already discussed.

Section 6.1. Recent analyses of safety of mefloquine in non-Australian military populations

Two articles have been recently presented in the literature examining efficacy and safety of mefloquine for malarial prophylaxis in a military setting. A case series undertaken by a medical officer in the UK Royal Navy (Adshead 2014) reported an overall incidence of 54% adverse events in navy personnel taking mefloquine during deployment with 13% experiencing an adverse event severe enough to warrant withdrawal from treatment (Adshead 2014). All the female personnel in the study experienced one or more adverse events, consistent with previous reports that mefloquine induced a higher rate of adverse events in women than in men (Ringqvist, Bech et al. 2015), although other articles report there to be no contraindication for use of mefloquine in female travellers (Lobel, Baker et al. 2001, Schlagenhauf, Blumentals et al. 2012). The high rate of adverse events reported in Adshead's

study trial is suggested to be *"due to the stressful environment in which deployed personnel operate"* (Adshead 2014).

In addition, a two-arm cohort study undertaken by Terrell et al (2015) examined the effect of mefloquine compared to doxycycline on the self-reported ability of troops to carry out their 'work' in British troops undertaking training in Kenya (Terrell, Forde et al. 2015). In this study 12.9% of melfoquine users reported that taking the drug had impacted their ability to 'do their job'. Only two notable neuropsychiatric criteria were reported 'strange dreams', 'sleep disturbance' and 'dizziness / vertigo) which were identified in 7.7%, 9.4% and 6.0% of users respectively (Table 1) (Terrell, Forde et al. 2015). Adshead's study (2014) also reported 'vivid dreams' and 'sleep disturbances' but a significantly higher proportion of respondents (39% and 38%, Table 1) (Adshead 2014). The apparent discrepancy between these two studies is not easy to ascertain given that operational deployment in either setting was not high impact. It is likely that the difference in data reported from these two trials may be related to underlying well-documented issues of self-reporting as an accurate system for the collection of data in military members (Terrell, Forde et al. 2015) when face to face interviews are not carried out, or reporting is undertaken in conditions that are suboptimal for thoughtful consideration by the participants (Terrel's questionnaires were undertaken in the airport whilst waiting for flights home from the operational area). The higher rate of reporting in these trials compared to some others, may well also represent an institutional change in attitude of the British Armed Forces to self-reporting of neuropsychiatric symptoms in serving military members, although this attitudinal change is not always supported by evidence when conversing with serving members on this matter directly.

The variability in AE reporting between clinical trials that occurred in the early years of uptake of mefloquine in various military organisations (UK, US, Japan) compared to trials

with civilian patients (Table 1). This data clearly shows wide variation in prevalence of symptoms reported across different primary cohort studies. For example, the number of individuals reporting symptoms related to sleep disturbance between the trials examined trial data examined ranged from 1% (Nasveld, Edstein et al. 2010) to 59% (Ringqvist, Bech et al. 2015). This is likely to be related, in part, to the two patient demographics examined in these studies (patients reported to a national register having presented with a neuropsychiatric side effect vs co-opted members of an active deployed military unit engaged in operational setting), where the former by their nature have a predetermined neuropsychiatric issue. However, this does not explain the apparent discrepancy between similar cohorts whose reported incidence of abnormal dreams varies widely (British troops deployed in low impact engagements: 7.7% (Terrell, Forde et al. 2015); 39% (Adshead 2014). These data suggest that use of self-reporting systems to capture incidence symptoms as relatively well-define as vivid dreams or nightmares is still open to significant confounders despite abnormal dreaming being clearly identified as a common side effect of mefloquine use.

What is also noticeable from comparison of published AE data across the trials examined is that, in general, trials that were fully or partly sponsored by commercial entities reported lower rates of AEs across all categories examples, than those that were not. The only noticeable exception to this rule was the 2002-2003 trial undertaken in Japanese soldiers deployed to East Timor. This trial is coincident with those carried out by the AMI (whose rates of AE reporting are already low compared to other trial cohorts) yet AE incidence reported by Fujii and colleagues represents the lowest rates across the majority of categories analysed (Table 1).

(Nasveld, Edstein et al. 2010)). There are two possibilities as to why this might be the case. The first is that troops engaged in this study were asked to self-report AE symptoms on return

from deployment, with all the inherent issues related to that modaility of data collection in military members as previously discussed. It is also possible, however, that reporting rates were even lower than in other military cohorts due to fundamental cultural differences in the reporting of any health issues related to mental health in his population although it is also possible that other pharmacogenetics factors are exerting a protective effect against development of AEs subsequent to mefloquine exposure in this cohort. Therefore the AE data from this study must be considered as an outlier in this analysis.

Section 6.2. Recommendations

- **That all the original ADF AMI antimalarial trial data is reanalysed by an independent third party to determine the actual incidence of reported adverse events in these studies and that this data reported in the scientific literature.**

- **That a formal retraction of 'safety' is issued in relation to the published articles to set the historical record straight on the interpretation of the aforementioned trial data.**

Section 7. Gender and frequency of adverse events subsequent to melfoquine exposure

The effect of exposure to mefloquine on women's health is something that has generally been overlooked in discussions surrounding use of mefloquine in the military setting to date, yet monitoring of exposure to quinoline antimalarials is of particularly important for female military personnel. Mefloquine has been reported to be generally contraindicated for use in women as a prophylactic treatment due to a higher incidence of adverse events (Peragallo, Sabatinelli et al. 1999, Schlagenhauf 2003, Adshead 2014, Ringqvist, Bech et al. 2015) and potential teratogenic risks during early pregnancy.

Female military members and civilian patients were specifically excluded from early clinical trials on the grounds of teratogenic risks to the unborn fetus, statements which are evidenced in the methodology presented in a number of clinical trials undertaken (Boudreau, Schuster et al. 1993). Two apparent exceptions to this rule were the aforementioned Army Malarial Institute administered trials, where female veterans were included providing they were identified not to be pregnant at the time of entry and were willing to take contraceptive medications (Kitchener, Nasveld et al. 2005, Nasveld, Edstein et al. 2010). Indeed, one AMI study of safety and efficacy of tafenoquine specifically looked at the difference in gastrointestinal adverse event profile between male and female veterans, identifying that female veterans suffered a higher rate of adverse events than their male counterparts (Edstein, Nasveld et al. 2007). This does not appear to have been reflected in data presented for the same drug in their 2010 report, again suggesting that the rate of adverse events had been downplayed in this study (Nasveld, Edstein et al. 2010).

The ethics of the inclusion of women in these trials is questionable. Although it could be argued that the likelihood of pregnancy occurring in female soldiers during active deployment was low, this still represented a cohort with an increased risk associated with their exposure, and one that had been specifically excluded from previous clinical trials on those grounds. For them not to be excluded from the two AMI trials seems to have placed those individuals under an undue level of risk, however minimal that might have been anticipated to be at the time.

The importance of the inclusion of a female demographic in the AMI trials is now becoming apparent. Significant long-term side effects, including hallucinations and psychosis, have been reported in female civilian travellers exposed to mefloquine for international travel. A study in 2008 reported that female military personnel were found to be twice as likely to have an adverse reaction to the drug than their male counterparts (Nevin, Pietrusiak et al. 2008). Other studies have followed suite with perhaps the most comprehensive case series reported by Ringqvist and colleagues 2015 that female travellers experienced a significantly higher rate of serious adverse events than their male counterparts (Ringqvist, Bech et al. 2015).

That women experience a higher rate of adverse events was also identified in the recent Royal Navy study where 100% of women taking mefloquine reported one or more adverse events (Adshead 2014). That female ADF veterans are now experiencing long-term health issues related to their exposure to mefloquine or other quinoline antimalarials used in these trials is testimony to the disregard showed to these participant cohorts during their recruitment. To date, the evidence that female participants experience higher rates of adverse events, both acutely and long term, subsequent to ingestion of mefloquine and tafenoquine has not been applied to the ADF AMI trial cohorts despite this suggesting that they are

potentially more likely to be experiencing long term health impacts than their male counterparts.

The underlying difference for this sex-related different in adverse event profiles is, as yet, unclear. However, a systematic review of case reports undertaken by Croft and Herxheimer (Croft and Herxheimer 2002) identified thyroid disturbance, either primary or secondary, as a potential contraindication to mefloquine exposure, as well as alcohol, hormonal contraception and medications known to cause liver or thyroid damage (Croft and Herxheimer 2002). Given the relatively high incidence of thyroid disease in women in general, and widespread use of hormonal contraceptives in all female patient populations, (indeed this was a specific inclusion criteria for some AMI trial cohorts) this also suggests that all quinoline antimlarials including mefloquine, tafenoquine and primaquine, should be used with caution in female military personnel.

Section 7.1. Concluding remarks

The severe acute and long-term health implications for use of mefloquine and tafenoquine in female military personnel means a highly detailed pre- and post-deployment screening protocol would be required if mefloquine is to be used in this population, or that quinoline antimalarials should be totally avoided in this veteran cohort.

Section 7.2. Recommendations

- **That a follow-up for female ADF members exposed to quinoline antimalarials in AMI trials is initiated immediately and appropriate compensation offered where long term health impacts are identified; that female ADF members and veterans**

are not exposed to mefloquine or tafenoquine for malarial prophylaxis and that safer alternatives must be preferentially administered for this group.

Section 8. Response to the Inquiry Terms of Reference:

(b) the support available for partners, carers and families of personnel who experience any adverse health effects of Quinoline anti-malarial drugs;

Section 8.1. Mefloquine poisoning – a formal recognition by the ADF but continuing administrative impediments to assessment and treatment.

Despite documentation present in the consent information that any health impacts of involvement in the AMI clinical trials would be resolved fully for the participants, there have been a number of practical impediments that have prevented ADF veterans exposed to Mefloquine and tafenoquine as part of AMI clinical trials gaining ready access medical support for both acute and long term adverse effects caused by these drugs.

There are a number of ways that 'support' can be considered when thinking about both short and long term impacts of quinolone antimalarials on veteran's health. Support might include: moral or emotional support including overt recognition of harm; support in terms of medical or therapeutic interventions, and organizational support to assist those affected in terms of carrying out their day-to-day activities or continuing in their workplace. Support applies both to the veteran themselves and their family, who often bear the brunt of the day to day management of long term or intractable health issues in the service member. In this section I will primarily consider the organizational support offered to mefloquine and tafenoquine veterans in Australia and how acknowledgement of the potential harms caused by these drugs,

and their involvement in AMI clinical trials, has impacted their ability to access medical support for their illness.

In Australia, mefloquine has been used both for malaria prophylaxis for several decades by Australian Defence Force personnel carrying out peacekeeping duties in South East Asian areas of operation. Despite this longevity of use, an association between exposure to mefloquine for malarial prophylaxis and the persistence of symptoms identifying a long-term adverse reaction to mefloquine was not formally recognized by the ADF until 2015, and only after outspoken calls from affected veterans and Ex-Service Organizations for them to do so.

In a statement released in November 2015 the Department of Defence Australia (DoD) acknowledged that '*some people do continue to experience ongoing issues'* after taking mefloquine for malarial prophylaxis (Defence 2015). At that time, this belated acknowledgement was the first, and only acceptance that exposure to mefloquine for military service had long term impacts on the health and wellbeing of ADF veterans. No formal statement was issued with effect that those who had been exposed to mefloquine during AMI clinical trials were entitled to additional recognition, support or compensation for their 'ongoing issues' other than those already available through the Department of Veterans Affairs (DVA) medical support system. The catch-22 of this situation quickly became apparent. A condition that was not recognized by DVA, such as the toxidrome caused by exposure to quinolone antimalarials, could not be claimed as a single entity through DVA compensation processes. To date, the majority of veterans who have experienced ongoing health issues related to their involvement in the AMU trials, and exposure to mefloquine and / or tafenoquine have remained undiagnosed or been diagnosed with 'other' conditions with similar symptomologies. Therefore, although the 2015 DoD statement represented a major

step forward in the recognition of mefloquine toxicity syndrome in Australian military personnel, it did not identify that the collection of symptoms associated with quinolone poisoning was not yet formally recognized as a disease state by the DoD or the ADF, or by the DVA medical support services it engages to provide care for serving personnel or veterans.

Although it might sound trivial, this situation is of key significance to those veterans trying to access treatment for quinolone poisoning through the Department of Veterans Affairs as without an approved claim lodged against an existing SOP, some types of care are currently unavailable to them. Even where an SOP does exist, making a claim is not a trivial process, and in some cases can take years to complete. Currently mefloquine is identified as a causal factor in 15 separate Repatriation Medical Authority (RMA) Statements of Principles (SOPs) including six SOPs that have the broader quinolone family of antimalarials identified such that tafenoquine would be covered by those SOPs. The most recent of these is an SOP for 'toxic retinopathy' approved recently, which further highlights the known causal relationship between 'toxic' exposure to quinolone antimalarials and significant neurological dysfunction.

Although the quantum of SOPs related to quinolone poisoning or toxicity reflects the diversity of symptoms that can be experienced by those individuals who have suffered long term adverse reactions to these drugs, the breadth and number of individual SOPs means that a veteran suffering from multiple symptoms related to quinolone exposure is currently required to make multiple claims for this one condition with all the inherent difficulty associated in doing so. Quinoline poisoning sits in a category similar to Gulf War Syndrome, which has been defined as a 'chronic multisystem illness', which now has a single SOP covering this condition, but yet has no single specific SOP exists for quinoline poisoning, and

indeed some components of the clinical effect – those associated with the neurocognitive effects of quinoline toxicity – are not covered at all by this process.

The need to lodge multiple claims for a single, complex, condition also represents a significant administrative challenge to those suffering long term adverse effects of taking these drugs. That there is no single SOP also is anomalous to the fact that there are detailed descriptions of the syndrome being present in the medical literature (Nevin 2012, Nevin 2015, Nevin 2015). This issue is currently being partially addressed by the Special Medical Council Review of the RMA's decision *not* to approve an SOP for "chemically acquired brain injury caused by Mefloquine, tafenoquine or primaquine" which would have gone some way to addressing this situation. The outcome of this current review is anticipated by the end of 2018.

One of the key issues surrounding the lack of a clear diagnostic entity from a claims perspective is that ADF veterans suffering from both the short term and long term neuropsychiatric effects of mefloquine poisoning have been commonly diagnosed by their symptoms alone as suffering from Post-Traumatic Stress Disorder (PTSD), bipolar disorder, or other neuropsychiatric disorders that present with similar but causally unrelated symptom profiles (Nevin 2015). Veterans suffering both acute and long term effects of quinolone poisoning have also been accused of malingering, or suffering from psychosomatic illness when their symptoms appeared intractable to the usual medications or treatment modalities for PTSD.

Of critical importance, and one of the reasons that the impact of ADF veterans exposures to quinolone antimalarials remained ignored for more than two decades, is that those affected

after exposure to mefloquine and / or tafenqouine during the AMI clinical trials (Kitchener, Nasveld et al. 2005, Nasveld, Edstein et al. 2010) had their drug reactions deemed as lacking in 'severity' and therefore dismissed in terms of their impact on the individual. This is clearly seen by the small number of adverse events reported from these studies, and the lack of formal reporting though regulatory adverse events databases. This gave a lasting impression that their symptoms were not drug-related, or were not significant enough for these veterans to consider them as important in the longer term. This false impression of the importance of the adverse events experienced by veterans at the time of the trials meant that they did not correlate these adverse events with their longer term health impacts. Had they done so, many would have sought medical advice earlier or more clearly articulated to their doctors that the onset of their ill-health correlated with their involvement in the trials thus opening doors to the right diagnostic techniques and treatments. This point is of critical note as some veterans have been retired from service on medical grounds subsequent to mefloquine and tafenoquine poisoning, yet this exposure was never considered as a causal in their illness and as such their medical treatment and compensation do not reflect this, yet their ADF careers ended prematurely because of it. Together, these additional stressors have potentially had a cumulative negative impact on the ongoing health of this veteran cohort.

Section 8.1.1. Concluding remarks

The lack of recognition of a syndrome caused by toxic exposure to quinoline antimalarials is exerts a similar barriers to care as that experienced by Vietnam veterans exposed to Agent Orange (Chang, Benson et al. 2017, Stellman and Stellman 2018) or Iraq veterans suffering from Gulf War Syndrome (Ismail and Lewis 2006). Now, after many decades of campaigning, the long term health impacts of these exposures are now being formally recognized by the RMA and other international military veterans organizations and charities

worldwide, sadly many veterans suffering from these syndromes died before their clinical disease was ever formally recognized by the organisations that caused it or those set up to administer their treatment. This situation is currently being mirrored for those veterans exposed to quinolone antimalarials and is one that needs to be rectified with some urgency. Establishment of an SOP for the systemic, neuropsychiatric and neurological symptoms associated with quinolone poisoning would be a major step in the right direction to address this shortfall.

The issue of difficulty in application of the DVA claims process, and impediments to care was raised by the QVFA in a number of meetings in 2016 with the Minister for Veterans Affairs, Minister Tehan, meetings which included Dr Ian Gardner, the Senior Medical Advisor to DVA. At these meetings Quinoline Veterans and Families Association requested that a Gold Card be issued to all ADF veterans exposed to mefloquine and / or tafenoquine as part of the AMI clinical trials, or during their military service. This request was rejected despite Dr Gardner indicating that this was 'possible' given that this precedent had already been set for those exposed to toxic foams and jet fuels as part of their ADF service. Automatic entitlement of all identified mefloquine and tafenoquine veterans to a DVA Gold card would actively facilitate better medical outcomes for this group and mitigate the long term health impacts impact of their involvement in the ADF AMI clinical trials.

Section 8.1.2. Recommendations:

- **That an SOP be established for chemically acquired brain injury subsequent to quinoline exposure, toxic quinoline encephalopathy, quinolone poisoning or similar, to facilitate claims and compensation for veterans and their families exposed to these drugs during ADF clinical trials or general military service.**

- **That all ADF veterans exposed to the quinolone antimalarials mefloquine and tafenoquine during their ADF service, or as part of ADF AMI clinical trials and regardless of operational status of exposure, be awarded a DVA Gold Card in recognition of their service to this country and potential impact on their health.**

Section 8.2. Moral injury, dual loyalty and mefloquine exposure in military members

The lack of recognition of the long term health impacts suffered by personnel involved in ADF drug trials represent a both moral injury (Edstein, Walsh et al. 2001, Kitchener, Nasveld et al. 2005, Charles, Blomgren et al. 2006, Charles, Blomgren et al. 2007, Nasveld, Edstein et al. 2010) and presents a conflict of interest, or 'dual loyalty' between researchers and their trial subjects. Dual loyalty in this context is defined as *'a role conflict between the clinical professional duties to a patient and obligations, express or implied, real or perceived, to the interests of a third party such as an employer, an insurer, the State, or military command'* (London, Rubenstein et al. 2006). These soldiers were harmed by the organization that was there to protect them whilst they protected their country by their involvement in clinical trials involving unregistered drugs or registered drugs already known to have a poor safety profile.Current controversy surrounds the informed consent process in the AMI studies as significant numbers of those involved in the trials state they received little information about the potential side effects of the drug they were given. Information available to the Quinoline Veterans and Families Association through Freedom of Information (FOI) requests, and through personal testimonies, indicated that the standards applied to engaging with participants to fully inform them of the risks associated with these drugs was low. A recent Freedom of Information (FoI) release has indicated that there were concerns raised at the time of these trials around the ethical conduct of these trials at the time, and particularly around the issue of the known adverse event profile of mefloquine and the process of informed

consent. The Australian Defence (Force) Human Research Ethics Committee (ADHREC) approved Protocol 249/01 '*Evaluation of mefloquine for malarial prophylaxis in non-immune soldiers'* in their meeting of 26 February 2001. Minutes of the ADHREC indicated issues with the protocol were noted by the Committee, specifically that *'mefloquine had potentially serious side effects of which ADMEC had been previously unaware'. CNS side effects, particularly of depression and psychosis caused considerable concern to the Committee, especially were they to occur in deployed troops.'* (RightToKnow 2016). These statements suggest that the potential impact on troops was clearly known by both the research team and institutional ethics committee at the time, yet no mitigation was put in place to limit the impact of their exposure on those troops involved.

That concerns were raised regarding the lack of information presented to the institutional ethics committee regarding the side effect profile of mefloquine at the time of the trials, again, suggests that the full spectrum of potential neuropsychiatric adverse events was not have openly relayed to those subjects in the trial either. These findings present a worrying pretext to those now suffering long-term adverse effects. Specifically, the influence of dual loyalty on those medical officers involved in the design and delivery of the trials (London 2005, London, Rubenstein et al. 2006), which were in part funded by the pharmaceutical company GlaxoSmithKline Research and Development Ltd and the United Stated Army Medical Material Development Activity (USAMMDA). The desire to generate data with a positive outcome for the funding agencies may have exerted undue influence on both the reporting outcomes of adverse events within the trial cohorts as well as impacting the desire to minimize voluntary withdrawals. It is therefore possible that that the maximum number of soldiers were recruited into the trials irrespective of the viability of conducting a clinical trial during an active war-like deployment; that the number of withdrawals from treatment was

minimized, and that adverse event reporting was misrepresented to improve the perceived benefits to the parent organization and funding agencies. The implicit pressures on the AMI staff carrying out the trial to deliver positive outcomes for these agencies likely biased results an resulted in drug continuation for some participants where withdrawal from treatment was indicated.

Section 8.2.1. Concluding remarks

The conflict of interest for those medical officers involved in administering the AMI ADF trials is highly likely to have influenced the reporting of adverse events both through formal channels such as the Australian therapeutic Goods Adverse Events Database, and in the trial records themselves as discussed previously in this submission. Dual loyalty by ADF medical staff also potentially influences the availability of veteran's trial medical records, an issue that has meant that veterans have been unable to easily prove which drugs / vaccines or other developmental medical products they have been exposed do during their military service. This has precluded them receiving proper recognition of their medical conditions related to the trial drugs, and has potentially cost lives through poor diagnoses and treatment choices by medical professionals unable to avail themselves of their patient's full medical history. This has added a layer of additional injury over their use as clinical subjects, who were subject to poor consent information and some levels of coercion around their involvement.

Section 8.2.2. Recommendations:

- **That ADF veterans are precluded by law from being engaged as subjects in clinical trials;**
- **That all AMI and other clinical trial records are immediately incorporated into each veteran's main medical record and those additional documents made available to veterans immediately;**
- **That the Government and ADF formally recognize the role played by ADF veterans in advancing our understanding of both the science and treatment of tropical diseases, including malarial, by their role in ADF-sponsored clinical trials, and that this is clearly acknowledged as a significant service to the organization and the wider medical community.**
- **That a Royal Commission be established into the use of ADF members in clinical trials, institutional links with the pharmaceutical sector, and treatment of clinical trials veterans both during their service and post-exit.**

Section 8.3. Accurate diagnosis of clinical effects and impacts on post marketing surveillance of quinoline antimalarials in the ADF.

The accurate diagnosis of mefloquine poisoning is critical to prevent a confounding diagnosis of Post-Traumatic Stress Disorder (PTSD) (Nevin 2015), or other neuropsychiatric illness (Ritchie, Block et al. 2013) in military personnel. Although these conditions are not mutually exclusive, chronic mefloquine poisoning can have significant implications for the treatment of symptoms common to both disorders. Eick-Cost et. al., (2017) that examined health outcomes for US service members that had been given mefloquine, doxycycline or atovaquone / proguanil for military operations using a longitudinal retrospective data analysis

comparing pharmacy transaction data and military medical surveillance data registered between 2008 and 2018 (Eick-Cost, Hu et al. 2017). Results of this analysis, which included the medical records from 36,538 individuals that had been given mefloquine, 318,421 that had been given doxycycline, and 12,881 that had been given atovaquone / proguanil, that the incidence of anxiety was increased in those soldiers given mefloquine compared to the other groups. Perhaps most interestingly, it also showed that the incidence of PTSD was higher in non-deployed individuals that had been given mefloquine compared to deployed soldiers. This suggests that mefloquine is inducing neuropsychiatric symptoms which are being manifesting as a 'PTSD-like' syndrome in this group, despite the fact that they have not seen active service and therefore encountered the necessary traumatic incident that is required for this as a primary diagnoses. Although potentially confounded by a misdiagnosis of PTSD in some cases, this study clearly identifies an increased risk of neuropsychiatric disorder in this group of veterans and the importance of both lodgement of drug exposure in the veteran's medical record, and appropriate reporting of adverse drug reactions by military organisations.

Another potential confounder is that the permanent chemical or structural changes in the central nervous system resulting from exposure to mefloquine (Quinn 2015) can be coincident with those caused by mild Traumatic Brain Injury, (mTBI), long-term exposure to psychotropic drugs, or complex PTSD. The difference in underlying aetiology can have major impacts on the efficacy of standard treatments. This assessment / treatment conflict has likely resulted in some veterans with long terms neuropsychiatric changes related to mefloquine exposure being labelled as 'treatment-resistant' when undertaking PTSD rehabilitation programs.

In support of this statement, a document discussing the special medical considerations required when treating (US) military personnel for malarial prophylaxis on deployment, the Centre for Disease Control and Prevention in the USA (CDC USA) noted that exposure to mefloquine may confound the diagnosis and management of PTSD (McGill 2016, Nevin 2017, Nevin 2017). Symptoms resulting from subtle neurosensory damage, including vertigo, balance disorders and visual disturbance including photophobia, in the absence of a severe initiating traumatic incident (such as would be the case for mTBI), can aid in distinguishing between the two syndromes, providing evidence of exposure is also present (Nevin 2015). Careful diagnosis will also indicate efficacious treatment modalities for mefloquine toxicity sufferers in the future and avoid unnecessary spending on interventions that are likely to be unsuccessful.

With a heavy reliance on self-reporting, which has questionable validity in a military setting (Nevin 2009, Nevin 2017), and where limited post deployment psychological monitoring is in place, there is significant scope for those suffering from adverse effects of exposure to mefloquine to remain unidentified in the system. As the symptoms of mefloquine toxicity can both abate, but also increase in intensity over time (Gogtay and Ferner 2015), it also cannot be assumed that post-operational psychological screening at 6 months is sufficient to identify all of those affected. A longer-term monitoring approach is needed with specific questions being included in yearly psychological health assessment protocols in order to identify those for which exposure to quinoline anti-malarial medication might be causal in their symptomology.

Failure of correct diagnosis of mefloquine poisoning can have serious consequences (Maxwell, Nevin et al. 2015). The efficacy of commonly used neuropsychiatric drugs for

treatment of affected personnel is unclear, and currently no studies been undertaken to identify best possible therapeutics for treatment of either the acute or chronic neurological or psychiatric symptoms. This presents the possibility that treatment of individuals affected by exposure to mefloquine with a complex of psychiatric medications could result in an exacerbation of symptoms rather than alleviation. This is anecdotally the experience of veterans exposed to mefloquine in military organisations worldwide where polypharmacy for acute psychosis resulting from exposure to chloroquine (a closely related compound) has been shown to cause a significant exacerbation of symptoms (Maxwell, Nevin et al. 2015). Polypharmacy is common in those with long-term neuropsychiatric disturbances resulting from mefloquine exposure and should also be avoided until better understanding of effective pharmacological interventions are known.

Section 8.4. Identification of the need for as personalised medical approach for safe prescribing of quinoline antimalarials drugs in the ADF

One predictor of potential adverse reactivity to medications is pharmacogenetic profiling. The enzyme Cytochrome P450 is a determinant of both drug efficacy of metabolism in humans and other species, and the pharmacogenetics profile required for normal metabolism of mefloquine and tafenoquine are known.

Tafenoquine requires normal CYP2D6 status for metabolism to its active (plasmodium-toxic) form (Marcsisin, Sousa et al. 2014, Vuong, Xie et al. 2015), and mefloquine is metabolised for detoxification and excretion by CYP2D6, CYP3A 4 & 5 (Fontaine, de Sousa et al. 2000, Ridtitid, Wongnawa et al. 2000, Ridtitid, Wongnawa et al. 2005, Hodel, Csajka et al. 2013, Staehli Hodel, Csajka et al. 2013). A role for CYP2C19 is suggested for the metabolism of both drugs.

The risks associated with unknown CYP allelotype status are well recognised by the general medical community, including those dealing with neuropsychiatric agents. Altered genetic profiles of certain CYP alleles have been linked to risk of suicide and exacerbation of clinical symptoms in patients receiving neuropsychiatric medications (Zackrisson, Lindblom et al. 2010, Lucire and Crotty 2011), and in treatment failure of antimalarial mediations. For this reason, statements related to CYP-drug interactions, and drug-drug combinations to avoid are commonly inserted in both practitioner and patient drug safety information. Indeed, knowledge of CYP processing is formally required for drug registration by all global regulatory bodies including the Federal Drug Administration in the USA and Therapeutic Goods administration in Australia.

In the ADF veteran cohort exposed to mefloquine and tafenoquine as part of the AMI clinical trials, and experiencing long term adverse health effects, 92% of individuals volunteering pharmacogenetics information we identified as being of poor or intermediate metaboliser status at the CYP2D6 and or 3A45 locus (Table 3).

The data above highlights the need for pharmacogenetics profiling for ADF veterans that have been, or are to be exposed to quinoline antimalarials. A number of those individuals exposed to both drugs were given mefloquine, after tafenoquine use in the ADF trials, as they had been identified to be treatment failures. Conversely, some were given tafenoquine in trials investigating tafenoquine for radical cure of Plasmodium vivax malaria as they had not been adequately protected by primaquine, the ADF standard eradication protocol, likely due to their CYP2D6 poor metaboliser status. This finding also highlights the need to CYP

screening to be undertaken in all current ADF members to ensure efficacy of current standard vivax eradication protocols.

Table 3. Pharmacogenomic status of ADF veterans exposed to mefloquine and tafenoquine that have experienced acute and / or long term health effects subsequent to exposure. Drug exposures are not necessarily presented in chronological order.

Exposure		CYP function			
Drug 1	**Drug 2**	**2D6**	**2D6**	**3A5**	**3A5**
Mefloquine		*5	*9	NT	NT
	Tafenoquine	*2	*41	NT	NT
Mefloquine	Tafenoquine	*1	*4	*3	*3
Mefloquine		*9	*41	NT	NT
Mefloquine		*10	*35	*3	*3
Mefloquine		*4	*41	NT	NT
Mefloquine		*4	*41	NT	NT
Mefloquine	Tafenoquine	*4	*9	NT	NT
Mefloquine		*1	*2	NT	NT
Mefloquine	Tafenoquine	*4	*41	NT	NT
	Tafenoquine	*4	*41	*3	*3
	Tafenoquine	*4	*6	*3	*3

Normal (extensive) function
Reduced function
Non-functional

Section 8.4.1. Concluding remarks

Correct diagnosis of mefloquine poisoning in military members, particularly in those cases where neurological symptoms are present and mefloquine exposure can be confirmed, is critical to determine appropriate and effective treatment (Quinn 2016). Certain symptoms associated with mefloquine toxicity are not usually present in other 'common' psychological or neurological syndromes experienced by military personnel allowing this differential diagnoses to be made. Given the issues with adverse event reporting, and the potentially confounding diagnosis of PTSD, identification and review

of all military personnel exposed to mefloquine during their active service should be undertaken with some urgency.

It is critical that the toxidrome caused by mefloquine poisoning is clearly recognised by military medical professionals and that CYP450npharmacogenomic profiling should be routinely undertaken on entry for all ADF members. Their CYP profile should then be taken into account when prescribing antimlarials for military operations and when considering diagnosis and treatment options for veterans affected by quinoline antimalarial medications. Appropriate treatment and rehabilitation programs are now urgently required to support the affected veteran cohort.

Section 8.4.2. Recommendations

- **That CYP450 pharmacogenomic profiling be implemented immediately for current ADF members, and all veterans involved in the AMI mefloquine and tafenoquine trials to determine their risk of adverse events related to these and other pharmacological agents.**
- **That a policy of immediate and complete adverse event reporting to the Therapeutic Goods Administration database is applied to all ADF medical practitioners, to ensure that AE reporting is both comprehensive and independently registered.**
- **That longitudinal data analyses be carried out to determine the risk of long term health impacts from exposure to quinoline antimalarials in ADF veterans, including potential secondary impacts on their children.**
- **That a working group be established encompassing veterans advocates experienced in the effects of quinoline toxicity with appropriate, independent advisers sourced from the military mental health community, family services,**

occupational health practitioners, brain injury rehabilitation specialists, neurologists, psychologists, cognitive and behavioural experts and psychiatrists, to establish a recommended assessment and treatment program for those affected by mefloquine and tafenoquine during their military service.

- **That this advisory panel be appropriately resourced to deliver a national outreach and rehabilitation program for quinoline veterans and families in Australia.**
- **That a program of research is funded to better understand and identify veterans experiencing long term health issues related to quinoline exposure during their ADF service.**

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ANNEXE A

Therapeutic Goods Administration Database of Adverse Events Notifications for mefloquine and tafenoquine between 1998 and 2004

Document 1

Case Line Listing

Cases Count: 32

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
163217	29/03/2001	[redacted]		M	25	[redacted]	Chloroquine -Suspected	[redacted]	Infection parasitic
							Tafenoquine CT -Suspected		
							Chloroquine -Other drug		
							Doxycycline Hyclate -Other drug		
							Primaquine Phosphate -Other drug		
							Quinine -Other drug		
163375	05/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
163376	05/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
164025	30/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
164026	30/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
164339	07/05/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
377817	22/03/2016			F	??	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected		Completed suicide
							Tafenoquine CT -Suspected		
392376	27/07/2016	[redacted]		M	28	[redacted]	Tafenoquine CT -Suspected	[redacted]	Depression
									Pain
									Post-traumatic stress disc
393834	23/08/2016			M	99	[redacted]	Mefloquine Hydrochloride -Suspected		Completed suicide
							Tafenoquine CT -Suspected		
396130	29/09/2016	[redacted]		M	??	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected		Brain injury
							Tafenoquine CT -Suspected		Toxicity to various agents
403837	18/02/2017	[redacted]		M	30	[redacted]	Tafenoquine CT -Suspected	[redacted]	Amnesia
									Depression
									Anxiety

Case Line Listing

Cases Count: 240

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
134254	14/12/1998	[redacted]			??	[redacted]	Mefloquine Hydrochloride -Suspected	[redacted]	Nausea Abdominal pain Hepatic function abnorma
136326	18/02/1999				??		Mefloquine Hydrochloride -Suspected		Rash maculo-papular
137945	30/03/1999				??		Lariam (Mefloquine Hydrochloride) -Suspected		Malaise Asthenia Depression Chest pain Tremor Suicide attempt Insomnia Nausea Dyspnoea Agitation Crying
139728	21/05/1999				27		Lariam (Mefloquine Hydrochloride) -Suspected		Depression Anxiety Palpitations
144297	01/10/1999				??		Lariam (Mefloquine Hydrochloride) -Suspected		Anxiety Aggression Depression Headache Abdominal pain Thinking abnormal
144740	18/10/1999				27		Mefloquine Hydrochloride -Suspected		Skin ulcer Rash maculo-papular

Case Line Listing

Cases Count: 240

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
145869	16/11/1999	[redacted]			27	[redacted]	ADT Booster (Diphtheria And Tetanus Vaccine NOS) -Suspected Lariam (Mefloquine Hydrochloride) -Suspected M-M-R II (Measles, Mumps, Rubella Vaccine) -Suspected Sabin Vaccine (Poliomyelitis Virus Vaccine Oral) -Suspected Stamaril (Yellow Fever Vaccine) -Suspected Typhim VI (Typhoid Vaccine) -Suspected	[redacted]	Headache Nausea Dizziness Abdominal pain Hyperhidrosis Pyrexia Syncope Testicular disorder
147627	04/01/2000				37		Lariam (Mefloquine Hydrochloride) -Suspected		Delirium Psychotic disorder Delusion Paranoia Pyrexia Rash maculo-papular Neurosis Confusional state
148799	10/02/2000				50		Lariam (Mefloquine Hydrochloride) -Suspected		Pain Nausea Pyrexia
149626	25/02/2000				40		Lariam (Mefloquine Hydrochloride) -Suspected		Chills Pyrexia
149742	29/02/2000				53		Lariam (Mefloquine Hydrochloride) -Suspected		Depression Mania Psychotic disorder Schizophreniform disorde Delusion Nightmare Hallucination

Case Line Listing

Cases Count: 240

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
150241	10/03/2000	[redacted]			46	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected	[redacted]	Asthenia Delirium Tremor Pyrexia
150242	10/03/2000				24		Lariam (Mefloquine Hydrochloride) -Suspected		Anxiety Insomnia Paranoia Agitation
154010	22/06/2000				55		Lariam (Mefloquine Hydrochloride) -Suspected		Depression Headache Nausea Urinary incontinence Nightmare Hypertension Diarrhoea
154180	26/06/2000				29		Lariam (Mefloquine Hydrochloride) -Suspected		Anxiety Depression
154477	06/07/2000				27		Lariam (Mefloquine Hydrochloride) -Suspected		Nausea Vomiting Hepatic function abnorma
154564	06/07/2000				5		Lariam (Mefloquine Hydrochloride) -Suspected		Headache
155330	12/07/2000				24		Lariam (Mefloquine Hydrochloride) -Suspected		Withdrawal syndrome Headache

Case Line Listing

Cases Count: 240

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
157185	31/08/2000	[redacted]			46	[redacted]	Fansidar (Pyrimethamine; Sulfadoxine) -Suspected Lariam (Mefloquine Hydrochloride) -Suspected Primaquine Phosphate -Suspected	[redacted]	Asthenia Headache Hypokinesia Visual impairment Encephalopathy Confusional state Photophobia Hyperaesthesia Seizure
157186	31/08/2000				31		Aspalgin (Aspirin; Codeine) -Suspected Lariam (Mefloquine Hydrochloride) -Suspected		Erythema multiforme Arthralgia Oedema peripheral
159141	08/11/2000				50		Lariam (Mefloquine Hydrochloride) -Suspected		Depression Nausea Myopathy Affect lability Diarrhoea
159554	27/11/2000				40		Lariam (Mefloquine Hydrochloride) -Suspected		Vomiting Salivary hypersecretion
160395	04/01/2001				32		Lariam (Mefloquine Hydrochloride) -Suspected		Anxiety
163176	30/03/2001				22		Lariam (Mefloquine Hydrochloride) -Suspected		Urticaria Tremor Depersonalisation/dereali disorder Dysphonia
164195	03/05/2001				??		Lariam (Mefloquine Hydrochloride) -Suspected		Seizure

Case Line Listing

Cases Count: 240

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
164196	03/05/2001	[redacted]			??	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected	[redacted]	Depression Suicide attempt Sleep disorder Agitation Abnormal dreams Nightmare Seizure
167930	27/08/2001				26		Lariam (Mefloquine Hydrochloride) -Suspected		Nightmare
167931	27/08/2001				26		Lariam (Mefloquine Hydrochloride) -Suspected		Withdrawal syndrome Depression Headache Skin exfoliation Agitation Tinnitus Palpitations
168290	10/09/2001				31		Lariam (Mefloquine Hydrochloride) -Suspected		Anxiety Back pain Dizziness Myalgia Nightmare Abdominal pain Decreased appetite
176672	26/06/2002				37		Hepatitis A Vaccine -Suspected Mefloquine Hydrochloride -Suspected Sabin Vaccine (Poliomyelitis Virus Vaccine Oral) -Suspected Yellow Fever Vaccine -Suspected		Anxiety Agitation Paranoia Fatigue Hyperhidrosis Palpitations Confusional state

Case Line Listing

Cases Count: 240

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
177412	23/07/2002	[redacted]			43	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected Levothyroxine Sodium -Other drug Zoloft (Sertraline Hydrochloride) -Other drug	[redacted]	Psychotic disorder Agitation Fatigue Confusional state
178500	26/08/2002				36		Lariam (Mefloquine Hydrochloride) -Suspected Havrix 1440 (Hepatitis A Vaccine) -Other drug		Rash Arthralgia Jaundice
180971	23/12/2002				27		Lariam (Mefloquine Hydrochloride) -Suspected		Nausea Insomnia Rash papular Dizziness
186149	22/05/2003				48		Lariam (Mefloquine Hydrochloride) -Suspected		Abdominal distension Paraesthesia Dizziness Flushing
189177	04/08/2003				44		Lariam (Mefloquine Hydrochloride) -Suspected		Ataxia Headache Dizziness Nightmare
189660	19/08/2003				50		Lariam (Mefloquine Hydrochloride) -Suspected		Arrhythmia supraventricul Chest pain Sinus bradycardia
190643	19/09/2003				50		Lariam (Mefloquine Hydrochloride) -Suspected		Bradycardia Extrasystoles
192300	18/11/2003				??		Lariam (Mefloquine Hydrochloride) -Suspected		Rash Nausea Agitation Heart rate decreased Dizziness Emotional disorder

Case Line Listing

Cases Count: 240

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
192301	18/11/2003	[redacted]			??	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected	[redacted]	Rash Nausea Agitation Dizziness Heart rate decreased Emotional disorder Pruritus
193035	10/12/2003				34		Mefloquine Hydrochloride -Suspected		Cognitive disorder Insomnia Visual impairment Feeling of despair Abnormal dreams Feeling abnormal
193091	12/12/2003				??		Lariam (Mefloquine Hydrochloride) -Suspected		Delusion Hallucination
193808	12/01/2004				28		Mefloquine Hydrochloride -Suspected		Illusion Agitation Paranoia
196205	03/04/2004				27		Lariam (Mefloquine Hydrochloride) -Suspected		Vaginal haemorrhage Abortion spontaneous
196357	08/04/2004				32		Mefloquine Hydrochloride -Suspected		Temporal lobe epilepsy Abnormal dreams Seizure
196788	27/04/2004				32		Japanese Encephalitis Vaccine -Suspected Lariam (Mefloquine Hydrochloride) -Suspected Merieux Inactivated Rabies Vaccine (Rabies Vaccine-merieux Hdcv) -Suspected		Urticaria Lip swelling Pruritus