QUINOLINE VETERANS AND FAMILIES ASSOCIATION

SUBMISSION TO THE FOREIGN AFFAIRS, DEFENCE AND TRADE REFERENCES COMMITTEE INQUIRY INTO THE USE OF THE QUINOLINE ANTI-MALARIAL DRUGS MEFLOQUINE AND TAFENOQUINE IN THE AUSTRALIAN DEFENCE FORCE

Introduction

QVFA welcomes the opportunity to address the Committee on the experiences of serving and former Australian Defence Force (ADF) personnel and their families who have been adversely affected by the quinoline antimalarial drugs mefloquine and tafenoquine. This submission focuses primarily on the adverse neuropsychiatric effects of these drugs, resulting from neurotoxic properties evident in the quinoline class since the 1940s. These effects have devastated the lives of many hundreds of ADF personnel, few if any of whom have received appropriate medical care or other support since their exposure to these drugs.

Mefloquine

Mefloquine is a quinoline antimalarial drug developed by the U.S. Army's Walter Reed Army Institute for Research (WRAIR) which has been widely used since registration in the early 1990s. This drug was initially used as the ADF's second line antimalarial, then from 2006 as the third line "drug of last resort" given the risk of neuropsychiatric side effects. The majority of ADF personnel (1,319) given mefloquine during their service were subjects in a series of Army Malaria Institute (AMI) clinical trials in East Timor in the early 2000s (Attachments 1 and 2).[1] Defence records indicate an additional 660 personnel were given the drug since 2001. Although no official data of ADF mefloquine prescriptions prior to 2001 is available, Defence malaria policy states that 5-10% of ADF personnel are intolerant of the first line antimalarial doxycycline.[2]

Defence has falsely claimed that mefloquine has only ever been used by the ADF as a second or third line alternative to safer medications such as doxycycline or malarone, and that all personnel issued mefloquine were prescribed this drug only after consultation with a doctor. There are many cases of personnel who were given mefloquine without previously having used doxycycline and many cases where mefloquine was issued by medics or other unqualified individuals without consultation with a doctor. This was particularly the case during the period of the quinoline clinical trials in East Timor from 1999 to 2002, when mefloquine was widely distributed simply because it was readily available, in contravention of ADF policy, Therapeutic Goods Administration (TGA) regulations and manufacturers warnings.

The dosing regimen for mefloquine prophylaxis approved by the TGA is one 250 mg tablet per week. During the Army Malaria Institute (AMI) clinical trials and elsewhere, the ADF has administered “loading doses” of 750 mg per week. There are also documented cases of AMI mefloquine trial subjects being given loading doses of up to 1,500 mg per week, i.e. six times the dose approved by the TGA.

The first case report of encephalopathy (brain disorder) attributed to mefloquine was published in the late 1980s, soon after the drug was first registered in Europe and there is now three decades of published research on the drug’s toxic effects (Attachment 3). Mefloquine is now known to be neurotoxic in some individuals, able to cause lasting or permanent brain damage,[3-5] with chronic symptoms typically misdiagnosed as PTSD or other psychiatric disorders.[6]

Tafenoquine

Tafenoquine is another quinoline antimalarial drug developed by WRAIR as part of the same drug discovery program as mefloquine. Tafenoquine is an 8-aminoquinoline, a particular class of drug well known for its neurotoxic properties since the late 1940s.[4] During WWII and the years that followed, having accepted the clinical evidence of neurotoxicity in several of the 8-aminoquinolines which had been widely used by allied troops, the U.S. government conducted a dedicated neurotoxicity screening program using primate models, in order to find a safe alternative treatment and prevention drug for P. vivax malaria (Attachment 4).[7] This program found extensive, direct physical evidence of permanent brain damage in primates administered 8-aminoquinolines, in parts of the brain linked to the chronic neuropsychiatric symptoms also exhibited by humans who are adversely affected by these drugs.[4] This screening program led to the eventual adoption of primaquine as the standard P. vivax antimalarial drug, which it remains to this day.

Due to its short elimination half-life, primaquine is used at relatively low doses of 15-30 mg per day for 14 consecutive days when used for post exposure prophylaxis (PEP) to "eradicate" the dormant liver stage of the P. vivax parasite.

Prior to the AMI clinical trials of tafenoquine in Bougainville and East Timor, tafenoquine did not undergo screening for neurotoxicity in primate models. Defence has since confirmed that it has never undertaken tafenoquine neurotoxicity testing in primates as a matter of policy.[8]

In 1998, an AMI clinical trial in Bougainville found that malarone (from another drug class) was as effective against malaria (less P. vivax eradication) and better tolerated than the existing ADF first line drug doxycycline. AMI recommended against the adoption of malarone due to cost, less than the cost of a cup of coffee per day.[9] Regardless, malarone replaced mefloquine as the ADF's second line antimalarial in 2006, when the latter drug was relegated to "drug of last resort" due to the risk of neuropsychiatric side effects.[2] Malarone is now regarded as so safe that it is sold over the counter (without prescription) in many countries.

Throughout the history of the use of primaquine, a significant proportion of individuals have contracted P. vivax malaria despite compliance with the recommended dose regimen. Drug failures have typically been attributed to poor compliance or assumed drug resistance in the malaria parasite. However there has never been any direct scientific evidence of P. vivax resistance to primaquine. This has only ever been an assumption. By late 1998 the ADF had two safe and effective drugs available for malaria prevention, and a PEP drug which had been the standard P. vivax prevention drug for 50 years.

Commencing in Bougainville in late 1998, AMI embarked on a series of tafenoquine clinical trials which then continued in East Timor until mid-2001, involving a total of more than 1,500 tafenoquine subjects (Attachment 1). The first of these trials was a PEP study which administered subjects in Bougainville then East Timor with up to 1,200 mg of tafenoquine over three days. The next study (Study 033) involving 1 RAR in East Timor, compared tafenoquine with mefloquine for weekly 200 mg prophylaxis, commencing with a 600 mg "loading dose". A third tafenoquine study administered the drug to a small number of individuals with relapsing P. vivax malaria, initially at 200 mg per day for three days then 200 mg weekly.

Since the conclusion of the AMI tafenoquine studies, there have been no follow up health studies on the original 1,540 tafenoquine study subjects to determine the chronic adverse health effects of this drug. In 2009, laboratory studies by WRAIR scientists found that tafenoquine is "the only antimalarial drug more neurotoxic than mefloquine".[10] Despite clear evidence of widespread, chronic neuropsychiatric illness among the ADF tafenoquine clinical trial subjects, and despite repeated requests, no longitudinal follow up studies have been undertaken.

Breaches of Human Research Ethics During and Following the AMI Clinical Trials

The current international standard for good clinical practice in clinical trials was mandated by the National Health and Medical Research Council (NHMRC) in 2000. Several specific aspects of that standard are relevant to the misconduct of the AMI clinical trials and the mistreatment of the trial subjects during and following the trials. Firstly, the standard describes "members of the armed forces" as vulnerable subjects "whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate." Secondly, "foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society." Thirdly, the standard states that "the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society." Fourthly, "during and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including those related to the trial." Finally, in obtaining the informed consent of trial subjects, the institution should adhere to "the ethical principles that have their origin in the Declaration of Helsinki".[11] Clear, systematic breaches of these ethical standards experienced by ADF quinoline veterans include:

- Not being fully informed of the serious safety risks posed by both drugs, particularly the risk of lasting or permanent brain damage evident in published papers many years prior to the conduct of the trials.
- Being denied access to the manufacturer's safety warnings for mefloquine.
- Not being informed that tafenoquine was not subjected to neurotoxicity testing on primates prior to the clinical trials.
- Being misinformed about the risks and benefits posed by both drugs compared to safer, effective alternatives already in use by the ADF.
- Being administered prescription and experimental drugs without prior health screening by medical doctors.
- Coercion to participate in the clinical trials, for example threats of being excluded from operational deployments if individuals did not "volunteer" to participate.
- Requests to be withdrawn from the study drug were denied even when serious adverse reactions were reported by study subjects.
- Absence of appropriate follow up screening and health care for study subjects who experienced adverse reactions clearly attributable to the drugs administered during the clinical trials.

Quinoline Drug Metabolism

One of the key barriers to understanding the safety risks posed by the quinoline antimalarials is that only a minority of individuals are adversely affected by the neurotoxic effects of these drugs. There is now clear medical-scientific evidence from published research on the drug metabolism which provides insights into which individuals are affected and why. This evidence needs to be acted upon to meet the medical needs of those who have been adversely affected and to prevent dangerous exposure to susceptible individuals in future.

In 2006 the U.S. Army solicited private industry proposals "to define the biological mechanisms of mefloquine neurotoxicity, identify genetic and other predispositions to mefloquine neurotoxicity, and identify whether mefloquine neurotoxicity may extend to other antimalarials as a class effect", stating:

> *Unfortunately, as many as 25% of individuals taking mefloquine at prophylactic doses (250 mg per week) and 70% of those taking it at treatment doses (1250 mg over 24 hours) experience neurological or psychiatric adverse effects. While most of these are minor (dizziness, anxiety, nightmares, reduced sleep), serious adverse effects such as psychosis also occur. The fact that only certain individuals appear to be adversely affected points to a genetic mechanism, possibly a single polynucleotide polymorphism (SNP) that is yet to be identified.*[12]

Unfortunately, this research was either not undertaken or remains unpublished. Regardless, there is now evidence that susceptibility to the neurotoxic effects of mefloquine and other quinolines may be determined by the Cytochrome P450 (CYP450) superfamily of enzymes (Attachment 5).[5] Interindividual variations in CYP450 activity in organs such as the liver and brain are a major focus of research into drug metabolism, given their known role in both drug efficacy and toxic reactions.

Part of the justification for the use of tafenoquine in the East Timor clinical trials including the PEP study (involving 3 RAR and 5/7 RAR) then Study 033 (involving 1 RAR) was the high rate of P. vivax malaria cases among troops returning from East Timor to Australia. At the time, ADF officials incorrectly assumed that this high rate of malaria cases was attributable to poor compliance (individuals not taking the drug) or drug resistance in the malaria parasite (despite no direct scientific evidence of primaquine resistance in the P. vivax parasite).

In 2013-2014, WRAIR found that both primaquine and tafenoquine require activation by one of the CYP450 enzymes - CYP2D6 - in order to be effective against the malaria parasite.[13-15] CYP2D6 metabolises a quarter of all clinically used drugs, with reduced CYP2D6 function (in individuals who are "poor metabolisers" [PMs] or "intermediate metabolisers" [IMs]) being a common cause of drug treatment failures or adverse drug reactions including in the SSRIs (standard treatment drugs for PTSD) and opioid pain medications.

Reduced CYP2D6 function is very common, e.g. PMs and IMs comprise around 12-23% of Caucasian populations. The high prevalence of CYP2D6 deficiency in the ADF population, vice poor compliance or parasite drug resistance (both unproven assumptions), is the most plausible explanation for the high rate of P. vivax cases among troops returning from East Timor in the early 2000s. Tragically, in seeking to replace primaquine with tafenoquine, the ADF gave 1,540 troops another drug from the same class which has the same limited efficacy but is even more neurotoxic than the existing "drug of last resort".[7]

CYP2D6 is also known to be active in the same regions of the brain which are affected by quinoline toxicity, where in "normal" individuals it plays a crucial role in clearing toxins from those parts of the central nervous system. One plausible explanation for the high incidence of chronic neuropsychiatric illness among the ADF tafenoquine veterans is that CYP2D6 individuals are unable to clear tafenoquine from their brain before it builds up to toxic levels, causing a lasting or permanent brain injury. Over the last two years, dozens of the AMI tafenoquine study subjects who have since experienced chronic neuropsychiatric illness have undertaken their own CYP2D6 tests, with every single case so far resulting in the PM or IM phenotype. WRAIR scientists have stated that “there is a need for the discovery and development of new safer antimalarial agents that treat relapsing strains of malaria and do not require CYP 2D6 metabolism for activity.”[15]

The ADF Surgeon General has rejected requests for ADF personnel to be screened for CYP2D6 deficiency prior to being administered tafenoquine in future. This is despite the fact that for the last several decades, all ADF personnel have been screened for G6PD deficiency as a specific safety precaution to prevent serious adverse reactions from primaquine and tafenoquine.[2]

Adverse Health Effects of Mefloquine and Tafenoquine

The adverse health effects of the quinolines are now well established in the medical-scientific literature. At the dosages used by the ADF, these drugs are able to concentrate at toxic levels in brain

regions including the brainstem, vestibular system and limbic system, causing lasting or permanent neuronal injury.[1,3-6] Since their exposure to the quinolines, many affected veterans have experienced chronic neuropsychiatric illnesses consistent with quinoline poisoning.[1] Symptoms of chronic quinoline poisoning experienced by hundreds of the ADF mefloquine and tafenoquine veterans can be broadly categorised as follows:

- **Psychiatric disorders** including depression, anxiety, bipolar disorder and schizophrenia.
- **Cognitive impairments** including memory and concentration difficulties.
- **Hearing problems** including tinnitus, hearing loss and hyperacuity.
- **Vestibular disorders** including dizziness, vertigo and spatial disorientation.
- **Neurological disorders** including neuropathies, seizures, Parkinson's disease and motor neurone disease (MND).

Numerous adverse event reports (AERs) for mefloquine and tafenoquine are now held by the TGA in the Database of Adverse Event Notifications (DAEN). Given that tafenoquine has not been registered in Australia, all of the tafenoquine adverse event reports in DAEN are from the ADF subjects of the AMI clinical trials. Numerous reports include completed suicide, suicide ideation, brain injury and various chronic psychiatric disorders as side effects of these drugs (Attachments 6 and 7). These reports contradict claims by various Commonwealth officials that there is no link between the quinolines and brain injury or chronic neuropsychiatric illness.

Individual ADF Medical Records and AMI Clinical Trial Records

One of the biggest barriers experienced by quinoline veterans in accessing appropriate care is poor ADF health recordkeeping. Mefloquine prescriptions are typically not recorded in individual ADF medical files and prior to 2001 there was no centralised ADF pharmaceutical database. Many individual medical records also include contradictory information, for example primaquine PEP recorded on the records of AMI tafenoquine subjects, contradicting their AMI trial case record which states they were given tafenoquine. There is no documentation in individual medical records to show that personnel were subjects in AMI clinical trials. AMI trial case records are held separately, with a separate system for requesting those records. Quinoline veterans and their families are typically unaware of these separate records or the process of requesting these records from AMI. In many cases, trial subjects who have requested these AMI trial records have found the information to be incomplete or contradictory. Numerous Coronial inquests into suicides by ADF mefloquine and tafenoquine clinical trial subjects have been completed without Coroners being provided with the relevant AMI trial case records for those individuals.

The Need for Dedicated Health Care and Follow-up Research

Quinoline veterans include current and former members of the Royal Australian Navy, Australian Army and Royal Australian Air Force, both men and women. Adversely affected veterans and their families are located in every Australian state and territory, including capital cities, regional towns and remote areas. Although some of these individuals were medically discharged from the ADF, the majority discharged of their own accord or for disciplinary or administrative reasons.

Affected veterans with chronic neuropsychiatric symptoms who seek medical help are almost universally diagnosed with PTSD without ever being referred to acquired brain injury (ABI) health specialists for proper screening, diagnosis or treatment. Many have undergone years of mistreatment with ineffective and dangerous medications including SSRIs, sometimes leading to the use of electro-convulsive therapy for "treatment resistant" PTSD or depression.[16] While QVFA welcomes recent improvements in mental health services available to ADF veterans including the Department of

Veterans Affairs (DVA) Non-Liability Healthcare (NLHC) program, the exclusion of ABI rehabilitation from this program has exacerbated the difficulties experienced by many veterans in accessing safe effective healthcare.

One of the biggest barriers to accessing appropriate healthcare and support services is the denials and misinformation from Defence and other Commonwealth officials on the serious health risks associated with the quinolines. Partly due to this misinformation and largely due to ignorance, quinoline veterans who raise concerns with their health practitioners about the possible link between these drugs and chronic neuropsychiatric illness are typically ignored. Some have been falsely informed they were abused as children.[17] At any given point in time, there are numerous serving or ex serving ADF quinoline veterans suffering from serious illnesses consistent with ABI who are not receiving appropriate health care, while admitted to ADF or DVA funded health facilities.[16] Last year alone there were at least eight ex serving and two serving ADF members who suicided without ever having been referred to ABI specialists for proper diagnosis or care.

The absence of appropriate, dedicated health care for quinoline veterans has also had a devastating flow on social effect. Family breakdowns have been common[18] and there have been many cases of unemployment, homelessness and incarceration. Rejection of DVA medical and disability claims has placed many affected veterans and their families under severe financial distress, relying on their own savings or charities to pay for tens of thousands of dollars in medical expenses to treat injuries that were attributable to their ADF service. There is a widespread sense of absolute betrayal particularly among tafenoquine veterans given that the pharmaceutical industry is now in a position to profit hundreds of millions of dollars from a drug which is clearly dangerous.

During the last several years, QVFA has repeatedly requested the Department of Defence, the Department of Veterans Affairs and and ex-service organisations to implement a dedicated outreach, rehabilitation and research program for adversely affected veterans and their families. Commonwealth officials who have refused to provide this support include the Chief of the Defence Force General Campbell, Surgeon General of the Australian Defence Force Air Vice Marshal Tracy Smart, DVA Secretary Liz Cosson, Minister for Defence Senator Marise Payne and Minister for Veterans Affairs Dan Tehan.

On 13 December 2016 QVFA wrote to Minister Tehan to propose a pilot outreach, rehabilitation and research program for quinoline veterans and families (Attachment 8). The proposed program would consist of, but not be limited to:

- Identification of all personnel administered mefloquine or tafenoquine during their ADF service, including serving permanent and reserve members, and ex serving personnel, with contact made to determine whether health information is required or desired.

- Assisting affected individuals to access relevant health records, including ADF medical files and Army Malaria Institute case records for those individuals who were exposed to quinoline drugs as clinical trial subjects.

- Education programs and information support to raise awareness of the adverse health impacts of exposure to these drugs.

- Design and implementation of training for health staff who will be engaging with those affected and their families.

- Evidence-based, scientifically designed programs of diagnosis and treatment; Programs of physical and mental rehabilitation for those affected.

- Social support for veterans and their families.

- Research into the long-term health effects of exposure to these drugs with a specific emphasis on comorbid effects of military service.

The implementing body for this program would be independent of the ADF and DVA, but with the relevant powers to direct those organisations to achieve appropriate outcomes for those affected. The implementing body would work with other organisations in each state that would be able to provide specialist care and rehabilitation for those suffering from disorders related to quinoline exposure, such as acquired brain injury (ABI), vestibular disorders, cognitive impairment, neurosensory hearing loss, sleep disorders, psychotic episodes and other health issues coincident with quinoline exposure.

The Minister for Veterans Affairs declined this proposal in January 2017, stating publicly that "The existing services and additional support the Government has implemented are meeting the needs of the ex-service community concerned." When QVFA requested DVA documents providing an explanation as to why this proposal was rejected, DVA responded with a briefing which was entirely redacted (Attachment 9). The four completely black pages of this document contradict reassurances by various senior officials and Ministers from the Departments of Defence and Veterans Affairs that the concerns of affected veterans are being handled with "full transparency".

Both Defence and DVA claim that existing support services are adequate to meet the needs of quinoline veterans and their families. This is clearly false given so few have been able to access ABI rehabilitation and the high prevalence of suicide among personnel who were administered mefloquine and/or tafenoquine during their service. Defence and DVA have also falsely claimed to have conducted health "outreach" programs for those effected. Health outreach is defined as "the provision of *clinical services* in an outreach setting", whereas the "outreach" activities conducted by these departments have not involved any clinical services whatsoever.

Inspector General of the Australian Defence Force

In 2015-2016 the Inspector General of the ADF (IGADF) conducted an inquiry into issues concerning the 2000-2002 AMI mefloquine clinical trials in East Timor. The IGADF inquiry report has been cited by Defence, DVA and other Commonwealth officials in their claims that the AMI mefloquine and tafenoquine trials were conducted ethically and lawfully. However the IGADF is only authorised to investigate breaches of "military justice" and by its own admission did not consult with the appropriate, independent experts or agencies necessary to reach such a conclusion such as the TGA or the NHMRC. Paragraph 15 of the inquiry report states:

> *The Directions required consultation with relevant subject matter experts as necessary. Expert evidence was received during the Inquiry from officers involved in the conduct of the anti-malarial dmg trials and from JHC. However, the Inquiry did not find the need to obtain expert advice from outside Defence on any of the issues being examined, including those that were the subject of complaint, as these issues generally required an assessment of evidence that did not call for expert opinion. The Inquiry did not examine the side effects that may have been caused by the use of the anti-malarial drugs, in particular mefloquine, which would have required independent expert opinion.*[19]

Perversely, the IGADF inquiry relied upon senior ADF officers who were directly involved in the AMI clinical trials, including Brigadier Leonard Brennan and Colonel Peter Nasveld, as so-called "independent experts" to clear themselves of any wrongdoing. The inquiry report further states that only six witnesses from 1 RAR were interviewed, despite the fact that at least 35 witnesses from that unit indicated they were willing to be interviewed by the inquiry officer. The inquiry officer was also informed that criminal offences had been committed under the *Therapeutic Goods Act 1989* but did not investigate those offences. The perverse findings of this inquiry suggest that the IGADF itself needs to be subjected to a judicial inquiry.

Department of Veterans Affairs and the Repatriation Medical Authority

Both serving and ex serving ADF personnel request medical care for chronic health conditions attributable to their use of mefloquine or tafenoquine are advised to submit claims to DVA, as a matter of policy. Broadly speaking, the DVA claims process consists of two steps. The first step is to demonstrate "liability" for the service related condition to establish an entitlement to medical care, then the second step is to demonstrate a level of "disability" arising from that condition to establish an entitlement to financial and other support. DVA delegates subject claims to Statements of Operating principles (SOPs) determined by the Repatriation Medical Authority (RMA). Although there is a number of RMA SOPs which recognise quinoline exposure as a causal or aggravating factor in a variety of psychiatric and neurological conditions, there is no SOP for ABI regardless of cause.

A 2017 "investigation" by the RMA found there was insufficient evidence of a link between quinoline exposure and ABI for it to determine an SOP for that condition. Commonwealth officials have cited this "investigation" as a justification for refusing to provide appropriate care for veterans adversely affected by mefloquine and tafenoquine, further claiming that the RMA is an "independent" authority. The RMA is funded entirely by DVA and answers to the Minister for Veterans Affairs. Members of the RMA do not have expertise in clinical neurotoxicology or ABI. The RMA did not examine any of the medical records of ADF veterans who were administered these drugs during their service. Perversely, the RMA cited an absence of a long-term safety study on the safety of these drugs in its determination, soon after a decision by the Minister for Veterans Affairs to reject a proposal for such a study.

One of the perverse outcomes of the RMA SOP system, coupled with DVA's recognition of all "mental health" conditions under the NLHC system, is that individuals who are correctly diagnosed with ABI cannot make successful DVA claims, while individuals who have been misdiagnosed with various psychiatric disorders such as PTSD can make successful claims. Over the last two decades many veterans' advocates and health professionals have had to "work the system" to ensure that quinoline veterans were able to get *some* help from DVA, regardless whether this was the *right* help. This has contributed directly to the current situation in which many adversely affected veterans with the symptoms of ABI have been subjected to dangerous psychiatric medications and ECT, indeed it has contributed directly to the high rate of veteran suicides. Several health experts testified to the recent Senate inquiry into veteran suicides to the effect that the perverse bureaucratic DVA system was determining diagnoses and treatments for injured veterans, when it should be veterans' treating health professionals who make those decisions with the *support* of DVA to provide the appropriate health care. These observations are supported by the experiences of many quinoline veterans.

In addition to these practical concerns, the DVA policy of subjecting claims from quinoline clinical trial subjects to arbitrary RMA criteria is unethical and unlawful. Commonwealth liability for the provision of medical care to these subjects *for any adverse events, including those related to the quinoline trials, during and following their participation in the trials*, was established from the moment those subjects were enrolled in the trials. Given that the international ethical standards for clinical trials are legal instruments (by TGA regulation) under Commonwealth law, on every occasion a Commonwealth delegate rejects a claim for medical care from an ADF clinical trial subject, that delegate has therefore broken the law. The DVA policy of subjecting these claims to arbitrary RMA criteria is itself unlawful.

GlaxoSmithKline

Tafenoquine is manufactured by GSK, who sponsored the 1998-2001 AMI clinical trials involving the use of this drug. Around 2010, GSK discontinued developing tafenoquine for malaria prophylaxis but continued to develop the drug for "radical cure" of P. vivax malaria. From that time, 60 Degrees Pharmaceuticals (60P) began to develop tafenoquine for malaria prophylaxis in conjunction with the U.S. Army Medical Materiel Development Activity (USAMMDA) (see below). Notably, scientific papers since published by GSK on the safety and efficacy of tafenoquine do not cite the AMI clinical trial reports, presumably because these reports are considered unreliable.

In late 2016 QVFA met with GSK representatives in Australia and the UK to discuss our concerns regarding the adverse effects of tafenoquine. During these meetings QVFA requested GSK to fund an independent longitudinal study among the AMI clinical trial subjects on the long-term safety of tafenoquine, to be published in a peer reviewed medical-scientific journal. This request was declined. One point that became apparent in these meetings is that GSK is fully aware that tafenoquine is metabolised by CYP2D6 and that the drug has limited efficacy for CYP2D6 PMs and IMs.

On 20 July 2018, the U.S. Food and Drug Administration approved the GSK application for tafenoquine in the “radical cure” of P. vivax malaria. This approval entitles GSK to an FDA "priority review voucher" (PRV) valued at up to US$350 million.

60 Degrees Pharmaceuticals and the U.S. Army Medical Materiel Development Activity

60P was founded in Washington D.C. In 2010 by Australian expatriate Dr Geoff Dow while he was a contracted employee of the U.S. Army. Dow had previously been employed at WRAIR on antimalarial drug research, then founded 60P while working on the development of tafenoquine as a contractor for USAMMDA. Dow's supervisor at USAMMDA was Colonel Bryan Smith, who has since retired from the U.S. Army and is now employed by Dow as the 60P Chief Medical Officer. During this period, Dow/60P was awarded the U.S. Army license for tafenoquine.

In 2014, 60P was awarded a USAMMDA contract to "assist in the development of tafenoquine as a malaria prophylactic drug for FDA-TGA (Food and Drug Administration-Therapeutic Goods Administration) approval first in Australia and then in the United States." 60P continues to receive USAMMDA funding for this purpose, including further tafenoquine clinical trials in Australia.

Also, in 2014, Smith was requested in writing to undertake follow up research on the AMI tafenoquine subjects, involving a senior U.S. military specialist doctor, to investigate the drug's long-term adverse health effects. USAMMDA was one of the sponsors of the 1998-2001 AMI clinical trials of tafenoquine. Smith acknowledged this request but declined to undertake the follow up research (Attachments 10-12). The following year, Dow stated in an interview that his motivation in registering tafenoquine was to obtain a U.S. FDA PRV valued at up to US$350 million.[20]

Having previously declined to undertake follow up investigation of the long term adverse health effects of tafenoquine on the AMI trial subjects when they were employed by USAMMDA, 60P employees continue to cite the original AMI Study 033 findings in a 2017 "integrated safety analysis" paper which provides the basis of their regulatory applications.[20] This paper fraudulently attributes the high rate of neuropsychiatric adverse effects experienced by 1 RAR soldiers in Study 033 to "PTSD",[20] despite the fact that the authors have not medically examined a single one of those veterans or undertaken any clinical follow up studies.[22,23]

Unlawful Conduct of Commonwealth Officials During and Following the AMI Clinical Trials

There is strong evidence of extensive criminal misconduct by various senior Commonwealth officials responsible for the care of serving and former ADF personnel administered mefloquine and tafenoquine during their service, for example:

- **Criminal negligence** by AMI officials in administering tafenoquine to 1,540 ADF personnel during the 1998-2002 clinical trials in Bougainville and East Timor, without prior neurotoxicity testing on primates.

- **Criminal offences** by senior ADF officials against the *Therapeutic Goods Act 1989,* namely that ADF officials exported the unregistered, experimental drug tafenoquine from Australia to East Timor in 1999 or 2000 without prior written approval, using the drug at high doses on 639 personnel from 3 RAR and 5/7 RAR. This evidence was provided to the TGA on 28 September

2016 (Attachment 13) and acknowledged in writing by the Minister for Health on 19 October 2017 (Attachment 14).

- **Scientific fraud** by AMI officials and other ADF medical officers, who did not record serious neuropsychiatric adverse events reported by the subjects during the AMI mefloquine and tafenoquine clinical trials including suicidality.[24]

- **Medical negligence** by AMI officials and other ADF medical officers, who ordered subjects to continue taking mefloquine or tafenoquine during the AMI clinical trials despite having reported serious neuropsychiatric adverse events including suicidality.[24]

- **Criminal negligence** by senior DVA officials in rejecting the proposed QVFA outreach, rehabilitation and research program presented to the Minister for Veterans Affairs on 13 December 2016, resulting in the further deaths of numerous serving and ex serving ADF personnel administered tafenoquine and mefloquine.

The Necessity for a Royal Commission of Inquiry

While QVFA acknowledges the support of this Committee in addressing the medical and other support needs of quinoline veterans and families, a Royal Commission of Inquiry is necessary to address criminal misconduct by ADF and other Commonwealth officials. A Royal Commission would have the powers and resources needed to investigate this misconduct, as well as the ability to appropriately support the victims.

Royal Commissioners act in multiple capacities performing functions under Commonwealth laws as follows:

- Evidence can be provided in different ways for difference purposes, including formal hearings, open or closed.

- Evidence is provided under oath.

- There are severe penalties for providing misleading or false evidence (up to $20,000 or 5 years imprisonment).

- Allegations can be made, substantiated and proven.

- Can refer information about suspected or alleged crimes to relevant law enforcement authorities.

- Where appropriate, penalties can be applied, including custodial sentences.

On 7 June 2018 QVFA presented Prime Minister Turnbull with a brief including evidence of the criminal misconduct outlined in this submission (Attachment 15), with a request to establish a Royal Commission and a proposed Terms of Reference (Attachment 16). The Prime Minister acknowledged this briefing with the words, “I’ll get back to you.”[25]

As a start point for its inquiry, the proposed Royal Commission would ideally seize the following documents:

- All documents held by Defence relating to the use of mefloquine and tafenoquine in the ADF, including but not limited to AMI records on the quinoline clinical trials.

- All correspondence between Commonwealth officials (including but not limited to the Departments of Defence, Veterans Affairs and Health), USAMMDA, GSK, 60P and Roche (the manufacturer of mefloquine).

- All documents held by GSK relating to the safety of tafenoquine, including but not limited to any unpublished toxicology studies.

- All documents held by Roche relating to the safety of mefloquine, including but not limited to any unpublished toxicology studies.

Conclusion and Recommendations

There is clear, extensive evidence of the harmful effects of mefloquine and tafenoquine, including lasting impact on many hundreds of Australian quinoline veterans and their families. Despite claims by Commonwealth officials that adequate help is available, the government has consistently denied the fact that these drugs are able to cause permanent brain damage resulting in widespread chronic neuropsychiatric illness and in some cases suicide. There is a compelling need for the Commonwealth to implement a comprehensive program of outreach, rehabilitation and research, led by experts in ABI and clinical neurotoxicology. Legitimate requests for such help, based on rigorous research and sound medical evidence, have been repeatedly declined.

The experiences of quinoline veterans and their families shows that the ADF is institutionally incapable of safely administering the quinoline antimalarials and conducting clinical drug trials in accordance with the relevant Commonwealth laws and international ethical standards. Additionally, the various Commonwealth institutions responsible for enforcing those laws and ethical standards have systematically failed to do so. The DVA policy of subjecting the medical care and disability support needs of clinical trial subjects to arbitrary RMA criteria is unethical and unlawful. The Commonwealth's dysfunctional and criminally negligent response to date, resulting in a combination of perverse policies and practices, is systematically preventing hundreds of seriously ill veterans and their families from receiving appropriate care owed to them by the country they served. This has resulted in multiple deaths and many more remain at risk of death.

QVFA recommends the Commonwealth undertake following actions to support the urgent needs of quinoline veterans and their families, and to prevent any recurrence of similar adverse public health outcomes in future:

- Amend the *Defence Act 1903* to prohibit the conduct of clinical drug trials on ADF personnel.

- Amend the individual ADF medical records of all AMI mefloquine and tafenoquine clinical trial subjects still serving in the ADF to include their AMI trial case records.

- Forward the AMI trial case records of ex-serving mefloquine and tafenoquine clinical trial subjects to those individuals, their next of kin and/or their doctors.

- Subject all ADF personnel to CYP450 screening on enlistment, with the results to be recorded on their medical file, as is currently the case with G6PD screening.

- Issue every serving or former ADF member who was administered mefloquine or tafenoquine during their service with a DVA Gold Card.

- Immediately implement a dedicated outreach, rehabilitation and research program to address the medical, social and other support needs of quinoline veterans and their families, to be led by independent health professionals qualified and experienced in ABI and clinical neurotoxicology.

- Contact every current or former ADF member who was given mefloquine or tafenoquine during their service in writing, screen them for chronic ABI symptoms and offer them ABI rehabilitation as part of the proposed outreach program.

- Report every suspected case of chronic quinoline poisoning identified during this screening process to the TGA.
- Remove responsibility for assessment and approval of disability claims by quinoline veterans from DVA and direct this to an independent agency led by health professionals qualified and experienced in ABI and clinical neurotoxicology.
- Prosecute ADF and other Commonwealth officials responsible for the criminal offences outlined in this submission for those offences.
- Establish a Royal Commission of Inquiry into the use of quinoline antimalarials in the ADF, including but not limited to the AMI mefloquine and tafenoquine clinical trials, in accordance with the proposed Terms of Reference at Attachment 13.
- Suspend further consideration of tafenoquine by the TGA until the conclusion of the recommended Royal Commission of Inquiry.

Stuart McCarthy

President, Quinoline Veterans and Families Association

27 August 2018

Attachments

1. Summary of ADF mefloquine and tafenoquine clinical trials, 1998-2002
2. S. McCarthy, “Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian Defence Force,” *Journal of Parasitology Research*, Article ID 287651, 2015
3. Select bibliography – Published research relating to the adverse effects of mefloquine and tafenoquine
4. J. A. Shannon, “Vivax malaria and the 8-aminoquinolines,” *American Journal of Medicine*, vol. 1, no. 5, pp. 581-82,1946.
5. J. Quinn, “Complex membrane channel blockade: A unifying hypothesis for the prodromal and acute neuropsychiatric sequelae resulting from exposure to the antimalarial drug mefloquine,” *Journal of Parasitology Research*, Article ID 368064, 2015
6. Therapeutic Goods Administration, Mefloquine Adverse Event Reports, 2018
7. Therapeutic Goods Administration, Tafenoquine Adverse Event Reports, 2018
8. QVFA, Quinoline veterans outreach program: Pilot proposal for Minister Tehan and the Department of Veterans Affairs, December 2016
9. Department of Veterans Affairs, Brief for Minister Tehan MC16-003615, 23 January 2017
10. Email from Colonel Bryan Smith to Commander (ret) Bill Manofsky, 10 February 2014
11. Email from Mr Geoff Dow to Commander (ret) Bill Manofsky, 7 February 2014
12. Email from Colonel Bryan Smith to Commander (ret) Bill Manofsky, 18 August 2014

13. Stuart McCarthy letter to the TGA, Breaches of the Therapeutic Goods Act by the Australian Defence Force during clinical trials of tafenoquine, 28 September 2016

14. Letter from the office of the Minister for Health to Amanda Rishworth MP, 19 October 2017

15. QVFA brief for Prime Minister Malcolm Turnbull: the ADF tafenoquine drug trials controversy and 60 Degrees Pharmaceuticals, 24 May 2018

16. Proposed Terms of Reference for a Royal Commission of Inquiry into the use of mefloquine and tafenoquine in the Australian Defence Force

References

1. S. McCarthy, “Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian Defence Force,” *Journal of Parasitology Research*, Article ID 287651, 2015. http://dx.doi.org/10.1155/2015/287651
2. Surgeon General Australian Defence Force, *Health Directive No 215: Malaria*, Department of Defence, Canberra, Australia, 2013.
3. E. Ritchie, J. Block, and R. L. Nevin, “Psychiatric side effects of mefloquine: applications to forensic psychiatry,” *Journal of the American Academy of Psychiatry and the Law*, vol. 41, no. 2, pp. 224–235, 2013. https://www.ncbi.nlm.nih.gov/pubmed/23771936
4. R. L. Nevin, “Idiosyncratic quinoline central nervous system toxicity: historical insights into the chronic neurological sequelae of mefloquine,” *International Journal for Parasitology: Drugs and Drug Resistance*, vol. 4, no. 2, pp. 118–125, 2014.
5. J. Quinn, “Complex membrane channel blockade: A unifying hypothesis for the prodromal and acute neuropsychiatric sequelae resulting from exposure to the antimalarial drug mefloquine,” *Journal of Parasitology Research*, Article ID 368064, 2015. http://dx.doi.org/10.1155/2015/368064
6. R. L. Nevin, “Mefloquine and post-traumatic stress disorder,” in *Forensic and Ethical Issues in Military Behavioural Health*, E. C. Ritchie, Ed., chapter 19, Borden Institute, Surgeon General US Army, Falls Church, Va, USA, 2014. http://www.cs.amedd.army.mil/FileDownloadpublic.aspx?docid=59eea54e-292d-4a35-9117-d9be6c40dac3
7. J. A. Shannon, “Vivax malaria and the 8-aminoquinolines,” *American Journal of Medicine*, vol. 1, no. 5, pp. 581-82,1946. https://doi.org/10.1016/0002-9343(46)90080-0
8. Department of Defence, FOI 329/17/18 Statement of reasons under the Freedom of Information Act, 28 March 2018. https://www.righttoknow.org.au/request/documents_relating_to_tafenoquin#incoming-12000
9. N.J. Elmes et al., “Malaria in the Australian Defence Force: the Bougainville experience,” *ADF Health*, vol. 5, no. 2, pp. 69-72, 2004. https://researchonline.jcu.edu.au/29759/
10. R. Agboruche et al, *In-vitro toxicity assessment of antimalarial drugs on cultured embryonic rat neurons*, macrophage (RAW 264.7), and kidney cells (VERO- CCl-81), 2009. https://muckrock.s3.amazonaws.com/foia_files/Research_Day_Poster.ppt
11. Therapeutic Goods Administration, *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*, Department of Health and Ageing, Canberra, Australia, 2000. https://www.tga.gov.au/publication/note-guidance-good-clinical-practice
12. U.S. Army Research Office, *Neurotoxicity Associated with Mefloquine, an Anti-Malarial Drug: Small Business Technology Transfer (STTR): Solicitation Topic Number A06-T034 (Army)*, 2006. http://www.acq.osd.mil/osbp/sbir/solicitations/sttr2006/army06.htm
13. J. W. Bennett et al., “Primaquine failure and cytochrome P-450 2D6 in Plasmodium vivax malaria,” *New England Journal of Medicine*, vol 369, no. 14, pp. 1381-2, 2013. https://www.ncbi.nlm.nih.gov/pubmed/24088113
14. S.R. Marcsisin et al., “Tafenoquine and NPC-1161B require CYP 2D metabolism for anti-malarial activity: implications for the 8-aminoquinoline class of anti-malarial compounds,” *Malaria Journal*, 2014. https://www.ncbi.nlm.nih.gov/pubmed/24386891
15. S.R. Marcsisin et al., “Primaquine pharmacology in the context of CYP 2D6 pharmacogenomics: Current state of the art,” *Pharmacology and Therapeutics*, vol. 161, pp. 1-10, 2016. https://doi.org/10.1016/j.pharmthera.2016.03.011
16. QVFA, Interview with Aaron and Rae King, 2017. https://vimeo.com/239018083
17. A. McCarren, Interview with Mark Armstrong, 21 May 2018. https://www.wusa9.com/video/news/investigations/anti-malaria-drug-investigation-mark-armstrong/65-8135658
18. QVFA, Interview with Mick and Naomi Kruizinga, 2017. https://vimeo.com/238923318
19. Inspector General of the Australian Defence Force, *Inquiry report into issues concerning antimalarial trials of the drug mefloquine between 2000 and 2002 involving Australian defence members deploying to East Timor*, Canberra, 2016. http://www.defence.gov.au/Publications/COI/Docs/COI-AntiMalarialTrials.pdf
20. L. Fosse, Therapeutics and travel medicine for tropical diseases such as dengue fever and malaria, CEOCFO Magazine, 21 September 2015. http://ceocfointerviews.com/interviews/60DegreesPharma15.htm
21. A. Novitt-Moreno et al, Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis, Travel Med Infect Dis, vol. 17, pp. 19-27, 2017. https://doi.org/10.1016/j.tmaid.2017.05.008
22. A. McCarren, Interview with Dr Geoffrey Dow, 21 May 2018. https://www.wusa9.com/video/news/investigations/anti-malaria-drug-investigation-dr-geoffrey-dow/65-8135627
23. A. McCarren, Interview with Dr Stephen Toovey, 21 May 2018. https://www.wusa9.com/video/news/investigations/anti-malaria-drug-investigation-dr-toovey/65-8135644
24. A. McCarren, Interview with Greg Harris, 21 May 2018. https://www.wusa9.com/video/news/investigations/anti-malaria-drug-investigation-greg-harris/65-8135654
25. SkyNews, Veterans confront Turnbull demanding royal commission into anti-malaria drugs, 7 June 2018. https://www.skynews.com.au/details/_5794567179001