Australian Government
Department of Defence

Foreign Affairs, Defence and Trade References Committee Inquiry into the use of Quinoline antimalarial drugs Mefloquine and Tafenoquine in the Australian Defence Force

Department of Defence

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EXECUTIVE SUMMARY

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1. Defence is a warfighting organisation. Its job is to defend Australia and its national interests and, in order to do this, its people are often deliberately sent into harm's way. With this reality comes immense responsibility and Defence takes its duty of care to its members very seriously. Defence invests heavily in ensuring appropriate force protection measures are in place to protect Australian Defence Force (ADF) members from the many hazards they might encounter in their service to the nation.

2. These hazards are often complex. Sometimes the greatest threat to the welfare of Defence members comes not from enemy combatants, but from the environment within which they must operate to achieve their mission. This requires force protection to be multifaceted and sophisticated, often with specific health measures. Just as combat soldiers would not be sent into a firefight without body armour, helmets and ballistic goggles; likewise Defence members would not be sent into a region where they are known to be vulnerable to a number of health threats without maximising protection in this domain.

3. Malaria is one such health threat. Despite the advancements made in combatting this deadly disease over many decades, it remains a serious risk for civilian travellers, to deployed ADF members, and to millions of people in Australia's immediate region and across the globe who live with the threat every day. With more than 400,000 dying from malaria each year its significance as a global health issue, and an operational issue for the ADF, cannot be understated.

4. In all of the ADF's major conflicts, from the First World War onwards, malaria has had an impact. It severely impacted the Australian Army's combat operations on three occasions: in Palestine, 1918; New Guinea, 1943; and Vietnam, 1968 and in more recent times, operations in Timor-Leste were affected when 64 ADF members became infected with malaria during the International Force East Timor (INTERFET) deployment and over two hundred more developed malaria on return to Australia. From 1998 to 2007, 637 cases of malaria were recorded in ADF members; between 2012 and 2017, there were 30 cases recorded, at an average of five per year; and to date in 2018, four cases have been recorded.

ADFMIDI

5. Defence contributes to global efforts to combat malaria through the Australian Defence Force Malaria and Infectious Disease Institute (ADFMIDI). Formerly known as the Australian Army Malaria Institute (AMI), ADFMIDI is a world-renowned institute that for the last five decades has been instrumental in the evaluation of resistance to antimalarial medicines. It has contributed to the development of diagnostics, vaccines, therapies, medical devices and preventive medications to protect the health and capability of the ADF and allied forces as well as supporting Australian public health responses and the global good.

Medications used in the ADF

6. There is no single medication that is 100% effective in preventing malaria, and which is also suitable for everyone. This is why it is important that Defence is able to select from a number of medications for the prevention and treatment of malaria. All medications have side effects but some individuals may also demonstrate intolerance to certain drugs. This is why Defence works to ensure that there is a range of preventative health options available for personnel deploying to malaria affected areas. Further to this, because the malaria parasite evolves over time and

develops resistance to antimalarial medications, ongoing development of new medications is absolutely necessary.

7. Antimalarial medications currently used within the ADF for prevention are doxycycline, atovaquone/proguanil (trade name Malarone™) and mefloquine (trade name Lariam™). Primaquine is used for eradication purposes but tafenoquine, while used in Defence studies, is not registered by the Australian Therapeutic Goods Administration (TGA) and so it is not used by the ADF.

8. Defence has always been conservative in its use of mefloquine. It has never been the first line medication for prevention of malaria, as has been the case in other militaries. It is currently the third line option and is only to be prescribed if an individual is unable to take either doxycycline or atovaquone/proguanil.

Side effects of mefloquine and tafenoquine

9. Mefloquine is one of three antimalarial medications approved by the TGA for malaria prevention in the Asia-Pacific region and the World Health Organisation (WHO) lists it on its essential Medicines List for both treatment and prevention of malaria. In 2010 it was estimated that over 35 million civilian travellers had used mefloquine for prevention of malaria worldwide and it is still a recommended preventive antimalarial for travellers to Timor-Leste.

10. Despite this, the ADF has consistently been quite conservative in its use of mefloquine, even though it is easier to use in a military context as it only requires a weekly dosage. It is used by the ADF as a third-line preventive antimalarial, meaning that it is only used when neither doxycycline nor atovaquone/proguanil can be taken by an individual.

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

12. Although its side effects are well known, mefloquine remains one of the most popular antimalarials for use by civilian travellers. It is commonly prescribed in the broader Australian community and during the last five years over 10,000 scripts have been issued per year on average.

13. In contrast, tafenoquine is a relatively new antimalarial medication which is chemically more closely related to primaquine. To date, more than 4,000 people, both military and civilian, have taken tafenoquine in clinical studies around the world. At this point it remains a medication that is only used within voluntary clinical studies as it is not registered anywhere in the world. It is currently being considered for registration by both the US Food and Drug Administration (FDA) and the Therapeutics Goods Administration (TGA) in Australia. If it is registered in Australia, it will be considered for use by the ADF.

14. Tafenoquine has not been shown to have any serious neuropsychiatric side effects, including in the long term. Like primaquine, the main concern regarding tafenoquine relates to people who are deficient in the G6PD enzyme. In those people, tafenoquine can cause red blood cell problems, potentially leading to anaemia. An eye condition, vortex keratopathy (small deposits in the cornea), has also been associated with long term tafenoquine use. This condition is also associated with other medications, such as chloroquine, which was used widely for malaria management before drug resistance became a problem, and some medications used to treat heart

conditions and cancer. The condition does not affect vision and has no symptoms. It is benign and resolves completely after tafenoquine is stopped.

Studies

15. ADFMIDI is tasked with the prevention of mission failure during tropical deployments of the ADF due to infectious diseases that are spread by insects, such as malaria and dengue. In support of this it has conducted a number of clinical studies over the years, not only to learn more about new and existing medications but to also help determine which drugs might be best suited to protecting military members who generally operate in more challenging environments than civilian travellers. Such studies are tightly controlled, not only by Defence policy but by national guidelines and mandatory ethics appraisals that are carried out by an independent committee of specialists.

16. Both mefloquine and tafenoquine (which is chemically quite distinct from mefloquine) were used in approved clinical studies during operations in Timor-Leste. This was deemed necessary to help determine if Defence should review its policy of prescribing doxycycline as the preferred antimalarial, after dozens of ADF members who had been taking the medication were diagnosed with malaria.

Defence response to concerns about antimalarials

17. In recent years a number of concerns have been raised about the conduct of the Defence antimalarial studies, which resulted in the Inspector General of the ADF conducting an Inquiry that ran from 2015 to 2016. While this Inquiry found the studies were conducted ethically and in accordance with national guidelines, Defence has continued to respond to concerns raised by undertaking a number of outreach activities to ensure an appropriate public health approach.

18. Defence has focused its efforts on being as transparent as possible while also emphasising that if individuals are concerned about any symptoms, or their prior use of antimalarials, they should consult their treating medical officer and consider putting in a claim with Department of Veterans' Affairs (DVA). Activities have included the commissioning of a literature review and more recently some targeted research into the issues; the creation of an information portal on the internet; the development of management guidelines for GPs, and the creation of a dedicated email address for those with concerns to contact Defence. All outreach activities have been carefully calibrated to ensure those with concerns can access information that might assist them to seek support while not causing undue alarm to others.

19. Defence has continued to remain fully engaged in antimalarial developments in order to inform Defence policy, such as by maintaining awareness of developments in scientific evidence, changes to the manufacturers' Product Information and registrations of new drugs. It also constantly reviews national and international best practice guidelines, both within the wider community and in the ways other militaries are protecting their forces.

Public health concerns

20. In recent years a number of advocates have sought recognition that their current health complaints have being caused by, or are related to, the past use of antimalarial medications administered by Defence. This has often been accompanied by personal attacks on a number of individuals in both Defence and broader government.

21. Defence recognises that many individuals involved in making these claims are concerned about the effect that taking antimalarials may have had on their long term health. Some of these

individuals have advised that they have been diagnosed with a mental health condition but are questioning whether these diagnoses are correct. Most of these individuals are former serving members, and while some appear to be receiving services through DVA, others may not be. This is particularly concerning because all current and former serving members are automatically eligible to access mental health care, no matter the cause of their condition, either through Defence or under the non-liability health care arrangements administered through DVA. Additionally, they and their families can access care though the Veterans and Veterans' families Counselling Service (VVCS).

22. A significant problem appears to be that, potentially due to the stigma associated with mental illness, many of these individuals are searching for a specific reason, preferably a physical one, for their condition. Defence is increasingly concerned about the possible public health effects that some of the claims by advocates may be having on vulnerable people who may struggle with accepting mental health concerns and thereby delay seeking appropriate treatment. For those who do have a mental health problem or have been diagnosed with a mental illness, the belief that there is a specific cause, an alternative diagnosis or "someone to blame" could be barrier to seeking appropriate care. Equally concerning would be if individuals who are not happy with their treatment, or who do not feel they are getting better fast enough, disengage from necessary health care.

Going forward

23. These concerns are why Defence's response has been swift, comprehensive, and appropriately focussed on encouraging people who are concerned to seek health treatment. Help is readily available to those individuals who are having health problems, be it through on-base garrison health facilities, local GPs, VVCS or DVA. Defence nevertheless understands that some veterans have trouble taking the first step.

24. For these reasons, Defence will:

a. Continue to update its antimalarial policy on a regular basis as evidence regarding safety, efficacy and drug resistance evolve.

b. Examine, with DVA, the outcomes of new research to determine if further research or intervention is required, and encourage and facilitate future requests for research that have scientific merit and are ethically sound.

c. Consider whether, if registered in Australia, tafenoquine warrants inclusion in Defence's malaria policy, and if this will in turn negate the requirement to retain mefloquine as a third-line antimalarial.

d. Continue to assist DVA in veteran outreach activities.

INTRODUCTION

1. Defence is a warfighting organisation. Its job is to defend Australia and its national interests through the application of lethal force where necessary and at the lawful direction of government. In order to do this, its people are often deliberately sent into harm's way. As a consequence, Defence has an extraordinarily large duty of care obligation to its people and must take all measures to ensure that risks are mitigated and ADF personnel are protected from harm to the greatest extent practicable.

2. Force Protection is a key element of this risk mitigation. Force protection refers to "all measures to counter threats and hazards to, and minimise vulnerabilities of, the joint force in order to preserve freedom of action and operational effectiveness"[1]. This includes appropriate and meticulous planning, protective equipment, defined rules of engagement and many other measures to ensure that soldiers, sailors and airmen/airwomen have the means to protect themselves. These hazards are often complex, and sometimes the greatest threat to the welfare of Defence members does not come from enemy combatants, but from the environment within which they must operate. This is why force health protection is also critical. Combat soldiers would not be sent into a firefight without body armour, helmets and ballistic goggles. Likewise Defence members would not be sent into a region where they are known they are vulnerable to a number of health threats, without maximising protection in this domain.

3. Malaria is a disease of military significance and is therefore a key health risk to deploying Defence members and to operational capability. Defence takes this threat seriously and dedicates a considerable amount of time and effort to ensure its members get the best possible protection in malarious areas. This includes using antimalarial medications. Unfortunately, no medication is 100% effective against malaria and none is completely without side effects, which is why Defence continues to contribute to the worldwide scientific effort to produce more effective and safer alternatives.

4. Defence is aware of criticisms surrounding the provision of antimalarials, in particular mefloquine and tafenoquine, to Australian Defence Force (ADF) members. These criticisms particularly relate to antimalarial studies conducted in Timor-Leste during operations in the early 2000s. Defence refutes claims that it used these medications inappropriately and without due care, and that it failed to provide appropriate ongoing care to the members involved in these studies. Defence's priorities were, and always have been, to ensure that ADF members are provided the best possible protection against health threats, and that those who become wounded, injured or ill are provided with high quality holistic health care for the duration of their service.

5. This submission will provide background on Defence's efforts to protect its personnel against the threat of malaria, the antimalarial medications used in recent years, and the studies it has conducted. It will also provide an overview of how Defence has responded to health concerns raised by a number of individuals over the past few years, before specifically addressing the Terms of Reference (TOR) for this Inquiry.

[1] Definition from Australian Defence Glossary. http://adg.eas.defence.mil.au/default.asp

MALARIA

About Malaria

6. Malaria is a deadly disease that kills hundreds of thousands of people and affects over two hundred million people worldwide every year[2]. It is said that a child dies from malaria every two minutes[3]. Much work is underway to eradicate malaria and as a consequence the number of deaths from malaria globally has almost halved since ADF personnel were first deployed into Timor-Leste in 1999[4]. It remains, however, a strategic health priority for Australia[5] and a disease of significance for the ADF, particularly as recent reports indicate that the disease is increasing in the region[6].

7. There are four types of human malaria, the two most common being:

a. Falciparum malaria *(Plasmodium (P.) falciparum)*. Falciparum malaria can progress rapidly to cause illness with complications, including cerebral malaria, which is often fatal. There are no residual liver stages with this type of malaria and, once eradicated from the blood, there are no relapses.

b. Vivax malaria *(P. vivax)*. Vivax malaria causes acute disease or chronic (long term) disability. While very incapacitating it is not usually fatal. This type often develops residual liver stages (hypnozoites) which remain dormant for weeks or months after initial treatment of the disease. These liver stages can cause further acute episodes of malaria or relapses whenever they awaken, producing a large number of parasites, which are then discharged from the liver into the blood stream.

8. Other types of malaria include ovale *(P. ovale)* and malariae *(P. malariae)*, which are much less common than falciparum or vivax malaria. Ovale and malariae malaria may persist for a number of years, similar to vivax malaria[7].

Malaria and the ADF

9. Australia was declared free from malaria in the middle of the twentieth century[8] but the disease is still endemic in many countries where the ADF deploys, particularly in our near region. The risk of malaria varies greatly by region depending on, for instance, whether an ADF member is in Vanuatu (low risk), Papua New Guinea (PNG) (high risk), Timor-Leste (high risk) or peace-keeping operations in Africa (very high risk).

10. Malaria is not only an individual, debilitating health threat but requires robust medical, logistic, and transportation systems to diagnose, treat, support, and evacuate casualties, with consequent effects on operational capability. In all of the ADF's major conflicts from the First World War (WWI) onwards malaria has been a significant and, at times the main, cause of

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[2] 2016 figures were 216 million affected, with 445,000 deaths. Source: Word Health Organization (WHO). World Malaria Report 2017 Available at: http://www.who.int/malaria/publications/world-malaria-report-2017/en/
[3] Costello T. Lets inject some sting into malaria fight. The Australian. 02 July 2018, p 12.
[4] WHO Global Health Observatory data: http://www.who.int/gho/malaria/epidemic/deaths/en/
[5] McGinn C. Global effort to end malaria: Bishop. The Australian website, 02 Jul 18. Available at: https://www.theaustralian.com.au/news/latest-news/australian-spend-to-end-regions-malaria/news-story/dd536a3a77211d4bd96b74839d987b3d
[6] Rolfe B. Malaria is resurging with a vengeance on our doorstep but the new drug tafenoquine offers hope. ABC News, 01 Jul 18. http://www.abc.net.au/news/2018-07-01/malaria-sweeping-asia-but-tafenoquine-offers-hope/9923622?pfmredir=sm
[7] More information can be found on the WHO Malaria information page at http://www.who.int/ith/diseases/malaria/en/
[8] Brown G. Control and Eradication of Malaria: Past, Present and Future. In Sykes, H. *Health*. Albert Park, Vic: Future Leaders. 2011, p 71

casualties. Malaria has severely impacted the Australian Army's combat operations on three occasions: in Palestine, 1918; New Guinea, 1943; and Vietnam, 1968[9].

11. Malaria is one of the few infectious diseases that can quickly fill hospital beds with sick soldiers and overwhelm evacuation assets when a military unit is unable to prevent infection. Malaria was a major cause of casualties in the US military during the Vietnam War with more than 80,000 cases and 137 deaths. Up to 1% per day of front line US infantry were evacuated with malaria during operations in the Central Highlands[10]. An epidemic in the Australian Army saw 440 Australian soldiers hospitalised from malaria infection from July to December 1968[11]. In more recent times, operations in Timor-Leste were impacted when 64 ADF members became infected with malaria during Australia's participation in the International Force East Timor (OP INTERFET) and over two hundred others developed malaria on return to Australia[12]. From 1998 to 2007, 637 cases of malaria were recorded in ADF members, of which 501 (78.6%) were from Timor-Leste; 61 from Bougainville, and 22 from the Solomon Islands[13].

12. Defence has not experienced any large deployments into highly malarious areas in recent years, however, cases of malaria in the ADF still occur. Between 2012 and 2017, 30 cases of malaria have been recorded in ADF members at an average of five per year, and four cases have been recorded so far in 2018. The maximum number of recorded cases in a calendar year in this period was 11 in 2015. This includes four cases that occurred on HMAS Newcastle after sailors were infected with falciparum malaria during a port visit to Dar-es-Salaam in Tanzania[14]. While all were successfully treated, it was estimated that the sailors were "1-2 days from requiring urgent medical evacuation and 3-4 days from death if not treated"[15].

13. Defence takes the risk of malaria and other diseases that are not commonly seen in Australia very seriously. Antimalarial medications are just part of a suite of protective measures to prevent this deadly disease, which are designed to break the link in the infection chain. This can be done by eliminating or treating the source, eliminating the vector (mosquitoes), or protecting the host from infection. Preventive measures include spraying with insecticides, dipping clothing in the insecticide permethrin16, using personal insect repellents, sleeping under bed nets, and ensuring ADF personnel do not expose untreated skin after dark. While these measures are important they do not guarantee 100% protection. This is why every military around the world that deploys troops into malarious areas also uses antimalarial medications as part of force health protection.

The Australian Defence Force Malaria and Infectious Disease Institute

14. Driven by the necessity of protecting its personnel, the ADF has established a world class capability in detecting, preventing and treating this deadly disease through its Australian Defence

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[9] Sweeney T. Malaria Frontline - Australian Army Research During World War II. Melbourne: Melbourne University Press; 2003

[10] Ognibene AJ, Barrett O'N (eds). Internal Medicine in Vietnam Volume II; General Medicine and Infectious Diseases. Office of the Surgeon General and Center of Military History United States Army, Washington, D.C., 1982

[11] Black R, Malaria in the Australian army in South Vietnam. Successful use of a proguanil-dapsone combination for chemoprophylaxis of chloroquine-resistant falciparum malaria. *Medical Journal of Australia*.: 1973; 1265-70

[12] Kitchener S, Auliff A, Rieckmann K. Malaria in the Australian Defence Force during and after participation in the International Force in East Timor (INTERFET). *Med J Aust*. 2000 Dec 4-18;173(11-12):583-5

[13] Elmes N. Malaria notifications in the Australian Defence Force from 1998 to 2007. *International Health;* 2 (2010) 130–135

[14] Rose G, Westphalen N, Shanks GD. Malaria Outbreak Aboard an Australian Navy Ship in the Indian Ocean. Journal of Military and Veterans' Health. Vol 24 No. 3. Available at**:** http://jmvh.org/article/malaria-outbreak-aboard-an-australian-navy-ship-in-the-indian-ocean/

[15] Ibid

[16] Permethrin is a versatile insecticide used for a variety of purposes. It has been shown to have little systemic absorption and therefore is considered safe for topical use in adults and children over the age of 2 months. (For more information, see: https://apvma.gov.au/node/19361)

Force Malaria and Infectious Disease Institute (ADFMIDI), formerly known as the Australian Army Malaria Institute (AMI).

15. The history of malarial research stretches back to WWI. In 1918, Number 5 Mobile Malaria Diagnosis Unit moved with the Australian Light Horse Brigades, who experienced a massive malaria epidemic during their Jordan Valley campaign. Over 100 Australian deaths were attributed to the disease[17].

16. At the beginning of the Pacific campaign of WWII there was a critical shortage of the primary antimalarial medication, quinine, in Australia as 90% of the world's supply was produced in Indonesia, which lay directly in the path of the advancing Japanese forces. The Australian Army established a malaria experimental group in Cairns in 1943 where malaria was then still present. Following the disruption of military operations due to malaria in Milne Bay, PNG, the group, with the assistance of Australian Malaria Control Units and Mobile Entomological Section, was able to develop effective malaria treatment and prevention regimens[18].

17. Number 1 Malaria Research Laboratory was established in 1967 to conduct research into malaria to minimise future impacts of the disease following the high rates of malaria experienced by ADF troops in Vietnam[19]. Originally located within the School of Public Health and Tropical Medicine in Sydney, it moved to the Ingleburn Army Camp in 1973 as the Army Malaria Research Unit (AMRU). In 1996, the unit moved to a purpose-built laboratory complex at Gallipoli Barracks in Brisbane and was renamed the Australian Army Malaria Institute (AMI).

18. Shortly after marking 50 years of malaria research in the ADF, the unit's name was changed to the ADFMIDI in 2017. This was a reflection of the broadening of its role in recent years to encompass all vector borne diseases of military significance. Its mission remains the prevention of mission failure during tropical deployments of the ADF due to infectious diseases that are spread by insects, such as malaria and dengue.

19. ADFMIDI is a leading military research unit for infectious disease surveillance and product development. It is a world-renowned, industry leader of malarial studies that has been instrumental in the evaluation of resistance to antimalarial medicines for five decades. It has contributed to the development of diagnostics, vaccines, therapies, medical devices and prophylactic drugs to protect the ADF and its allies, and has supported Australian public health responses and the global good. It has also contributed significantly to regional health security by minimising the effects and spread of these diseases in the region in which the ADF operates. ADFMIDI has extensive international linkages and is a World Health Organization (WHO) Collaborating Centre for Malaria and Reference Laboratory. It is recognised amongst the malaria research community as a vital player in the field of malaria control, particularly across the Asia-Pacific region (see Annex A[20]). This is clearly demonstrated by the following quote:

> *"…The most important assets of the AMI are the intellectual quality, high motivation and impressive productivity of the scientists who work there. They are major "players" in the malaria community. Their work is highly regarded and frequently forms the basis for policy decisions on antimalarial use in the region. The proximity of Australia to malarious regions allows them to work directly in the field, and they have made major contributions to my particular area of study, resistance to antimalarial drugs".*[21]

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[17] Howie-Willis I. *An Unending War: The Australian Army's struggle against malaria 1885-2015*. Big Sky Publishing, 2016, p 73

[18] Sweeney T. Malaria Frontline Australian Army Research During World War II. Melbourne University Press; 2003

[19] Rieckmann K, Sweeney A. Army Malaria Institute: its Evolution and Achievements. First Decade: 1965-1975. J Mil Veterans Health. 2012;20(2):170–24

[20] These letters were provided to Joint Health Command as part of an internal review of the unit's roles and functions in 2012.

[21] Professor Carol Hopkins Sibley, University of Washington School of Medicine. Annex A, p 4

ANTIMALARIAL MEDICATIONS

20. Preventive medications remain an integral part of all malaria prevention plans. The ADF selects from a number of antimalarial medications for the prevention and treatment of malaria. There is no single medication that is 100% effective in preventing malaria and suitable for everyone.

21. All medications have side effects and the Australian Product Information sheets (PI)[22] for all antimalarials currently used by the ADF, which include a complete list of side effects, are at Annex B. Some individuals may also demonstrate intolerance (sensitivity) to certain drugs. This is why Defence seeks to ensure there are a range of preventative health options available for personnel deploying to malaria affected areas. The malaria parasite evolves over time and develops resistance to antimalarial medications therefore ongoing development of new medications is also necessary.

22. Antimalarials are designed to prevent or treat malaria and work in three main ways:

a. Prevention (prophylaxis) is where drugs are taken regularly, either once a day or once a week, to prevent the disease. Antimalarials taken for prevention must be taken continuously while in country, but also prior to entering a malarious area to ensure appropriate levels of protection are reached prior to exposure to the risk of infection. Sometimes this involves the use of a loading dose, particularly for those medications taken once a week.

b. Eradication (post-exposure prophylaxis), is where a drug is taken for a period after leaving a malarious area in order to eliminate the parasite from the liver and blood stream. Eradication may require different drugs than those used for ongoing prevention, or the same drugs but at higher doses.

c. Treatment of malaria - if prevention and eradication measures are ineffective for any reason medications are used to treat malaria infected patients.

History of antimalarials used by Defence since 1989

23. In the 1980s an element of the ADF regularly conducted field exercises in PNG, where the incidence of malaria was high despite the use of protective measures including antimalarial medication. At that time, the usual antimalarials taken for malaria prevention were chloroquine and dapsone/pyrimethamine (Maloprim™). These were taken together once a week commencing two weeks before departure and continuing for four weeks after return. A two week course of primaquine was also taken when leaving the malarious area to eradicate any malaria parasites that might still have been present in the body.

24. In 1988, 99 soldiers were deployed to PNG for a field exercise. One soldier became sick with malaria while taking antimalarials for prevention, and 22 suffered malaria attacks after completing the prevention and the eradication course of primaquine. Several soldiers were infected with two types of malaria. The high attack rates (25%)[23] were similar to those seen in WWII in the Pacific, and higher than that during the Vietnam War. The timing and type of malaria strongly suggested that the current medications were no longer protective against malaria and that

[22] The Product Information (PI) sheet is produced by the manufacturer of the medication and provides information for health practitioners and includes a summary of scientific information relevant to the safe and effective use of a prescription medicine. The sheets may differ from country to country but the PI's provided at Annex B. Tafenoquine does not have a PI as it is not a registered medicine.

[23] Edstein M, Walsh D, Eamsila C, Sasiprapha T, Nasveld P, Kitchener S, Rieckmann K. Malaria prophylaxis/radical cure: recent experiences of the Australian Defence Force. *Med Trop (Mars)*. 2001;61(1):56-8

the current primaquine eradication regimen was becoming less effective in eradication and preventing relapses.

25. Due to these concerns, a number of studies were conducted to determine the most effective regimen for prevention of malaria. The 1989 *Australian National Health and Medical Research Council (NHMRC) Malaria Guidelines for Medical Practitioners* recommended both mefloquine (trade name Lariam™) and doxycycline for areas with drug resistant malaria.

26. In 1989, ADFMIDI (then AMRU) participated in a study involving troops deploying to PNG, Malaysia and Thailand[24]. This study aimed to answer questions about whether the problem was drug resistance or non-compliance in taking the antimalarial medications by the soldiers. The study compared mefloquine (which had been registered in Australia the year before) to the standard regime of chloroquine and dapsone/pyrimethamine. Doxycycline was also tested in a similar manner comparing it to the standard regime of chloroquine and dapsone/pyrimethamine. The findings of the studies were that both mefloquine and doxycycline were effective in preventing malaria while deployed, as no one taking either of the medications developed malaria while overseas. After return to Australia, 10% of those who had taken mefloquine and 20% of those who had taken doxycycline were diagnosed with relapsing malaria. No cases occurred in individuals who took both doxycyline (for prevention while deployed) and primaquine (for eradication on return). Blood testing confirmed that all the medications were being taken properly.

27. While both mefloquine and doxycycline were shown to be effective in preventing malaria while deployed, doxycycline was subsequently chosen to be the first line antimalarial for the ADF. This decision was based on an examination of the strengths and weaknesses of both. Despite the disadvantages of once a day dosage, the advantages of doxycycline were that it was a well-established medication with many years of experience in its use and a known range of side effects. As an antibiotic it was also effective against other infections commonly seen in the field.

28. Mefloquine had the advantage of once a week dosage (like previously used antimalarials) but was a much newer drug, with a smaller experience base and a small risk of serious neuropsychiatric side effects, thought at the time to be between 1 in 10,000 to 20,000 people[25]. More common side effects such as dizziness and vertigo were considered likely to impair military performance. Doxycycline was therefore determined to be the first choice for malaria prevention for the ADF and mefloquine the second. Mefloquine became the third-line preventive antimalarial for the ADF in 2006 behind atovaquone/proguanil (see also paragraph 31).

29. Today, three antimalarial medications are approved by the Australian Therapeutic Goods Administration (TGA) for malaria prevention in the Asia-Pacific region – doxycycline, atovaquone/proguanil and mefloquine. Defence uses all three of these medications, in this order, for prevention of malaria in its members. Defence still uses primaquine for eradication, which is also approved and registered by the TGA.

Doxycycline

30. Doxycycline remains the first line medication for malaria prevention in the ADF to this day. It is an antibiotic that is widely used in Australia to treat a variety of infections, including respiratory and skin infections, and is effective in preventing malaria. Because of its antibiotic properties, it also provides protection against other infections that soldiers may be exposed to on deployment, such as leptospirosis and scrub typhus.

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[24] Rieckmann K, Yeo A, Davis D, Hutton D, Wheatley P, Simpson R. Recent military experience with malaria chemoprophylaxis. *Med J Aust*. 1993 Apr 5;158(7):446-9.
[25] Edstein MD, Walsh DS, Eamsila C, Sasiprapha T, Nasveld PE, Kitchener S, Rieckmann KH. Malaria prophylaxis/radical cure: recent experiences of the Australian Defence Force. *Med Trop (Mars)*. 2001;61(1):56-8

31. When used for malaria prevention, doxycycline needs to be taken every day starting at least two days before entering a malarious area and continuing for two weeks after leaving the area. Because it is a daily dose, it needs to be taken with food, and compliance can be a problem, particularly in the field. Cases of malaria occur in people who have failed to take the tablet every day, or who have experienced episodes of vomiting.

32. The doxycycline PI (Annex B) contains a list of known side effects. Generally doxycycline is very well tolerated; however, as with all drugs, it does have side effects. Doxycycline commonly causes gastrointestinal (gut) upset, such as heartburn and vomiting, which can be minimised by taking the medication with food. It can also cause photosensitivity (an increased risk of sunburn) and, like most antibiotics, thrush. Doxycycline is not suitable for pregnant women or young children as it can affect developing teeth. Rarely, it has been associated with psychiatric symptoms, such as depression and anxiety. Some people cannot tolerate doxycycline and need to be prescribed a different antimalarial before entering a malarious area.

Atovaquone/Proguanil (Malarone™)

33. This medication is a combination of two medications in one tablet. Atovaquone/proguanil was tested for use in prevention in ADF personnel in Bougainville during the late 1990s[26]. It was registered for use in Australia for treatment of malaria in 1998 and approved for prevention in late 2001. Atovaquone/proguanil formally became the second-line preventive antimalarial for the ADF when the policy was next updated in 2006. It is used when doxycycline is either not tolerated or is not suitable. Atovaquone/proguanil also needs to be taken daily starting at least two days before deployment to a malarious area and continuing for one week after leaving the area.

34. The atovaquone/proguanil PI is at Annex B. The medication is generally very well tolerated but does have some unwanted side effects. It can cause gastrointestinal upset (usually when using treatment doses rather than the lower doses used for prevention of malaria) and other side effects may include skin rash, fatigue, fever and liver problems. Neuropsychological symptoms, such as sleeping problems, vivid dreams, dizziness or hallucinations, are uncommon but can occur in some cases.

Mefloquine (Lariam™)

35. Mefloquine is approved by the TGA, and listed on the World Health Organisation's (WHO) Essential Medicines List for both treatment and prevention of malaria[27]. In 2010 it was estimated that over 35 million civilian travellers had used mefloquine for prevention of malaria worldwide[28].

36. Mefloquine remains one of the most popular antimalarials for use by civilian travellers and is still a recommended preventive antimalarial for travellers to Timor-Leste[29]. It is commonly

[26] Elmes N, Bennett S, Nasveld, P. *Malaria in the Australian Defence Force: the Bougainville experience.* ADF Health, 2004, 5 (2). pp. 69-72.
[27] The WHO Essential Medicines List includes the most effective and safe medicines needed in a health system. The 20th edition (updated March 2017) is available at: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf
[28] Schlagenhauf P, Adamcova M, Loredana Regep L, Schaerer M, Rhein H-G. The position of mefloquine as a 21st century malaria chemoprophylaxis. *Malaria Journal* 2010, 9:357
[29] Centre for Disease Control and Prevention. *Malaria Information and Prophylaxis, by Country [T]*. CDC website, https://www.cdc.gov/malaria/travelers/country_table/t.html

prescribed in the broader Australian community[30] where during the last five years over 10,000 scripts have been issued per year on average[31].

37. For the reasons articulated in paragraphs 27 and 28, Defence has consistently been more conservative in its use of mefloquine compared to other militaries, even though it is easier to use in a military context due to its once a week dosage. It is used by Defence as a third-line preventive antimalarial, meaning that it is only used when neither doxycycline nor atovaquone/proguanil can be taken by an individual.

38. In contrast the use of mefloquine in the US military was not limited to personnel who could not take doxycycline until 2009[32] and in other militaries this occurred much later (see TOR 6). According to the Surgeon General of the Canadian Forces

In the early 2000s, mefloquine was the most often used antimalarial. This started changing in the mid-2000s...[33].

39. Mefloquine can be used for both malaria prevention and for treatment. For prevention, mefloquine is taken once weekly, which is an advantage over other medications that have to be taken daily, particularly in a military context.

40. Individuals with particular medical conditions or those taking some other medications may not be able take mefloquine. In particular, mefloquine should not be taken for malaria prevention by people who have, or have had, a psychiatric condition, seizures, kidney disease or liver disease. For these reasons, Defence health policy requires that ADF members be properly informed of the potential side effects of mefloquine and that the drug only be prescribed by a qualified medical practitioner after the member has been provided information about the drug's side effects.

41. The mefloquine PI (Annex B) contains a list of known mefloquine side effects. Mefloquine is known to cause unusual dreams and can cause psychiatric symptoms in some people, including disturbed sleep, anxiety, paranoia, depression, hallucinations and psychosis. Dizziness and loss of balance have also been reported as side effects from the use of mefloquine. For this reason, the medication is not used in ADF aircrew.

Long term neuropsychiatric effects of mefloquine

42. Normally side effects, including neuropsychiatric[34] side effects, resolve within days to weeks after stopping mefloquine. Mefloquine has a half-life (persistence in the bloodstream) of two to four weeks[35], which is longer than other antimalarials, therefore side effects that emerge while taking mefloquine have been reported to persist after cessation of the medication and sometimes for several months.

43. Defence has always acknowledged that, in rare cases, neuropsychiatric side effects may be long lasting or permanent, however, this has only been reported in individuals who had symptoms while taking the drug, or that emerged shortly after ceasing it, and whose symptoms continued beyond this period. Symptoms have not been demonstrated to emerge, for the first time, more than a year after ceasing medication as by that time all traces of medication have left the body. In fact

[30] Leggat P. Trends in antimalarial prescriptions in Australia, 2005 to 2009. *J Travel Med*. 2012 Dec;19(6):357-60
[31] Defence sourced this data from Australian Statistics on Medicines and Roche Products Pty Limited, the manufacturer of Lariam™. For a year by year breakdown, see:: http://www.defence.gov.au/Health/HealthPortal/Malaria/Anti-malarial_medications/Mefloquine/default.asp
[32] Eick-Cost A, Hu Z, Rohrbeck P, Clark L. (2016). Neuropsychiatric Outcomes after Mefloquine Exposure Among U.S. Military Service Members. *Am J Trop Med Hyg,* 2017; 96(1):159-166
[33] Quoted in Ellis N (Chair). *Mental Health of Canadian Veterans: A Family Purpose*. Report of the Standing Committee on Veterans Affairs, House of Commons Canada, June 2017. p 27
[34] The term 'neuropsychiatric' side effects refers to both nervous system and mental health related symptoms..
[35] For more information on the pharmacology of mefloquine, see the Lariam™ PI at Annex B

it is biologically implausible that this would occur as once the drug has left the body it is no longer active.

44. Defence is aware of assertions that long term neuropsychiatric effects associated with mefloquine use are common[36]. There is no evidence of this in the existing scientific literature or in the worldwide experience of using the medication, although the actual incidence of long term or chronic problems is difficult to ascertain.

45. The Lariam™ PI in Australia states that the drug "…may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behaviour. On occasions, these symptoms have been reported to continue long after Lariam has been stopped" [37]. It also notes that "In a small number of patients it has been reported that some neuropsychiatric events (including depression, dizziness or vertigo and loss of balance) may continue for months or longer after discontinuation of the drug"[38]. However, it does not specify the actual incidence of these effects, nor does it refer to the emergence of these symptoms years after the ingestion of the medication.

46. The Australia Consumer Medicine Information for Lariam™ notes that serious effects include "…change in mood, for example, excitement, depression, restlessness, confusion, agitation, aggression, feeling anxious or nervous, irrational ideas, hallucinations, suicidal thoughts or panic attacks, strange or disturbing thoughts or moods; these may also occur after Lariam ™ has been stopped" but that "Serious side effects are rare"[39].

47. The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency reported in February 2014 that they had analysed the available data and interpreted that the occurrence of long term and/or persistent neuropsychiatric adverse reactions associated with mefloquine was "very rare"[40].

48. What is clear is that there is no evidence of an emerging global public health issue. This was noted by the Canadian Surgeon General in the Canadian Standing Committee on Veterans Affairs Review, *Mental Health of Canadian Veterans: A Family Purpose*, in 2017:

> *More than 17,000 Canadian Armed Forces personnel and tens of millions of people worldwide have received mefloquine since it was first licensed to prevent and treat malarial infection. We are aware of the potential short-term side effects of mefloquine; however, even given this extensive use of mefloquine, severe neuropsychiatric adverse effects have very rarely been associated with its use.* [41]

49. These observations were echoed by Vice Admiral Ray Griggs, then Vice Chief of the Defence Force, at Senate Estimates in May 2018:

> *Around 35 million prescriptions of mefloquine have been made globally. So what troubles us, and what we've been trying to grapple with for a few years now, is: why does this issue seem to*

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[36] McCarthy S. *Diagnosis and Management of Mefloquine Toxicosis in Military Veterans, Part 1*. International Mefloquine Veterans' Alliance website, 10 May 2016. Available at: https://imvalliance.org/2016/05/10/stuart-mccarthy-diagnosis-and-management-of-mefloquine-toxicosis-in-military-veterans-part-1/comment-page-1/

[37] Roche. *Product and Consumer Medicine Information Licence, Lariam ®, Mefloquine Hydrochloride* (Australia). Therapeutic Goods Administration website, updated 10 Jan 2018, https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=PI&q=Lariam&r=/

[38] Ibid

[39] Australian Consumer Medicine Information: Lariam™. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-CMI-01105-3

[40] European Medicines Agency. *Pharmacovigilance Risk Assessment Committee, Minutes of the meeting of 3-6 February 2014*, EMA/158631/2014, 6 February 2014, p. 21. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2014/03/WC500163384.pdf

[41] Ellis NR (Chair). *Mental Health of Canadian Veterans: A Family Purpose*. Report of the Standing Committee on Veterans Affairs, House of Commons Canada, June 2017.p 27.

manifest in a military population? Some of the rates and numbers that have been put forward by the anti-mefloquine advocates are significant, and, if you extrapolate those rates out to the 35 million prescriptions across the globe, why are we not seeing the same sort of manifestation across the globe? No-one in the ADF has denied that mefloquine has side effects and can have serious neuropsychiatric side effects. But the incidence of that, we would maintain, on the evidence that is available, is that that is very, very much lower than what is claimed. So the fact that we don't see this manifesting across either the Australian community, in those sorts of numbers, or the global community, in the 35 million, is something that we still don't understand.[42]

Numbers of Defence members who have taken mefloquine

50. It is because of the potentially severe nature of side effects in some individuals, and therefore the conservative approach adopted by Defence, that the number of Defence members who have taken mefloquine is relatively small. The total number of ADF members who have taken mefloquine between 2001 and 20 June 2018 is approximately 1,983. Most of these (1,319) were personnel who deployed to Timor-Leste in the early 2000s and participated in formal studies conducted by the then AMI.

51. Excluding those members prescribed mefloquine during the Timor-Leste studies, approximately 664 ADF members were prescribed mefloquine in the period January 2001 to 20 June 2018[43]. The number of ADF members prescribed mefloquine each year has decreased during that time, with on average 76 members being prescribed the drug each year during 2001-2005, 33 members each year during 2006-2010 and 19 members each year during 2011 to 2015. In the past two years, the figure has been five and two respectively.

52. ADF dispensing data for the period 2010 to 2017 is detailed in Table 1 and shows that mefloquine is prescribed less frequently than atovaquone/proguanil, and much less frequently than doxycycline.

Year	Mefloquine	Atovaquone/ proguanil	Doxycycline[44]
2010	25	105	3536
2011	26	100	4721
2012	13	152	7313
2013	20	187	6436
2014	35	183	5954
2015	15	101	5951
2016	5	81	7784
2017	2	102	5615

Table 1: ADF antimalarial prescribing information 2010 to 2017.

[42] Griggs R. In Official Hansard for Wednesday 30 May 2018, Foreign Affairs, Defence and Trade Legislation Committee Senate Estimates, p 59

[43] The numbers of members who took mefloquine prior to 2001 are difficult to ascertain as prescribing and dispensing information was held on paper records and local systems in individual health centres and pharmacies and were not centralised before this date

[44] This number represents members prescribed doxycycline for any reason and not just as an antimalarial.

Primaquine

53. Primaquine (trade name Primacin™) is an antimalarial medication used to prevent and treat relapses of malaria. It is given to people as they leave a malarious area as eradication (post exposure prophylaxis), to kill any malaria parasites that may still be present in the body. Primaquine is taken twice daily for 14 days, commencing the day of leaving a malarious area.

54. The primaquine PI, including known primaquine side effects, is at Annex B. Gastrointestinal symptoms such as nausea, vomiting, and diarrhoea are common and it is recommended that primaquine be taken with food. Individuals taking the medication are advised not to drink alcohol while taking it.

55. Primaquine can cause red blood cell problems in people who lack the glucose-6-phosphate-dehydrogenase (G6PD) enzyme, causing anaemia. All ADF personnel are tested for this enzyme at entry into service and are not prescribed primaquine if they are deficient in it.

Tafenoquine

56. Tafenoquine is a relatively new antimalarial medication which is chemically closely related to primaquine. Tafenoquine, whilst also a quinoline, is not closely related to mefloquine and acts quite differently in the body. To date more than 4000 people, both military and civilian, have taken tafenoquine in clinical studies around the world. Tafenoquine has successfully treated relapsing malaria (i.e. continued infections long after exposure) when combined with another medication called chloroquine.

57. At this point tafenoquine remains a medication that has only been used within voluntary clinical studies as it has not been registered anywhere in the world. It is currently being considered for registration by both the United States Food and Drug Administration (FDA) and the TGA in Australia. If it is registered in Australia, it will be considered for use by Defence.

58. As tafenoquine is not a registered drug, information on its side effects is limited to that available from studies (see TOR 3 and 5). Like primaquine, the main concern in using tafenoquine is in people who are deficient in the G6PD enzyme. In those people, tafenoquine can cause red blood cell problems, causing anaemia.

59. An eye condition, vortex keratopathy (small deposits in the cornea), has been associated with long term tafenoquine use. This condition is also associated with other medications, such as chloroquine, which was used widely for malaria management before drug resistance became a problem, and some medications used to treat heart conditions and cancer. The condition does not affect vision and has no symptoms[45]. It is benign and resolves completely after tafenoquine is stopped.

60. The main advantage of tafenoquine is that it is effective for prevention, eradication and treatment of malaria. Like mefloquine it is taken once a week, but appears to have fewer serious side effects. In terms of eradication it is longer acting than primaquine so fewer doses are needed thus improving compliance.

[45] Digital Reference of Ophthalmology. *Vortex Keratopathy or Cornea Verticillata.* Available at: http://dro.hs.columbia.edu/vortexk.htm

Chemical Difference between Mefloquine and Tafenoquine

61. Mefloquine (a quinolinemethanol) and tafenoquine (an 8 amino-quinoline) are of the same overall chemical class but are chemically quite distinct. That both names end in "quine" is a convention used for naming antimalarial drugs and does not indicate chemical equivalence.

62. The basis of modern pharmacology is that different molecules (which could be very closely related chemically) may have very different effects. Over the last century, more effective drugs with fewer adverse events have evolved as the understanding of both malaria and human pharmacology has improved. Mefloquine is better than quinine; tafenoquine is better than primaquine. Neither are perfect and the process of improving antimalarial drugs is an iterative one based on findings from clinical investigations and real world experience.

Registration of tafenoquine

63. The US Army has played a pivotal role in the development of antimalarials to protect its troops. This is because, while malaria is a disease of military significance it has also been described as a 'disease of poverty'[46]. Diseases that are more prevalent in poorer countries rarely stimulate the commercial interests of major pharmaceutical companies as it is difficult for them to recoup the development costs of drug in question. Due to this lack of a true profit motive, many drugs such as tafenoquine would fail to make it to the commercial market if it was not for funding by militaries and not-for-profit entities such as the Medicines for Malaria Venture (MMV).

64. MMV's mission is "…to reduce the burden of malaria in disease-endemic countries by discovering, developing and delivering new, effective and affordable antimalarial drugs." [47] Its donors include both public (governments, including the Australian Government[48], and academic institutions), private sector entities and charitable organisations (such as the Bill and Melinda Gates Foundation). MMV is working with GlaxoSmithKline Pharmaceuticals (GSK), who jointly developed tafenoquine with the US Army's Walter Reed Army Institute of Research (WRAIR)[49], to develop tafenoquine as a single-dose treatment for the radical cure of liver-stage infections (prevention of relapse)[50]. On 12 July 2018 an FDA advisory committee voted to recommend approval of single-dose tafenoquine in patients 16 years and over for this purpose[51].

65. Another pharmaceutical company, 60° Pharmaceuticals (60P), has secured research and licensing agreements with the U.S. Army and is developing tafenoquine for the prevention of malaria in individuals traveling to endemic areas, supported by in-kind financing from the US Army[52]. The FDA's Antimicrobial Drugs Advisory Committee will meet on 26 July 2018 to discuss tafenoquine's use in the prevention of malaria in adults for up to six months[53].

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[46] Stevens P. Diseases of poverty and the 10/90 gap. 2004. Available at: http://www.who.int/intellectualproperty/submissions/InternationalPolicyNetwork.pdf
[47] More information see the Medicines for Malaria Venture website, https://www.mmv.org/
[48] Medicines for Malaria Venture. *MMV welcomes continued Australian Government Support.* 24 Mar 2015, website, <https://www.mmv.org/newsroom/news/mmv-welcomes-continued-australian-government-support
[49] Edstein MD, Kocisko DA, Walsh DS, Eamsila C, Charles BG, Rieckmann KH. Plasma concentrations of tafenoquine, a new long-acting antimalarial agent, in Thai soldiers receiving monthly prophylaxis. *Clin Infect Dis.* (12):1654-8, January 2004
[50] Medicines for Malaria Venture. *Improving Clinical Management of P. Vivax Malaria,* website, April 2018, <https://www.mmv.org/access/products-projects/improving-clinical-management-p-vivax-malaria>
[51] Walker M. FDA panel backs tafenoquine for 'radical cure' of malaria. Medpage Today website, available at https://www.medpagetoday.com/infectiousdisease/generalinfectiousdisease/74008
[52] Sixty Degrees Pharma, *Research and Development,* website, https://60degreespharma.com/research-development/
[53] US Food and Drug Administration. Updated information: July 26, 2018: Antimicrobial Drugs Advisory Committee Meeting Announcement. Available at: https://www.fda.gov/AdvisoryCommittees/Calendar/ucm611960.htm

66. Defence, and particularly ADFMIDI, have informal relationships and collaborate closely with a number of military, academic and not-for-profit entities, including WRAIR and MMV, however, have no direct financial relationships with the drug companies associated with the development of tafenoquine. Defence has been supportive of the submission by the US Army for the registration of tafenoquine in Australia. It has also provided assistance, upon request, in the form of provision of data from its tafenoquine studies to both the TGA and FDA, but is not actively driving the registration process. If tafenoquine is registered in Australia the benefit for Defence would be the knowledge that another drug will be available to help protect ADF personnel against a deadly disease, and the satisfaction that Defence has contributed to the international body of knowledge regarding this antimalarial.

Neuropsychiatric side effects associated with tafenoquine

67. Defence acknowledges that mild and moderate neuropsychiatric side effects have been reported in individuals participating in tafenoquine studies, including in Defence studies. These include vertigo, sleepiness, abnormal dreams, dizziness and insomia.

68. Defence is not aware of any clear evidence that tafenoquine produces serious neuropsychiatric side effects, including in the long term. Defence notes, however, that a number of entries relating to tafenoquine have been made to the TGA's online Database of Adverse Event Notifications (DAEN) [54] in the past two years, which included reports of long term neuropsychiatric effects.

69. DAEN contains information from reports of adverse events that the TGA has received in relation to medicines, including vaccines, used in Australia. It only publically displays adverse events information on medicines that are available for general marketing in Australia, i.e. medicines that have been entered on the Australian Register of Therapeutic Goods. Information on adverse events for unapproved medicines that may be accessed through clinical studies, such as tafenoquine, is collected by TGA but these are not usually published on the DAEN.

70. TGA's information on the DAEN stresses that:

a. The reports received by the TGA contain suspected associations that reflect the observations of an individual reporter.

b. Adverse events are suspected of being related to a medicine, but this relationship is usually not certain - the symptom may be related to the underlying illness or to other factors.

c. There might be no relationship between the adverse event and the medicine - it may be a coincidence that the adverse event occurred when the medicine was taken[55].

71. Six adverse events associated with tafenoquine use were reported to TGA by the Defence clinical study staff in 2001, five of which relate to the vortex keratopathy already mentioned and one to the recurrence of malaria. An administrative error by TGA allowed entry of adverse events to the database subsequent to the study period. This was unusual as this would normally only be possible for a registered medication on the market in Australia. The remaining 26 of the 32 total entries relating to the use of tafenoquine have been entered into the database since 2016, some 15 years after the study. 18 of these were entered in a ten day period following a social media

[54] Department of Health Therapeutic Goods Administration. *Database of Adverse Event Notifications*. TGA website. Available at: https://www.tga.gov.au/database-adverse-event-notifications-daen
[55] Department of Health - Therapeutic Goods Administration. *About the DAEN - medicines*. TGA Website. https://www.tga.gov.au/about-daen-medicines

campaign in early in 2017 (see Annex C). The entries related to tafenoquine have since been removed from the online DAEN by the TGA.

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

Studies examining neurotoxicity in tafenoquine and related drugs

73. Defence is aware of claims that tafenoquine has been shown to be neurotoxic based on an unpublished 2009 laboratory study[56]. This study was a student experiment conducted under the WRAIR College Qualified Leader (CQL) program[57]. This program invites college students who are interested in Science, Technology, Engineering and Mathematics (STEM) careers to be matched with practising Department of Defense scientists as mentors in a professional laboratory environment.

74. The experiment appears to be the only piece of research in this field conducted by the author. A poster was produced detailing the outcomes of the experiment but it was not considered to meet the quality requirements for publication (see letter from the US Army to Dr Remington Nevin[58] regarding his Freedom of Information request for the poster at Annex D).

75. There is no evidence that a cell culture toxicity model (the test used in this case) has any relevance in human testing or clinically. Many drugs will kill cells in cell culture. For example, aspirin at normal blood concentrations is highly toxic to mammalian and insect cells, however aspirin is not reported to be neurotoxic at normal therapeutic doses. The data in isolation is therefore misleading. A subsequent academic study demonstrated that high doses of tafenoquine in rats did not provide evidence of neurological toxicity[59].

76. Defence is also aware that some advocates have drawn conclusions about neurotoxicity from experiments conducted in earlier drugs from the same class as tafenoquine[60]. As stated in paragraph 62, it is problematic to draw conclusions from the effects of one drug and apply it to the entire class. The story of modern medicine is the continual development of newer, more effective and safer drugs. Neurotoxicity cannot be automatically extrapolated from the results of testing related drugs in the 1940s. In fact primaquine, the most closely related drug to tafenoquine, has widely and safely been used in Defence and throughout the world for many years.

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[56] Agboruche RL. 529.3 In-Vitro Toxicity Assessment of Antimalarial Drug Toxicity on Cultured Embryonic Rat Neurons, Macrophage (RAW 264.7), and Kidney Cells (VERO-CCl-81). Available at: https://www.scribd.com/document/379808512/In-Vitro-Toxicity-Assessment-of-Antimalarial-Drugs-on-Cultured-Embryonic-Rat-Neurons-Macrophage-RAW-264-7-and-Kidney-Cells-VERO-CCl-81

[57] DCSTEM Network. *College Qualified Leaders*. Website: https://www.dcstemnetwork.org/resource/college-qualified-leaders/

[58] Dr Nevin is an ex-US Army doctor who has written extensively about his concerns regarding mefloquine and tafenoquine. He is the Executive Director of the 'Quinism Foundation', which "promotes and supports education and research on quinism, the family of medical disorders caused by poisoning by mefloquine and related quinoline drugs" (http://www.quinism.org/). He also offers Expert Witness Trial services for $500 per hour (http://www.remingtonnevin.com/feeschedule.pdf)

[59] Dow G, Brown T, Reid M, et al. Tafenoquine is not neurotoxic following supertherapeutic doses in rats. *Travel Medicine and Infectious Diseases*. 17; May–June 2017, pp 28-34.

[60] McCarthy S. Radio Interview with Hamish McDonald, ABC Radio National. 6 June 2018

Cytochrome p450 enzymes (CYP2D6)

77. Defence is aware of claims that the absence or poor functioning of an enzyme called CYP2D6 has implications for the efficacy and safety of tafenoquine. Most drugs are metabolized in the liver by a large set of related enzymes known as cytochrome p450. These enzymes vary a great deal between individuals on a genetic basis (genetic polymorphism). As drug metabolites are often the active form of the medication, cytochrome polymorphisms can influence the drug effect.

78. 8-aminoquinolines such as primaquine and tafenoquine have a complex metabolism that is poorly understood even 70 years after the introduction of the first examples of this class of drug. Failures to cure relapses during a malaria vaccine investigation lead to the discovery that some individuals who were "poor metabolisers" on the basis of cytochrome 2D6 (a common minority of European populations) were not cured by primaquine. Such findings have been extended in genetically modified mice and confirmed in some human studies.

79. Although primaquine has been shown to require metabolism in the liver by cytochrome 2D6 for efficacy, this has not been shown for tafenoquine, which appears to be much less dependent on any such metabolism. It is thought that tafenoquine operates on the blood stages of malaria by a different mechanism that does not involve CYP2D6 activation. A 2014 study in mice did seem to indicate that lack of this enzyme may alter the effectiveness of tafenoquine, and that a higher dose may be required for treatment in those who are poor metabolisers[61]. A later study in humans indicated that cytochrome status did not determine treatment outcome[62]. It should be noted, however, that relatively few poor metabolisers have received tafenoquine, therefore these findings remain provisional.

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

81. Defence is also aware that some individuals are requesting that blood testing be undertaken in those who were participants in the Defence tafenoquine studies to determine whether they are poor metabolisers of the enzyme. For the reasons articulated above, there is no clinical reason for such testing to be undertaken. The outcomes of testing would not change treatment or management of any health issues. The only clear reason for testing would be for those individuals who fail relapse treatment with primaquine, as poor metaboliser status would indicate that continuing with primaquine would be unhelpful.

[61] Marcsisin S, Sousa J, Reichard G, 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 J.* 2014; 13(1), p 1
[62] St Jean PL, et al. Tafenoquine treatment of *Plasmodium vivax* malaria: suggestive evidence that CYP2D6 reduced metabolism is not associated with relapse in the Phase 2b DETECTIVE study. *Malar J.* 2016; 15:97

Number of ADF personnel who have taken mefloquine or tafenoquine

82. The maximum number of Defence personnel who have taken mefloquine and tafenoquine in the ADFMIDI studies, and the number of prescriptions of mefloquine outside of these studies since 2001, is 3,523. It is likely that this is an overestimate as there may be some overlap in these groups. This data is presented in Table 2 and in more detail in Annex E.

Circumstances of provision	Mefloquine	Tafenoquine
Personnel provided medication as part of study		
Tafenoquine eradication study (Bougainville and Timor-Leste 1999-2000)		1017
Tafenoquine prophylaxis study (Timor-Leste 2000-2001)	162	492
Mefloquine and Doxycycline prophylaxis study (Timor-Leste 2001 - 2002)	1157	
Tafenoquine Malaria Treatment study (Australia 2001-2)		31
Personnel individually prescribed medication outside of the studies	664	Nil
TOTAL	**1983**	**1540**

Table 2: Number of ADF members provided mefloquine and tafenoquine during studies, and number of individual prescriptions for mefloquine from 2001 to 20 June 2018.

ADF ANTIMALARIAL STUDIES 1999-2002

83. ADFMIDI has a long history of conducting world leading research to determine the best and safest antimalarials for use in ADF personnel. As detailed above, the establishment of a new antimalarial regimen in the late 1990s emerged from research conducted when previous regimes failed. A similar scenario appeared to be developing in Timor-Leste in 1999, where the first case of malaria was seen in an Australian Army soldier within one month of deployment. A total of 64 cases of malaria were recorded during INTERFET in soldiers taking the standard anti-malaria regime, and a further 212 had the onset of malaria after return to Australia[63].

84. The reasons for these high rates of illness were unknown. It could have been a compliance problem – that is the soldiers were finding it difficult to take their daily dose given operational considerations - or perhaps malaria was becoming resistant to doxycycline. While efforts were redoubled to emphasise the importance of compliance and personal protective measures, Defence also re-evaluated whether the use of doxycycline was best practice, particularly as other militaries were using mefloquine as a frontline medication at that time.

85. Atovaquone/proguanil was not considered as an alternative at this time as, although it had been studied by Defence (see paragraph 33), it had not yet been approved in Australia for use in this role and experience with its use was limited. The benefit of mefloquine over both of these medications was that its once a week dosage was thought to make compliance less of a problem.

86. Table 3 provides a summary of the three studies and one treatment activity conducted by Defence using mefloquine and tafenoquine between 1999 and 2002. All of the ADFMIDI studies were voluntary and participants were provided with information about potential side effects that was consistent with relevant product and consumer medication information available at the time.

Study	Antimalarial	No. of participants	Location and date	Personnel involved
Evaluation of safety and adverse effects of mefloquine in the prophylaxis of malaria[64]	Mefloquine Doxycycline	1157 388	Timor-Leste (2001 to 2002)	4 RAR 2 RAR
Evaluation of the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prevention of malaria[65]	Tafenoquine Mefloquine	492 162	Timor-Leste (2000 to 2001)	1 RAR
Evaluation of tafenoquine for eradication of vivax malaria[66]	Tafenoquine Primaquine	1017 464	Bougainville (1999) Timor-Leste (2000)	3 RAR, 5/7 RAR, others
Evaluation of tafenoquine for the treatment of malaria[67]	Tafenoquine	31	Australia (2001 to 2002)	Various

Table 3: ADF antimalarial studies 1999 to 2002

[63] Kitchener S, Auliff A, Rieckmann K. Malaria in the Australian Defence Force during and after participation in the International Force in East Timor (INTERFET). *Med J Aust*. 2000 Dec 4-18;173(11-12):583-5
[64] Kitchener S, Nasveld P, Gregory R, Edstein M. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. *Med J Aust* 2005; 182 (4): 168-171.
[65] Nasveld P, Edstein M, Reid M, Brennan L, Harris I, Kitchener S, Leggat P, Pickford P, Kerr C, Ohrt C, Prescott W et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrob Agents Chemother*. 2010 Feb;54(2):792-8.
[66] Elmes N, Nasveld P, Kitchener S, Kocisko D, Edstein M. The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of *Plasmodium vivax* malaria in the Southwest Pacific. *Trans R Soc Trop Med Hyg*. 2008 Nov;102(11):1095-101.
[67] Kitchener S, Nasveld P, Edstein M. Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria. *Am J Trop Med Hyg*. 2007 Mar;76(3):494-6.

Mefloquine studies

87. In 2000, mefloquine was known to be effective against malaria, had been registered in Australia for over ten years, was recommended for use in NHMRC guidelines, was commonly used by civilian travellers, and could be taken once a week. Further, the findings of the previous tafenoquine studies in Timor-Leste, where mefloquine was the comparator drug, indicated that mefloquine was generally well tolerated in the ADF population (although as with all antimalarial drugs not suitable for everyone). Mefloquine was also the antimalarial of choice for other militaries. A contemporaneous quote from Health Canada was that:

When used properly, Lariam is a drug that is safe and effective. While there are risks associated with even the proper use of Lariam, these are far outweighed by the benefits of being protected against a potentially fatal infection.[68]

88. Defence could have decided to change its policy and switch to a new regime using mefloquine as the preferred first line antimalarial. Instead, Defence exercised further due diligence by deciding to conduct a study to see if mefloquine offered any advantages over doxycycline. The advantages of this approach were that Defence was able to control, closely monitor and document the use of mefloquine and compare it with doxycycline use, both in terms of efficacy (ie protection against malaria) and tolerability (side effects). In addition, a 2000 Cochrane Review had noted that "There is an urgent need for a pragmatic, randomised study which will address the tolerability of mefloquine prophylaxis under field conditions…".[69]

89. The objective of the mefloquine study was to compare the side effects and effectiveness of mefloquine with those of doxycycline under typical field conditions. The study population was drawn from battalion groups deploying to Timor-Leste during April to October 2001 and October 2001 to May 2002. The majority of the individuals involved in the study came from the Second Battalion, Royal Australian Regiment (2 RAR) based in Townsville, and the Fourth Battalion Royal Australian Regiment (4 RAR) based in Sydney[70]. 1157 soldiers took mefloquine and 388 took doxycycline.

90. These ADF field studies were done according to strict ethical and scientific standards. The study protocols were carefully reviewed prior to the study by the then Australian Defence Medical Ethics Committee (ADMEC), a properly constituted human research ethics committee compliant with the National Statement on Ethical Conduct in Human Research. The Committee was charged with being certain that testing of the medication under these conditions was ethical, particularly in a Defence setting, and scientifically correct. This included confirmation that participation was voluntary and that researchers obtained informed consent. The Committee also considered the Cochrane Review as part of its deliberations. ADMEC was later renamed the Australian Defence Human Research Ethics Committee (ADHREC).

91. Participation in the study was optional and voluntary. A number of activities were undertaken to ensure deploying personnel were fully informed of the risks and benefits of participation before they made their decision. They were given a written information sheet and a verbal briefing, and were asked to sign a consent form if they agreed to participate (see Annex

[68] Mr. Dann Michols, Director General, Therapeutic Products Directorate, Health Protection Branch, Health Canada, Standing Committee on Public Accounts, 18 November 1999. Quoted in Ellis N (Chair). *Mental Health of Canadian Veterans: A Family Purpose*. Report of the Standing Committee on Veterans Affairs, House of Commons Canada, June 2017, page 23

[69] Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. *Cochrane Database Syst Rev.* 2000;(4):CD000138. For more information on Cochrane Reviews, see para 199

[70] 4 RAR was renamed the 2nd Commando Regiment on 19 June 2009

F)[71]. Common, uncommon and rare side effects associated with mefloquine use (obtained from the manufacturer's PI) were presented during enrolment and were listed in the information and consent form. Participants were also advised that they could withdraw from the study at any time.

92. Not all deploying members volunteered to participate in the studies, and participation in the studies was not a pre-requisite for deployment. It is believed that at least 400 soldiers declined to volunteer and still deployed[72]. To provide deploying personnel with appropriate protection against malaria, those who chose to not participate in the studies were prescribed an antimalarial medication in accordance with extant health policy, which included the options of doxycycline or mefloquine. At least 388 of these individuals deployed on doxycycline and this group was used as the control group for the study[73].

93. Each participant was medically assessed prior to starting the study, during deployment and before return to Australia. Participants were also assessed if they developed any side effects or experienced any adverse events. Those having significant adverse side effects were examined by medical and nursing officers, the medication was ceased, and the findings recorded while in Timor-Leste. 75 individuals (6.5%) were unable to tolerate the specific antimalarial they were assigned and had to be switched to an alternative.

94. Detailed written records were kept at all phases of the study with this information later analysed. The study's findings were subsequently published in the Medical Journal of Australia in 2005[74].

95. 57% per cent of soldiers using mefloquine reported at least one adverse event, compared with 56% using doxycycline. The most commonly reported adverse effects of both drugs were sleep disturbance, headache, tiredness and nausea. There were three serious neuropsychiatric events reported in people taking mefloquine. Two of these individuals had undisclosed medical conditions that would have prevented the prescription of mefloquine if they had been known to medical staff. For the other individual, this was the first time they had presented with this type of problem.

96. Soldiers who did not report side effects were still questioned about symptoms, and routine blood samples were taken from some study participants to be certain that there were no chemical or blood problems that developed without symptoms.

97. One soldier developed malaria while in Timor-Leste during the study period. He had started on mefloquine but became infected after changing to doxycycline and had difficulty complying with the daily regimen. Despite a primaquine eradication course, eight soldiers who were taking mefloquine presented with malaria after returning to Australia.

98. Overall, the study found that mefloquine was generally well tolerated and concluded that it should continue to be used for those who cannot tolerate doxycycline. No lasting effects were noted during these studies. Of those soldiers still taking mefloquine at the end of their deployments 94% indicated they would use mefloquine again.

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[71] Two similar but slight different versions of the Information and Consent Form are provided at Annex D. The information about mefloquine side effects in each is basically the same however is expressed in slightly different ways between the two versions.
[72] Inspector General ADF. *Inquiry Report into issues concerning antimalarial trials of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*. 2016, paragraphs 158, 170, 233. Available at http://www.defence.gov.au/Publications/COI/Docs/COI-AntiMalarialTrials.pdf
[73] Kitchener S, Nasveld P, Gregory R, Edstein M. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. *Med J Aust* 2005; 182 (4): 168-171.
[74] Ibid.

99. Follow up occurred over several months following return from Timor-Leste. Soldiers were also provided with an information card that detailed their deployment to a malarious area and the medication they had been taking. They also had ongoing health surveillance through the ADF Annual Health Assessment, and later the Periodic Health Examination throughout the rest of their service careers (see paragraphs 116 to 126).

100. As previously mentioned, mefloquine was also used as the comparison antimalarial in the Timor-Leste tafenoquine studies (see paragraph 107a) due to its similar once a week dosage. A total of 162 individuals were given mefloquine as part of this study. This means that the overall number of ADF personnel who took mefloquine as participants of studies in Timor-Leste was 1,319.

Tafenoquine studies

101. Tafenoquine was used by Defence in two separate studies between 1999 and 2001 in Bougainville and Timor-Leste, and as treatment for relapsing malaria in Australia from 2001 to 2002. The studies were both Phase III studies. This means that they were preceded by extensive laboratory testing, animal testing, and Phase I and II studies in over a 1000 people[75].

102. Staff from ADFMIDI had previously collaborated with the US and Thai Components of the Armed Forces Research Institute of Medical Sciences, Bangkok, on evaluating the effectiveness of tafenoquine as a preventive antimalarial in Thai soldiers[76]. These earlier studies indicated that the drug offered a safer alternative to other preventive drugs such as mefloquine, while still having the advantage of once a week dosage.

103. The maximum number of ADF members who were administered tafenoquine was 1,540[77], of which the vast majority (1,017) received the medication for only three days. The safety and efficacy of tafenoquine was examined for:

a. Long term prevention in Timor-Leste (2000-2001): 492 personnel.

b. Eradication (a three day course) in Bougainville (1999) and Timor-Leste (2000): 1,017 personnel.

c. Treatment of relapsing malaria on return to Australia (2001-2002): 31 personnel[78].

104. The majority (85%) of participants in the prevention study were from the First Battalion Royal Australian Regiment (1 RAR) based in Townsville. For the eradication study, the largest represented units were the Fifth and Seventh Battalion Royal Australian Regiment (5/7 RAR) based in Darwin (28% of total participants), and Third Battalion Royal Australian Regiment (3 RAR) based in Sydney (21%), however participants came from 113 units in total across all three Services. The use of tafenoquine for treatment of relapsing malaria occurred in individuals from various units.

105. For the two studies, members were provided with detailed information and were asked to sign consent forms if they wished to participate (see Annexes G – prevention study; and H –

[75] For more information on drug studies see paragraphs 108 to 110)
[76] Edstein M, Walsh D, Eamsila C, Sasiprapha T, Nasveld P, Kitchener S, Rieckmann K. Malaria prophylaxis/radical cure: recent experiences of the Australian Defence Force. *Med Trop (Mars)*. 2001;61(1):56-8
[77] It is likely that the actual number of ADF personnel who received tafenoquine is lower than 1,540. There was overlap in these groups, i.e. members may have appeared in more than one study. In addition, there is a discrepancy of four in the eradication study numbers between data held at the ADF Malaria and Infectious Disease Institute (1,013) and that published in the scientific literature (1,017).
[78] Note that this activity was not a study per se but a quality assurance activity, given the drug was given to actively treat individuals with malaria.

eradication study[79]). The drug was administered in accordance with ADMEC approved study protocols and participation was voluntary. For the use of tafenoquine as treatment, approval was sought from the Therapeutics Goods Administration (TGA) for supply and use of tafenoquine for each individual under the Special Access Scheme[80]. This was also voluntary and those who agreed to take tafenoquine to treat their relapsing malaria provided consent.

106. The studies showed that tafenoquine is an effective antimalarial medication with a similar rate of adverse events but different side effect profile than mefloquine. The most common side effects reported were gastrointestinal (nausea, vomiting and diarrhoea) and headache. These symptoms were mild and resolved quickly. No serious neuropsychiatric effects were recorded in tafenoquine participants although 12% of both groups in the prevention study reported headaches.

107. More detail on the three studies is provided below.

a. **Prevention of malaria**[81]. Participation in the double-blind, randomised control study was offered to a battalion group deploying to Timor-Leste for a six month period. Three quarters of the participants took tafenoquine (492) and one quarter took mefloquine (162), with a three day loading dose and subsequent weekly dose. No diagnoses of malaria occurred for either group during deployment but 0.9% of those who had taken tafenoquine and 0.7% of the mefloquine users developed *Plasmodium vivax* up to 20 weeks after finishing the mediations. The personnel were monitored closely during the study and for six months afterwards. One hundred people were randomly chosen for more detailed assessment of their eyes and respiratory function. An incidental finding in this study was the development of an eye condition (vortex keratopathy) in some people taking tafenoquine (see paragraph 59). A letter regarding this finding and its implications was sent to all participants who had taken tafenoquine. A draft copy of this letter is at Annex I.

b. **Eradication of vivax malaria**[82]. This study aimed to compare the effectiveness and tolerability (side effects) of tafenoquine and the standard eradication medication, primaquine, in preventing malaria relapses. Participants were enrolled at the end of their deployment and were provided with one of three tafenoquine dosage regimes (400 mg daily; 200 mg twice daily; or in Timor-Leste only, 200mg daily) over three days (1,017 participants), or the standard 14 day dose of primaquine plus doxycycline (464 participants). While the relapse rate for those who took tafenoquine in Bougainville was lower than the standard course of primaquine and doxycycline, there was no statistically significant difference. However, the relapse rate for those who took the lower dose of tafenoquine (200mg daily) in Timor-Leste was significantly lower that both those who had taken 400mg of tafenoquine once per day and those who had taken primaquine and doxycycline[83]. The lower dose of tafenoquine also had fewer side effects than the higher doses and produced rates of adverse events equivalent to that of primaquine plus doxycycline. All participants were followed up for 12 months after completion of the eradication course.

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[79] For the eradication study, there were several different versions of the Information Sheet and Consent Form for the variations in the regimens. Four versions are provided in Annex G. Note that an early name for tafenoquine, as printed on the forms, was 'etaquine'.

[80] More information on this Scheme is available at https://www.tga.gov.au/form/special-access-scheme

[81] Nasveld P, Edstein M, Reid M, Brennan L, Harris I, Kitchener S, Leggat P, Pickford P, Kerr C, Ohrt C, Prescott W, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrob Agents Chemother*. 2010 Feb;54(2):792-8.

[82] Elmes N, Nasveld P, Kitchener S, Kocisko D, Edstein M. The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of *Plasmodium vivax* malaria in the Southwest Pacific. *Trans R Soc Trop Med Hyg.* 2008 Nov;102(11):1095-101.

[83] In Bougainville the relapse rate for those who took 200mg twice a day for three days (1.2%) was lower than those who had taken 400mg daily for three days (2.3), and both were lower than primaquine plus doxycycline (3.4%). For

c. **Treatment of malaria**[84]. ADF personnel with a confirmed diagnosis of relapsing vivax malaria were given the option to take tafenoquine after previous treatments had failed. Approval to use the medication for this purpose was obtained from the TGA under the Special Access Scheme. Of the 31 personnel who commenced this treatment, 27 completed the full eight week course. Treatment was terminated early in four patients due to the unexpected adverse event in the prevention studies (vortex keratopathy as mentioned in paragraph 107a). No adverse events were reported during the treatments and the medication was well tolerated. One patient had a further relapse after completing treatment, giving a recorded cure rate of 96%.

Development and testing of new drugs

108. It is extremely important that new antimalarial medications continue to be developed and tested due to the ability of the malaria parasite to evolve and become resistant to currently used drugs. Clinical studies, such as the ones undertaken by Defence, are how new medications are evaluated to ensure they are effective and safe. These studies must be done before medications can be formally approved by regulators and become accessible to the general population. This is why it was important for Defence to contribute to the development of a new medication by conducting carefully and ethically designed clinical studies of tafenoquine, a drug which offers great potential as an antimalarial.

109. Defence's tafenoquine studies were undertaken as part of accepted processes for developing and testing new drugs (see Annex J). Drug development is a long and expensive process in which the vast majority of promising molecules are weeded out as chemistry is sequentially tested in the laboratory, then animals, then humans. A common success rate when starting from a class of molecules is approximately 1:50,000. To take a new molecule to registration is an eight stage process[85]:

a. find successful molecules ("hits")

b. test these molecules in the laboratory

c. develop a lead compound (best of set of related molecules)

d. test drug safety in laboratory (including animals)

e. Phase I clinical testing in humans in limited numbers to test for adverse events from expected human regimen (n=100)

f. Phase II testing including safety and ability of drug to treat the disease in humans (n=600)

g. Phase III full field studies in the situation meant for the drug when introduced against a comparator drug of known efficacy, i.e. a real life test (n=3000)

h. Registration with the appropriate regulatory agency

110. This complex process has been developed over generations and is the best available method to deliver safe and effective drugs.

Timor-Leste the lowest relapse rate was seen in those who took low dose tafenoquine (200mg daily) at 4.9%, followed by tafenqouine 200mg twice daily (5.3%); primaquine plus doxycycline (10%) and tafenoquine 400mg daily (11.0%).

[84] Kitchener S, Nasveld P, Edstein M. Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria. Am J Trop Med Hyg. 2007 Mar;76(3):494-6.

[85] This process is illustrated at the Medicines for Malaria Venture website at: https://www.mmv.org/sites/default/files/content/infographic/files/RandD.Process.pdf

Conducting studies in Defence

111. Defence notes the serious public allegations that have been made regarding the conduct of these antimalarial studies[86] [87]. Defence strongly refutes that there is any evidence of misconduct relating to these studies.

112. In the case of mefloquine, the antimalarial was already in use around the world, was licensed for use in Australia and was the first line antimalarial for many other militaries. Tafenoquine was not registered but had proceeded down the standard drug development pathway, including having been previously tested in humans. Participants in all studies provided informed consent, participation was voluntary, and the drug was administered in accordance with Ethics Committee approved study protocols and/or by permission from the TGA. The conduct of the studies was the subject of an Inspector General ADF (IGADF) Inquiry, which did not find evidence of misconduct (see paragraphs 135 to 139).

113. Defence also rejects claims that informed consent is not possible in military populations and the assertion that clinical studies should not be conducted on these personnel[88].

114. Research in military populations, including the issue of consent, is addressed explicitly in the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research[89]. Guidance is provided for both researchers and ethics committees to ensure adequate protections in terms of the overriding principles of research merit, research integrity, justice, beneficence and respect. As detailed in paragraph 90, these studies, like all ADFMIDI research, were conducted in accordance with these guidelines and with the approval of the extant Defence human research ethics committee (ADMEC or ADHREC).

115. It is an accepted scientific tenet that studies of therapeutic agents need to be conducted in the population in which they will be used. With respect to malaria risk, the ADF population is not comparable to the native population of a malarious country, who has a degree of immunity to malaria, nor is it comparable to recreational travellers to malarious areas for short periods. ADF members are exposed to a far greater level of threat because of the nature of the work they do, their living conditions, and often a lack of normal infrastructure. In order to provide them with appropriate force protection measures Defence needs to understand how those measures will work in the military operating environment. For this reason it is imperative that Defence continues to conduct scientific studies in an ethical and considered manner.

Health monitoring of study participants

116. A feature of ADFMIDI studies was the intense monitoring and health support that was provided both during and after the studies. Unlike civilian travellers who are prescribed mefloquine before venturing far beyond the reaches of western medicine, ADF members always

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[86] International Mefloquine Veterans' Alliance. *Statement by Major Stuart McCarthy on Extensive Criminal Misconduct by Senior Australian Defence Force Officials*. Website, 21 May 2016. Available at: https://imvalliance.org/2015/12/22/statement-by-major-stuart-mccarthy-on-extensive-criminal-misonduct-by-senior-australian-defence-force-officials/

[87] McCarthy S. Prime Minister Turnbull Must Support Diggers Used as Drug Guinea Pigs. International Mefloquine Veterans' Alliance website, 23 Dec 16. Available at: https://imvalliance.org/2016/12/23/major-stuart-mccarthy-prime-minister-turnbull-must-support-diggers-used-as-drug-guinea-pigs/

[88] For an example of these claims, see Lloyd P. Timor veterans condemn ADF inquiry clearing military of wrongdoing in anti-malaria drug trial. ABC News website. Available at: http://www.abc.net.au/news/2016-10-04/adf-clears-military-of-wrongdoing-in-anti-malaria-drug-trial/7902498

[89] National Health and Medical Research Council. *National Statement on Ethical Conduct in Human Research (2007) (Updated 2018). Chapter 4.3: People in dependent or unequal relationships*. Available at: https://www.nhmrc.gov.au/_files_nhmrc/file/publications/national-statement-2018.pdf

deploy with integral health support to allow easy access to health care when problems develop. This was the case during the deployments to Timor-Leste.

117. The design of the studies also mandated more regular health reviews of the participants than would normally occur. Participants who reported symptoms were assessed and the drug was ceased if required. Even if health care was not actively sought by participants they were asked about any specific symptoms and/or were asked an open ended question "do you feel differently in any way since starting the new treatment?" on numerous occasions.

118. Participants also underwent periodic blood tests to check liver and kidney function, blood count and methaemoglobin level. All participants were followed up for six to 12 months from the end of the studies, which was considered enough time for late onset side effects to present. Participants were also given a study card that advised them and their medical practitioner of what to do and who to contact if they were to develop fever during or in the six months after the study. A subgroup of the participants in the study comparing tafenoquine and mefloquine for prevention of malaria underwent additional testing to actively look for adverse effects that could be related to the medication, based on the available scientific evidence at the time. This included specialist eye examinations, electrocardiography, lung function tests and chest x-ray.

119. As well as the specific follow up conducted as part of the studies, all ADF members are provided comprehensive health services, including for mental health, regardless of the cause any problems that might arise. These include the monitoring of general health status as well as occupational and operational fitness. Defence health practitioners follow the national guidelines for preventive health activities, as issued by the Royal Australian College of General Practitioners[90].

120. As well as general GP services, members are routinely screened for health problems in a number of circumstances as detailed below. If at any time an issue is identified during these assessments, members are referred for follow up assessment and treatment. All ADF members who participated in the studies were provided Defence health services and underwent regular assessments for the duration of their time in Defence, therefore there were multiple opportunities over the years to report any ongoing symptoms they may have been experiencing.

121. **Deployment health assessments**. Opportunities to identify and/or report possible adverse events/effects related to medications taken during a deployment include the return to Australia medical examination at the end of a deployment, and the post deployment health assessment, conducted three months after return to Australia. Post deployment health checklists identify likely health threats/exposures so that these can be specifically asked about during these assessments.

122. For each deployment, members receive a pre-briefing about health threats in the operational area and are provided with a health card, listing these threats and potential exposures. This also occurred for the participants in the studies. If they develop symptoms or problems during or post deployment, they can show the card to their medical practitioner, so that the doctor can consider these conditions when assessing the member.

123. **Mental Health.** Defence undertakes mental health screening processes which provide opportunities for Defence members to be identified as requiring assistance for mental health problems. Mental health screening is conducted for all members who have deployed on operations. Defence members complete a Return to Australia Psychological Screen (RtAPS), which consists of a questionnaire and screening interview, within the seven day period prior to returning from deployment. Defence members who are unable to complete an RtAPS prior to their return to Australia are offered the screen upon their return. Defence members also participate in

[90] Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th Edition. Available at: https://www.racgp.org.au/your-practice/guidelines/redbook

Post Operational Psychological Screening (POPS) between three and six months following their RtAPS. The POPS also consists of a questionnaire and screening interview.

124. In addition to the mental health screening, ADF members receive training in physical and mental resilience and in recognising health problems in themselves and others. They are encouraged to seek help early and have ready access to Defence health practitioners. If required, they may also self-refer to psychology and mental health services without having to see a doctor first. The ADF Health and Wellbeing portal[91] provides information on a range of health issues and services for ADF members, ex-members and their families.

125. **Periodic Health Assessments.** Prior to 2011, ADF members received annual health assessments. These assessments involved the member answering a series of questions designed to identify any current symptoms or significant injuries or illness in the previous 12 months. Annual health assessments for non-specialist occupations were ceased in 2011 in favour of a revised comprehensive periodic health examination framework using an evidence-based approach based on age. Again, those who participated in the studies received these regular assessments throughout their service careers.

126. **Separation health assessments**. Prior to separation from the ADF, members undergo a comprehensive health examination that includes formal psychological screening. This is an opportunity to check that all necessary treatment and any outstanding Department of Veterans' Affairs (DVA) claims have been completed. It also provides baseline information for future civilian health care providers. It aligns closely with the ADF post-discharge general practitioner health assessment[92], which is available to ex-serving ADF personnel.

[91] The ADF Health and Wellbeing Portal is at: http://www.defence.gov.au/Health/HealthPortal/
[92] For more details see: https://at-ease.dva.gov.au/professionals/assessment-and-treatment/adf-post-discharge-gp-health-assessment

DEFENCE'S RESPONSE TO CONCERNS ABOUT ANTIMALARIALS

127. For the past few years, Defence has come under considerable scrutiny regarding its use of mefloquine and tafenoquine. These concerns have related to three major themes: the conduct of the studies; claims that a large number of participants of the studies are experiencing long term neuropsychiatric effects (or brain injury) from the medications; and the need for ongoing health care for those individuals who have taken these antimalarial medications. There have also been calls for mefloquine use to be banned by Defence and for tafenoquine not to be registered.

128. Defence has responded to these concerns by undertaking a number of activities to ensure an appropriate public health approach. The Defence approach has been to ensure transparency of its use of these medications while emphasising that if individuals are concerned about any current symptoms, or their prior use of antimalarials, they should consult their treating medical officer and consider putting in a claim with DVA.

129. Responses have included the following:

a. The commissioning of an independent review of published literature on the neuropsychiatric effects of mefloquine conducted by Professor Alexander McFarlane, Director of the Centre for Traumatic Stress Studies, University of Adelaide in 2016 (Annex K). Professor McFarlane's review concluded that there is no specific way to diagnose long term mefloquine effects and no specific treatment except to treat the symptoms, which can resemble those of many other mental health conditions. More detail on the outcomes of the review is provided in TOR 5.

b. A review of the Defence policy on antimalarials to ensure it reflects the most up-to-date information on these medications. A new version of the policy is due to be published later this year.

c. An analysis of health outcomes from individuals who took mefloquine during Defence studies. This is covered in TOR 3.

d. Research has been commissioned by Defence and DVA to examine health outcomes in those who took mefloquine in Timor-Leste (see TOR 3).

e. A number of specific outreach activities have been undertaken (paragraph 130).

f. An Inspector General ADF (IGADF) Inquiry has been conducted (paragraphs 135 to 139).

g. Letters were sent by the Surgeon General of the ADF (SGADF) to the Repatriation Medical Authority (RMA) requesting a review of their Statements of Principles (SOPs) regarding antimalarials (see paragraphs 140 to 145).

h. Provision of support to DVA, particularly in relation to the Government response to the 2015 Senate Inquiry *Mental health of Australian Defence Force members and veterans* (see paragraphs 146 to 148).

i. Defence responded to a Comcare request to review the use of mefloquine by the ADF (see paragraphs 149 to 150).

Defence Outreach Activities

130. Defence outreach activities have been designed to provide current and former serving members with information about the medications of concern, detail on the studies, and to encourage them to seek help. Specific activities include:

a. Participation by senior Joint Health Command (JHC) personnel in a public forum in Townsville on 13 March 2016 to demonstrate Defence's commitment to actively engage with those who believe they have been adversely affected by mefloquine and explain what Defence has been doing to address the issue[93].

b. The release of media statements and internal communications products to encourage individuals who are concerned to seek health care and advice regardless of the cause of that problem. For serving members, this is through their local JHC health facility; for veterans, options include their regular General Practitioners (GP), via the DVA mefloquine hotline or through accessing non-liability healthcare and the Veterans and Veterans' families Counselling Service (VVCS). A copy of the 2016 Defgram on this issue is at Annex L.

c. The development of a comprehensive web resource, *Malaria, mefloquine and the ADF* for current and ex-serving ADF members and their families[94]. A link to the web resource is available from the home page of both the Defence intranet and internet websites.

d. The creation of an email address for individuals to contact JHC directly with their concerns (adf.malaria@defence.gov.au).

e. The development and release of clinical guidelines to assist Defence health practitioners with the management of members who are concerned about mefloquine. The current version, dated 09 June 2016, is publicly available on the ADF Malaria webpage and is at Annex M. The letter was also shared with DVA. Dr Ian Gardner, DVA Principal Medical Advisor (PMA), subsequently sent a letter to peak medical bodies and Primary Health Networks in October 2016 for distribution to all GPs, notifying them of these guidelines and providing information on access to DVA services.

f. A presentation by senior JHC personnel to several ex-service organisations (ESO) and to the DVA / ESO Round Table Meeting on 12 April 2016.

g. Support to the DVA outreach activity in Townsville in December 2016, in the form of a briefing of local GPs by senior Joint Health Command staff (paragraph 147a).

131. Since August 2015 Defence, through JHC, has answered over 400 requests for information, study documentation and/or general advice from concerned individuals. In some cases this has involved extensive personal engagement over a number of occasions with individuals who have specific concerns.

132. Defence's outreach response has been extensive and appropriately focussed on encouraging people concerned about their health to seek health treatment. DVA have also responded with specific initiatives and access pathways for those concerned. Despite these efforts, advocates have not been satisfied with the response of either Department.

133. The majority of those who participated in the ADFMIDI studies are no longer serving. Defence acknowledges that some veterans do not find it as easy to access health care after they have left the organisation as they may have done while still serving. Indeed this could be why advocates remain unsatisfied. It could also explain the relatively small numbers who have reached out for individual support despite the numerous avenues available.

134. This suggests that any future outreach activities would be more beneficial if they focused more broadly on encouraging all veterans with any health concerns to seek help, rather than

[93] Dorsett, J. *Former soldiers, families face military officials in Townsville over anti-malaria drug side effects*. ABC News website. 14 March 2016. Available at: http://www.abc.net.au/news/2016-03-13/families-face-military-officials-anti-malaria-drugs-townsville/7242982

[94] The *Malaria, mefloquine and the ADF* website can be accessed at: http://www.defence.gov.au/Health/HealthPortal/Malaria/default.asp

specifically focussing on this group. It remains pivotal that veterans and their families understand the services available to them regardless of their diagnosis, many of which can be accessed through DVA or through their GP, who are best placed to investigate, manage and if necessary refer patients for specialist advice.

Inspector General ADF Inquiry

135. In September 2015, then Major Stuart McCarthy made a submission to the Inspector General ADF (IGADF) concerning "…what he submitted was unethical, unlawful and negligent use by Defence of the antimalarial drug mefloquine"[95]. In response to this complaint, the IGADF conducted an Inquiry into *Issues concerning antimalarial studies of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*.

136. The report of the Inquiry found that the studies were conducted ethically and in accordance with both the ADMEC and later ADHREC approved protocols and NHMRC National Guidelines[96].

137. Other findings of relevance regarding the conduct of the studies included:

a. There was appropriate justification to examine new antimalarial medications (tafenoquine) due to the threat of malaria, the significant number of cases in Timor-Leste among INTERFET troops, the once a week dosage and a perceived better side effect profile than mefloquine.

b. There was reasonable justification to undertake a study of the use of mefloquine, an already approved and registered antimalarial drug, given the lack of any significant long term studies of mefloquine in an operational field setting and the need to test whether known neuropsychiatric (as opposed to neurotoxic) side effects would impact on the operational effectiveness of Australian soldiers.

c. The medical support provided to the participants before, during and following the two studies was appropriate and there was no evidence that any medical issue at the time was not followed up with appropriate and proper medical care.

d. Soldiers were not compelled or coerced by command to participate in the antimalarial drug studies, and all were appropriately informed of the side effects and that the studies were voluntary.

e. There was no failure by the investigators to disclose neurotoxic effects of the medications.

138. The Inquiry made three recommendations:

a. "Joint Health Command consider a mechanism to ascertain whether any other participants in the 2000 to 2002 AMI studies who took mefloquine…may have had a history of a health condition, which would have been a contraindication to mefloquine use. This would ensure that any previous health condition inconsistent with the prescription is identified, and where necessary possible treatment provided through the Department of Veterans' Affairs (DVA) or Defence."[97]

b. "In future medical studies involving Defence personnel, study investigators be given access to the Defence eHealth System to enable any relevant medical history of

[95] Inspector General ADF. *Inquiry Report into issues concerning antimalarial trials of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*. 2016, p 1. Available at http://www.defence.gov.au/Publications/COI/Docs/COI-AntiMalarialTrials.pdf
[96] Ibid, Findings 2 and 3, p i
[97] Ibid, p iii

contraindicators to be identified at the time of obtaining a Defence member's consent to participate in the study."[98]

c. "The ready acceptance by soldiers of advice or encouragement provided to them by military persons in authority, combined with a potential belief that participation in the study was expected is an issue worthy of further consideration in the conduct of any future medical studies, particularly in the context of a pre-deployment for an overseas operation"[99].

139. Defence responded to these recommendations as follows:

a. As members' medical records of that time period are in hard copy it was deemed impractical to review every case. In addition, such a finding was unlikely to have a bearing on the current management of individuals. Instead, JHC took the approach to review the medical records of all those writing to seek information on their participation in the studies. A finding of pre-existing health conditions of concern has only been made in a small number of cases. This information is also available to DVA for any member making a claim.

b. The Defence eHealth System (DeHS) was implemented in 2014 and provides ready access to a member's health documents in both the garrison and deployed environment. This will allow any current and future medical researchers to review the member's records before prescribing a medication.

c. The issue of informed consent in military populations is a consideration of every proposal examined by the new Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC)[100] and is covered under the National Statement on Ethical Conduct in Human Research (see paragraph 114).

Repatriation Medical Authority

140. The RMA is an independent statutory body, established under the Veterans' Entitlement Act, comprising five medical practitioners who are eminent in their fields of medical science. The RMA's role is to determine the Statements of Principles (SOPs) for any injury, disease or death that could be related to Australian Defence Force service. The SOPs are legislative instruments that list the factors that can cause certain medical conditions, and are based on national and international medical-scientific evidence. The SOPs are used by DVA in the assessment of compensation claims under two of its three Acts. They are periodically reviewed by the RMA.

141. Prior to 2016, antimalarials were recognised in 11 SOPs as a causal or aggravating factor, including for the onset and worsening of depressive disorder and bipolar disorder. In April 2015, the then SGADF wrote to the RMA to request whether they would consider inclusion of mefloquine under other SOPs (Annex N). The letter included a copy of an unpublished paper by then Major Stuart McCarthy, in which he highlighted a potential association with minor traumatic brain injury (concussion) and posttraumatic stress disorder (PTSD). The letter states "Whilst I cannot identify any scientific evidence to support a causal relationship it may be appropriate to examine these SOPs as well".

142. The RMA advised that it would conduct reviews in respect of three SOPs: anxiety disorder, panic disorder and suicide and attempted suicide. A review of the SOPs for

[98] Ibid, p iii
[99] Ibid, p vi
[100] The Government's "Smaller Government - Towards a sustainable future" Ministerial Paper proposed a merger of ADHREC it with the DVA HREC. This was formally actioned on 1 Jul 17. The Ministerial Paper is available at: https://www.financeminister.gov.au/sites/default/files/publications/towards-a-sustainable-future.pdf

schizophrenia was notified at the same time in response to a separate, unrelated request. The SOPs for anxiety disorder were amended to include substance/medication induced anxiety disorder (SMIAD) in the definition, and also listing relevant drugs (including mefloquine) as factors (amendments 99 and 100/2016). The panic disorder SOPs were not amended on the grounds that if exposure to a drug/medication/substance results in a panic attack, even in someone who has a panic disorder diagnosis, the appropriate diagnosis would be SMIAD and the relevant SOP would be the anxiety disorder SOP. The SOPs for suicide and attempted suicide were reviewed in full, and a factor for taking mefloquine was included in the new SOPs (65 and 66 of 2016). The SOPs for schizophrenia were also reviewed in full, and a factor for taking specified drugs (including mefloquine) was included in the new SOPs (83 and 84/2016).

143. In April 2016, as an outcome of the Townsville forum (paragraph 130a), the current SGADF wrote to the RMA asking that they also examine an association between tafenoquine and any conditions that had SOPs that included primaquine and chloroquine as causal or aggravating factors, on the basis that tafenoquine may share similar side effects to other drugs in its class (Annex O). The RMA responded by letter on 24 Jun 2016 and advised that it would not undertake a review on the basis that "…tafenoquine was already covered in the SOPs for six conditions, with the factors expressed as 'quinine derivatives', antimalarials'…etc" – that is, a "drug class effect". (Annex P). It also stated that SOPs for nine other conditions that listed primaquine or chloroquine but did not cover tafenoquine (on the basis of the 'drug class effect') would not be reviewed as there was no existing literature at that time that provided evidence of an association with these conditions.

144. In February 2017, the RMA agreed to notify an investigation into chemically-acquired brain injury, following a request from the President of the Repatriation Commission and the Chair of the Military Rehabilitation and Compensation Commission. The investigation was completed in August 2017, and found that there is insufficient sound medical-scientific evidence to determine that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury[101]. Subsequently, the Repatriation Medical Authority has declared that it does not propose to make a Statement of Principles concerning chemically-acquired brain injury caused by these antimalarial medications.

145. An application has been made to the Specialist Medical Review Council to review the RMA decision not to create SOPs for chemically-acquired brain injury. Defence understands that this review is ongoing.

Outcomes from the Senate Inquiry into the Mental Health of Australian Defence Force members and Veterans (2015)

146. The 2015 Senate Inquiry into Mental Health heard evidence from several individuals about the alleged health concerns relating to mefloquine use. Tafenoquine does not appear to have been raised in this evidence. The Committee made two recommendations relating to this matter[102].

a. **Recommendation 5:** *The committee recommends that Defence and DVA contact ADF members and veterans who have been administered mefloquine hydrochloride*

[101] Repatriation Medical Authority. *Statement of Reasons Re: decision not to make Statements of Principles for chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine*. Available at: http://www.rma.gov.au/assets/Other/4a9cc6832a/RMA-Statement-of-reasons-chemically-acquired-brain-injury-29-August-2017.pdf

[102] Senate Standing Committee on Foreign Affairs Defence and Trade. *Mental health of Australian Defence Force Members and veterans*. Available at: https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Foreign_Affairs_Defence_and_Trade/ADF_Mental_Health/Report

(mefloquine) during their service to advise them of the possible short-term and long-term side effects and that all ADF members and veterans who have been administered mefloquine during their service be given access to neurological assessment.

b. **Recommendation 6:** *The committee recommends that the report for the Inspector General of the Australian Defence Force's inquiry to determine whether any failures in military justice have occurred regarding the Australia Defence Force's use of mefloquine be published immediately following the completion of the inquiry.*

147. Recommendation 5 was agreed in principle by the Government, in that "…ADF members and veterans who have been administered mefloquine should continue to be advised of its possible side effects, and agrees that appropriate neurological assessments should continue to be available", noting that neurological assessments were already available to both groups[103]. The Response outlined the outreach activities that had already been undertaken and also outlined four specific new activities. Defence has supported DVA in undertaking these commitments with oversight by the DVA-Defence Links Committee, including:

a. Provision support to the DVA mefloquine outreach program in Townsville in December 2016[104].

b. Provision of advice to Government that included the directed requirement to "…examine the issues raised, (and) consider existing relevant medical evidence…". This was provided in the form of a report on 4 November 2016.

148. Recommendation 6 was noted and the report has been published (see paragraphs 135 to 139).

Comcare Review

149. In 2016 a complaint about Defence studies and the use of mefloquine was made to Comcare. Comcare internally reviewed the complaint and provided a copy of the review to Defence with a recommendation that Defence undertake follow-up and surveillance of any neuropsychiatric side effects of mefloquine use occurring in current and past ADF members.

150. Defence provided a response to Comcare on 13 April 2016 regarding its response to the concerns raised (Annex Q). Comcare responded that they were "…confident that Defence is taking reasonably practicable steps to ensure the safety of its workers in the use of Mefloquine[105]".

[103] Australian Government Response to the Foreign Affairs, Defence and Trade Committee Report. Available at: https://www.dva.gov.au/sites/default/files/files/publications/corporate/Australian%20Government%20Response%20Senate%20Inquiry%20Mental%20Health.pdf
[104] Department of Veterans' Affairs. Townsville mefloquine outreach program. VetAffairs, Vol 33 No.1, Autumn 2017. Available at: https://www.dva.gov.au/about-dva/publications/vetaffairs/vol-33-no1-autumn-2017/townsville-mefloquine-outreach-program
[105] Comcare. Official Correspondence to SGADF (email), 17 May 2016

TERM OF REFERENCE 1 – Current and past prescribing policies and practices

151. Antimalarial medications are part of a suite of protective measures to prevent malaria. The medication prescribed will depend on the likelihood of compliance with drug ingestion, the potential or known side effects of the drug(s), and the efficacy of the medication in specific regions. These considerations are developed as part of the general planning for particular operations and are articulated in the Health Support Plan.

152. The majority of prescriptions for antimalarial medications in Defence are given as indicated in the Health Support Plan for a particular operation or exercise. Some are also given for travel into malarious areas outside of deployments, such as business or holiday travel and routine postings.

153. Defence antimalarial policies have evolved over a number of years but doxycycline has consistently been the antimalarial medication of choice for prevention since the early 1990s.

154. A summary of the evolution of Defence malaria policies is at Annex R. The 2000 policy, which was current during the initiation of the ADFMIDI studies is at Annex S, and the current policy from 2013 is at Annex T. The policy is currently under review with a new version expected to be published in late 2018.

Mefloquine

155. As mentioned previously in this submission, Defence has consistently been conservative in its use of mefloquine, only using it in individuals who could not tolerate the first and second line antimalarials or as part of a study. Defence's practices have differed from many other militaries, who have not only used mefloquine as a first line medication for prevention against malaria in some regions, but have also sometimes used the medication without face-to-face consults or individual prescriptions.

156. Defence policies on the prescription of mefloquine have consistently been informed by the manufacturer's PI, national and international best practice guidelines and available scientific evidence applicable at the time. As the global experience with, and understanding of, mefloquine has evolved over the years, so too have recommendations for its use, as articulated in Center for Disease Control and Prevention (CDC) guidelines and reflected in Defence health policy on malaria prevention. The manufacturer's PI has also been refined over time to reflect increased knowledge about side effects and precautions.

157. As mefloquine is taken weekly, it takes several weeks for it to reach protective levels in the body. This is a problem for getting forces ready for deployment at short notice and so Defence uses a loading dose prior to deployment to achieve protective levels more quickly. This involves taking one dose on each of three days in the week before deployment. This also allows any side effects to be seen before deployment and the medication stopped if necessary.

158. The Lariam™ PI in Australia does not specifically recommend a loading dose of mefloquine, however, states that prevention of malaria with Lariam should be initiated one week before arrival in a malarious area. Product information varies from country to country; for example, the Lariam™ PI for New Zealand, specifically recommends a loading dose for "last-minute" travellers[106]. The CDC recommends that mefloquine be started two or more weeks before

[106] See New Zealand PI for Lariam™ on the New Zealand Medicines and Medical Devices Safety Authority website: http://www.medsafe.govt.nz/profs/datasheet/l/lariamtab.pdf

entering a malarious area and does not specify a maximum duration of treatment, judging it to be suitable for long term prevention[107].

Tafenoquine

159. Defence policy has never included the use of tafenoquine. This antimalarial has only ever been used by Defence in the studies mentioned earlier in this submission, and in accordance with both the ADMEC and later ADHREC approved protocols and NHMRC National Guidelines.

[107] See CDC Fact Sheet at: https://www.cdc.gov/malaria/resources/pdf/fsp/drugs/mefloquine.pdf

TERM OF REFERENCE 2 – Current and past policies and practices for identifying and reporting adverse drug reactions

160. Policies and practices for reporting drug reactions are different for clinical study situations and in general clinical practice.

161. Care must be taken when interpreting various studies or reports on drug safety. This particularly relates to the reporting of 'Adverse Events' and 'Adverse Effects' (also known as 'side effects'). Whilst these terms sound similar, their meaning is very different. An 'Adverse Event' refers to an untoward occurrence associated with (but not necessarily caused by) a medication. Most clinical drug studies report all 'Adverse Events' that are detected during the conduct of study, whether a causal relationship has been established or not. For example, records from the mefloquine and tafenoquine studies include adverse events such as 'spider bites' which are obviously not related to the use of medication. In contrast, an "Adverse Effect" is an occurrence where a causal relationship is assessed as likely or possible. Often in order to establish such causality substantial further research and analysis is required especially if the event is unexpected or not explainable by the general understanding of how the particular medication works.

During Research

162. In research studies, particularly clinical studies or studies of medication safety and tolerability, identification of adverse effects is actively sought. As detailed in paragraph 117, participants in the ADFMIDI (then AMI) antimalarial studies were closely monitored, regularly reviewed and asked specific and/or open ended questions about possible effects of the medication. This allowed participants to report any symptoms, injuries or events that may or may not have been related to the medication. A report in and of itself does not infer causality, only that the symptom, injury or event was experienced. They also underwent a number of medical tests during the course of the study and in some cases for some months afterwards (see paragraph 118)

163. The National Statement on Ethical Conduct in Human Research requires that researchers regularly report progress of the research project to the human research ethics committee that approved it. It also requires that any serious adverse events be reported on occurrence so that a decision can be made as to whether the research should continue. Researchers using unregistered medicines (eg. tafenoquine) are also required to report adverse events to the study sponsor and medical monitor. In 2001, vortex keratopathy was identified in ADF members who had taken long term tafenoquine (six months). This was reported to the TGA and the study sponsor. This resulted in the concurrent use of tafenoquine for treatment of malaria being suspended by the sponsor (see paragraph 107c). Subsequent follow up of the individuals affected determined that the condition was benign and reversible.

In clinical practice

164. Reporting of adverse events following administration of any medication, particularly new, unexpected or serious adverse events, is encouraged both in the Australian community and in Defence. The TGA has had an adverse event reporting scheme, the DAEN, in place for many years through which anyone can make a report (see paragraph 69). Defence policy mandates the reporting of actual and suspected adverse drug reactions by health staff to both the TGA and JHC. A copy of the current policy is at Annex U. The JHC Pharmacy and Therapeutics Committee (PTC) monitors adverse drug reaction reports made within Defence. PTC records indicate no adverse drug reports have been received for mefloquine. As tafenoquine has not been prescribed

in clinical practice, as it is still an unregistered medicine, the PTC has received no reports relating to this medication.

165. As detailed in paragraph 119 to 125, an ADF member has access to comprehensive health care and undergoes regular assessments during the course of their career. This allows for early identification of health problems or reporting of any possible symptoms, including side effects of any medications they may be taking. They also undergo mental health screening.

166. Defence health policy regarding malaria has consistently provided guidance regarding potential side effects of each antimalarial medication, based on what was known at the time, and on reporting of adverse events. From 1994, guidance was also provided about monitoring ADF personnel on these medications, particularly those on long term doxycycline. This guidance was refined and expanded over the years in line with advances in knowledge and the global understanding of these medications. From 2006, the policy more explicitly articulated the need for ADF members to promptly report any adverse effects to their medical officer and the health monitoring requirements of ADF members on long term prevention.

TERM OF REFERENCE 3 – The nature and extent of any adverse health effects in ADF personnel

167. Defence has always acknowledged that mefloquine can cause side effects, including neuropsychiatric problems, while individuals are taking the drug. This is why Defence is conservative in its use of this drug and ensures that members are aware of the side effects before prescribing it. These symptoms usually disappear when the drug is stopped but can persist for some time afterwards due to its long half-life. Rarely these symptoms can continue long after the drug has been ceased and become long term problems. There have been no cases in the literature where healthy individuals suddenly develop neuropsychiatric effects many years later. In relation to tafenoquine, while Defence acknowledges that mild and moderate neuropsychiatric side effects have been reported in individuals participating in tafenoquine studies, it is not aware of any clear evidence that tafenoquine produces serious neurotoxic or neuropsychiatric side effects, including in the long term.

During the Studies

168. The adverse events experienced by ADF members while taking the medication during the mefloquine and tafenoquine studies are well documented in the literature and summarised in Annex V.

Mefloquine

169. The most common side effects of those taking mefloquine during the Defence studies were sleep disturbance, headache, tiredness and nausea. As previously mentioned, three serious adverse events of a neuropsychiatric nature were noted during the mefloquine versus doxycycline study. In one of these cases it was the first time that the participant had experienced these symptoms. The two other individuals had a previous history of mental health concerns and appear not to have declared this to researchers[108]. They would not have been given the medication if this history had been known.

170. In reviewing cases over the past few years, Defence has uncovered a small number of cases of other individuals who were included in the mefloquine studies despite having a history of mental health issues. This included a case that was raised by the spouse of a former serving member during a story on the ABC's 7.30 program. In all cases Defence acknowledged the error, apologised, and offered to provide assistance to help access support services and engage with DVA[109].

171. A review of these subsequently identified cases found that the extant technological constraints significantly contributed to these oversights, with doctors involved in the briefing, consent and prescribing process for the studies unable to access the paper medical records of individuals. This reliance on individual members to identify significant conditions was far from ideal, but reflects an unfortunate reality of the time. It should be noted that the consent form for the study clearly states 'If you have had any anxiety attacks or serious depression in the past you also may not be able to use mefloquine. If you have experienced this type of reaction…please

[108] Kitchener S, Nasveld P, Gregory R, Edstein M. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. *Med J Aust* 2005; 182 (4): 168-171.
[109] Welch, D. *ADF admits soldier shouldn't have been included in East Timor anti-malaria drug trial,* 7:30 Report, posted 22 Aug 2016, video and transcript. Available at: http://www.abc.net.au/news/2016-08-22/adf-admits-soldier-should-have-been-excluded-anti-malaria-test/7772322

discuss this with the (study) Medical Officer'. Fortunately the development of the Defence electronic health record (DeHS) now greatly reduces this reliance on the individual to self-declare significant health issues. The DeHS now allows all Defence health personnel access to a current and comprehensive medical record irrespective of location in Australia and on fixed bases in deployed settings. This will ensure that medical officers have more awareness of a member's history and pre-existing health conditions in future studies

Tafenoquine

172. The most common side effects of the tafenoquine prevention study were nausea, vertigo, diarrhoea, abdominal pain, abnormal dreaming and somnolence (drowsiness) [110]. 18 (4%) severe adverse events were recorded in the prevention study. These were not all necessarily drug related; for example three were injuries and six were gastroenteritis. No major side effects were observed in the eradication study and no severe neuropsychiatric adverse events were observed in any individuals taking tafenoquine in Defence.

Long term health effects

173. Defence has only identified two instances in which members may have had long term, continuing neuropsychiatric side effects after ceasing mefloquine, and no cases among those who took tafenoquine. Both of the members were provided with appropriate treatment while in Defence.

174. Defence only has information on the health of ex-serving members who participated in the antimalarial studies from during their period of service and does not have details on their current health status. Case reviews indicate that many individuals continued to serve in the ADF, and even deployed on operations, long after they had taken the antimalarial in question. Given Defence's comprehensive health care, surveillance and medical review system any long term effects of the medications should have been evident well before these individuals transitioned from service. It should also be noted that, while the vast majority of study participants have left full time service, many others continue to serve and remain fit and healthy.

Suicide database

175. The ADF suicide database includes all suspected and confirmed deaths by suicide in serving members since 2000. A review of the database has revealed two individuals who were prescribed mefloquine[111]. One of these individuals was involved in the Timor-Leste studies and the other was prescribed it for routine prevention. Both deaths occurred more than 15 years after they had taken mefloquine and there was nothing in their clinical history that would implicate mefloquine as a causal factor in these deaths[112]. Both members had remained medically fit for a prolonged period after they took the medication, and deployed on multiple subsequent occasions.

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[110] Nasveld P, Edstein M, Reid M, Brennan L, Harris I, Kitchener S, Leggat P, Pickford P, Kerr C, Ohrt C, Prescott W, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrob Agents Chemother*. 2010 Feb;54(2):792-8.

[111] The total number of individuals on this database is 135 as of 13 July 18

[112] Both RMA SOPs related to suicide or attempted suicide only include 'taking mefloquine' as having a possible connection with the outcome when the event occurs within three months ('SOP 66 – balance of probabilities') or six months (SOP 65 – 'reasonable hypothesis') of taking the medication. These SOPs can be downloaded at https://www.legislation.gov.au/Details/F2018C00152/Download (SOP66) and https://www.legislation.gov.au/Details/F2018C00189 (SOP 65)

Analysis of Medical Data

176. Due to the concerns raised about the use of mefloquine, Defence conducted an internal analysis of its Medical Employment Classification (MEC) data in early 2016 to determine whether there was an association between being prescribed mefloquine and being at increased risk of either being medically discharged or developing Post Traumatic Stress Disorder (PTSD). The purpose of this quick analysis was to uncover any apparent trends in fitness for service or PTSD in this group that would indicate further investigation or research was warranted.

177. The analysis of individuals participating in the studies showed that there was no significant difference in the number of members who were unfit for service between the group who had taken mefloquine and the group who had not. It was also found that there was no significant difference in the number of PTSD cases between those taking mefloquine and those not taking mefloquine in any of the studies or when all the studies are combined.

178. The main limitation on this analysis is that the clinical history of individuals who discharged prior to 2007 was not readily available due to limitations in the Defence database. In addition, no information relating to the medical status of individuals post separation from the ADF was available for the analysis. However, it was considered that a trend should have been detected if there was truly a major public health concern associated with taking mefloquine during Defence studies.

Further research

179. Defence has been, and continues to be, supportive of research into ADF members who have taken antimalarials, including mefloquine and tafenoquine. Defence and DVA have recently jointly funded a research project on 'Self-reported health of ADF personnel after use of antimalarial drugs on deployment', to be conducted by the University of Queensland (UQ) utilising de-identified data extracts from the Bougainville, Timor-Leste, and Solomon Islands deployment health studies. Study participants were asked what antimalarial they had used as part of these studies, which were conducted in 2007 and 2008.

180. The study will examine the following research questions:

a. Did deployed veterans who reported taking mefloquine have different rates of mental and general health outcomes compared to veterans who reported taking doxycycline or other antimalarials?

b. Did deployed veterans who reported taking primaquine on return to Australia have different rates of mental and general health outcomes compared to veterans who did not?

c. Did deployed veterans report a significant reaction to specific medications received during their deployment or raise use of antimalarial drugs as an area of concern in response to open ended questions?

181. This research project received approval from the DDVA HREC on 22 May 2018 and the contract with UQ was signed on 31 May 2018. The final report is due in November 2018.

TERM OF REFERENCE 4 – Support available for partners, carers and families of personnel

182. Defence recognises that good health and resilience are fundamental to the wellbeing of ADF members and their families. Due to the unique demands of military service, Defence continues to support members and their families throughout their service career and during their transition to civilian life.

Specific support to families concerned about antimalarial use

183. Defence continues to invite any current or former serving members and their families with concerns to contact the email address: adf.malaria@defence.gov.au. As noted, Defence has also developed a comprehensive external website (*Malaria, Mefloquine and the ADF*[113]) that allows anyone to freely access a variety of information if they have concerns. Further support and information is also available from DVA by calling their help line (1800 555 254) and asking to speak with the DVA mefloquine claim team, or by emailing client.support@dva.gov.au.

Other Support to Families

The ADF Family Health Program

184. The provision of basic healthcare to the dependants of permanent ADF members and dependants of Reservists on Continuous Full Time Service (CFTS) was an initiative of the Commonwealth Government as identified in "Labor's Plan for Defence" November 2007. The initiative formed part of the Government's retention and recruitment strategy for Defence. The Government introduced the National ADF Family Health Program in 2014.

185. The National Program provides registered families financial support for their basic healthcare needs. The National Program provides the following benefits to eligible dependants:

a. The reimbursement of the full gap for all services with a Medicare Benefit Schedule item number accessed in a general practice, and

b. A financial year allocation of $400 per dependant to use toward specialist consultations or a range of allied health services.

186. As 28 June 2018 48,684 dependants representing 20,683 ADF Families are registered for the National Program.

General Support Services

187. Defence works hard to further enhance relationships with Ex Service Organisations (ESO) to assist ADF members and their families throughout their military careers, and help facilitate the transition of ADF members back into the community. ADF members and their families are made aware of the services and support available through ESOs throughout their ADF career via various mechanisms such as regional Welcome Events, base open days, unit family days, structured briefings and regional level partnerships.

[113] Defence's *Malaria, Mefloquine and the ADF* is at:
http://www.defence.gov.au/Health/HealthPortal/Malaria/default.asp

188. Additional support available to ADF members and their families includes a range of telephone helplines that provide triage services inclusive of mental health. These helplines include the All-Hours Support Line, and DCO's Defence Family Helpline.

189. The All-hours Support Line (ASL) is a confidential telephone service for ADF members and their families that is available 24 hours a day, seven days a week. It is designed as a triage line to help members and their families access ADF or civilian mental health services more easily. JHC has contracted VVCS to provide this service. If the caller's issue requires emergency assistance it is initiated immediately. If it requires referral to a Garrison Health Centre that referral is processed to the closest on-base Health Centre the following day.

190. The Defence Family Helpline provides ADF members, their partners, children and relatives support from a social worker or other human services professionals. The helpline is available all hours and international free call numbers are also available. Partners of ADF members and other family members requiring long term assistance or specialist services including mental health services can be connected to VVCS or other specialist support services available in their local community.

191. The VVCS provides free and confidential counselling and mental health support to current and former ADF members with at least one day of service, along with their partners and children. VVCS provides direct counselling and support through an integrated 24/7 national network, including 25 centres located across Australia, and a network of more than 1,200 outreach counsellors nationally.

192. They also offer a wide range of other education support services for Defence children including specialised staff to advise families on education issues, financial assistance for education costs incurred by relocation, resources for relocating students and information about the different state and territory schooling systems.

193. In May 2018, the Family Support Package was introduced, which provides extended child care assistance and counselling for the immediate family members of veterans who have served in recent overseas conflicts. It also provides support to spouses/partners of veterans who have died during or upon return from warlike service through the provision of counselling, child care and household assistance.

ADF Transition Support

194. Defence provides a transition support service for all permanent ADF members or Reservists on Continuous Full Time Service leaving the ADF, and their families which is coordinated and delivered by the Defence Community Organisation (DCO). Services provided include personalised assistance to prepare for transition, referrals to appropriate support, and assistance with administration. ADF Transition services are delivered through 13 ADF Transition Centres nationally. ADF Transition services are also delivered at outreach centres in remote locations.

195. In July 2017, Defence implemented a new ADF Transition business model which enhanced the existing transition process by delivering, in addition to administrative elements, individualised career coaching and mentoring services to ADF members and their families and referrals to further support and services.

196. ADF Transition coaches work with ADF members and their families to develop an individualised Transition Action Plan, with a focus on career development, finding employment, continuity of healthcare, family support and social connectedness.

TERM OF REFERENCE 5 – International evidence/literature available on the impact of Quinoline antimalarials

197. Medical research is usually subject to peer review, where independent qualified and experienced medical professionals review the quality and suitability of a proposed article prior to publication in a medical journal. Articles range from large meta-analyses of all available literature, to large cohort studies with statistical significance, through to case reports on one or few patients. Non-scientific articles including opinion pieces and newspaper articles are often used by anti-mefloquine advocates to argue specific points, however, do not necessarily represent evidence.

Mefloquine

198. A large body of literature exists regarding the use, efficacy and side effect profile of mefloquine. The size and extent of this literature is one of the reasons that Defence commissioned a review by Professor McFarlane in early 2016 (Annex K). The major findings of this review were:

a. There are various theories on how mefloquine might cause neuropsychiatric effects based on its underlying action.

b. There are varying conclusions about its potential toxicity.

c. These variations are, in part, explained by the differences of the methodology used in the published reports.

d. The serious side effects of mefloquine have been known for many years, but continuation of effects after ceasing medication is a concern raised in recent years.

e. There is no specific way to diagnose chronic mefloquine effects as many symptoms are shared with other conditions such as PTSD.

f. There is no specific treatment except to cease the drug when symptoms develop and to treat the symptoms.

g. The literature available at the time of this review does not address some questions, including:

   i. Are some individuals pre-disposed to adverse effects?

   ii. Does mefloquine modify the response to trauma?

Systematic Reviews

199. One of the most powerful forms of evidence are large systematic reviews, which aggregate the data from a number of studies, in order to increase the statistical power available to make findings which may have not been obvious in the individual studies. The largest, and probably most respected, organisation that conducts these reviews is the Cochrane Library. Two such reviews have been undertaken on mefloquine (and one on tafenoquine).

200. **Mefloquine for preventing malaria during travel to endemic areas**[114]**.** This review attempted to summarise the efficacy and safety of mefloquine used for prevention for malaria in

[114] Tickell-Painter M, Maayan N, Saunders R, Pace C, Sinclair D. Mefloquine for preventing malaria during travel to endemic areas. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD006491.

travellers. The review looked at a large body of literature, including 20 Randomised Controlled Studies (RCT) (11,470 participants); 35 cohort studies (198,493 participants); and four large retrospective analyses of health records (800,652 participants). Nine RCTs explicitly excluded participants with a psychiatric history, and 25 cohort studies stated that the choice of antimalarial agent was based on medical history and personal preference. Most RCTs and cohort studies collected data on self-reported or clinician-assessed symptoms, rather than formal medical diagnoses. While all studies looked at both efficacy and safety, the following is focussed on the latter.

201. *Mefloquine safety versus atovaquone-proguanil.* Participants receiving mefloquine were more likely to discontinue their medication due to adverse effects than atovaquone-proguanil users. There were few serious adverse effects reported with mefloquine (15/2651 travellers) and none with atovaquone-proguanil (940 travellers). Based on the available evidence, best estimates of absolute effect sizes for mefloquine versus atovaquone-proguanil are 6% versus 2% for discontinuation of the drug, 13% versus 3% for insomnia, 14% versus 7% for abnormal dreams, 6% versus 1% for anxiety, and 6% versus 1% for depressed mood.

202. *Mefloquine safety versus doxycycline:* No difference was found in numbers of serious adverse effects with mefloquine and doxycycline or numbers of discontinuations due to adverse effects. Mefloquine users were more likely to report abnormal dreams, insomnia, anxiety, and depressed mood (all low or very low uncertainty evidence due to the number of reports). The findings of the single cohort study reporting adverse events in short-term international travellers were consistent with this finding but the single RCT in military personnel did not demonstrate a difference between groups in frequencies of abnormal dreams or insomnia. Mefloquine users were less likely to report dyspepsia, photosensitivity, vomiting, and vaginal thrush. Based on the available evidence, best estimates of absolute effect for mefloquine versus doxycyline were: 2% versus 2% for discontinuation, 12% versus 3% for insomnia, 31% versus 3% for abnormal dreams, 18% versus 1% for anxiety, 11% versus 1% for depressed mood, 4% versus 14% for dyspepsia, 2% versus 19% for photosensitivity, 1% versus 5% for vomiting, and 2% versus 16% for vaginal thrush.

203. Only three serious adverse events were reported from six RCTs, none of which were attributed to the drug regimen (1/592 mefloquine users versus 2/629 placebo; 6 studies; 1221 participants). By comparison in cohort studies, seven serious adverse effects (all attributed by study authors to the drug regimen) were reported among 913 mefloquine users, compared to none in 254 travellers who did not use antimalarials (2 studies, 1167 participants), although the difference was not statistically significant. Five of these were psychological (depression) and two were neurological adverse effects (dizziness).

204. The authors concluded that the absolute risk in short-term travellers appears low with all three established antimalarial drugs. The choice of which drug to use would depend on how individual travellers weighed up the importance of specific adverse effects, pill burden and cost. For example the once-weekly dosing of mefloquine, versus the increased frequency of abnormal dreams, anxiety, insomnia and depressed mood.

205. **Deaths and parasuicides associated with mefloquine chemoprophylaxis (prevention): A systematic review.** A previous edition of the Cochrane Review on mefloquine included a table in an annex relating to mefloquine and death. The Cochrane Infectious Diseases Group editorial team audited this table, which listed case reports of deaths, and deaths due to suicide that had been attributed to mefloquine[115]. Some of the sources listed related to when the drug was used in treatment of malaria at notably higher doses than that used for prevention; others counted deaths

[115] Tickell-Painter M, Saunders R, Maayan N, Lutje V, Mateo-Urdiales A, Garner P. Deaths and parasuicides associated with mefloquine chemoprophylaxis: A systematic review. *Travel Medicine and Infectious Disease* 20 (2017) 5–14

in reviews that were not verifiable; and a number of other errors and double counting were observed across reviews. The Co-ordinating Editor of the Group made the decision to withdraw the review because this information appeared misleading.

206. The updated review included publications up to 11 Jul 2017 and identified 2523 citations of which 71 studies mentioned mefloquine being potentially linked to death or parasuicide. Of these 17 were unique publications reporting death or parasuicide and eight had sufficient detail to make a causality assessment. Nine additional publications searched spontaneous drug reporting databases but none provided sufficient detail to assess causality. The difficulty in the assessment of causality was noted as a limiting factor in many of the reports assessed.

207. Two deaths were identified with a probable association and were classified as idiosyncratic drug reactions (rare and unpredictable reactions, not usually dependent on the dose) due to pulmonary fibrosis (a lung disease), and exfoliative illness (a skin disease similar to dermatitis) with neutropaenia (reduced white blood cells). Eight deaths were categorised as either "unlikely" or "unclassifiable"; and one parasuicide was classified as having a "possible" causal relationship although there was no information available on past medical history or other medication.

Military Studies

208. Most studies on mefloquine effects have been undertaken on civilian travellers, however, two large and significant studies have occurred in US military populations.

209. A retrospective analysis of US military health records between 2002 and 2004 was undertaken to examine the adverse events of antimalarials[116]. It compared numbers of hospitalisations in military personnel who had been prescribed mefloquine and were deployed to active duty in malarial areas (8,858 personnel), with those who had not taken mefloquine and either resided in Europe or Japan (156,203 personnel), or had been otherwise deployed (232,381 personnel). Mefloquine users were statistically less likely to be hospitalised (after deployment) with mood disorders, or for any cause, than military personnel who did not receive any antimalarial agents but who were deployed to a war zone.

210. A more recent study looked specifically at the occurrence of neuropsychiatric outcomes in military members who were prescribed mefloquine compared with other antimalarials from the period 1 January 2008 to 30 June 2013[117]. A total of 367,840 individuals were evaluated, of which 36,538 received mefloquine, 318,421 received doxycycline, and 12,881 received atovaquone/proguanil. This study relied on medically diagnosed neuropsychiatric outcomes, rather than self –reported symptoms as used in many other studies. The study found that:

a. Deployed members on mefloquine had an increased risk of anxiety compared with doxycycline recipients.

b. Conversely, non-deployed cohorts demonstrated a statistically significant protective effect of mefloquine compared doxycycline for adjustment disorder, insomnia, anxiety disorder, depressive disorder, vertigo and PTSD. The mefloquine cohort did not demonstrate a statistically significantly elevated risk for any outcome.

c. Non-deployed members on mefloquine had an increased risk of PTSD compared with atovaquone/proguanil recipients.

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

[117] Eick-Cost A, Hu Z, Rohrbeck P, Clark L. (2016). Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members. *American Journal of Tropical Medicine and Hygiene*. 96(1):159-166

d. Both deployed and non-deployed members on mefloquine had an increased risk of tinnitus (ringing in the ears) compared with atovaquone/proguanil recipients.

e. Six percent of the mefloquine cohort had a neuropsychiatric issue in the year before receiving mefloquine. When comparing these members to those without a history of neuropsychiatric problems, the ratio of relative risks for adjustment disorder, anxiety, insomnia, and PTSD were higher (not statistically significant) for mefloquine compared with doxycycline.

211. The study concluded that "on a population level, this study did not find an association between mefloquine and NPO (neuropsychiatric outcomes) among U.S. military service members, with the exception of anxiety, tinnitus, and PTSD for some sub-cohorts. Among service members with a history of a NPD (neuropsychiatric disorder) during the year before beginning prevention, mefloquine was associated with an increased risk of subsequent diagnosis of the same outcome". The same result was found for doxycycline. The study reinforced the requirement for appropriate medical screening before prescribing mefloquine.

Tafenoquine

212. Due to the fact that tafenoquine has not been registered, far less literature exits. A list of published studies, with a brief summary of each, is at Annex W.

213. The Cochrane Library conducted a systematic review in 2015 on the literature surrounding the use of tafenoquine as compared with primaquine in the prevention of the relapse of vivax malaria[118]. It found that there was no difference between tafenoquine and primaquine with regard to serious adverse events at a number of different dosage regimens. In addition, tafenoquine had good efficacy in preventing relapses of vivax malaria when used in total doses above 300mg, and may be better than primaquine. It was noted that, as tafenoquine could be given as a single dose versus the 14 day course of primaquine, this could provide a significant advantage in terms of compliance. The review paper suggested further research with increased numbers was required to confirm the results

214. The overarching theme emerging from the studies on tafenoquine is that the medication is well tolerated and has no evidence of increased adverse events compared with other antimalarials of long standing use (primaquine and chloroquine). There is no evidence in the literature of tafenoquine causing long term neuropsychiatric side effects. Interestingly a more recent randomised study of 120 volunteers taking 200mg of tafenoquine for 6 months did not demonstrate the previously described eye effects (vortex keratopathy)[119].

[118] Rajapakse S, Rodrigo C, Fernando SD. Tafenoquine for preventing relapse in people with Plasmodium vivax malaria. Cochrane Database Syst Rev. 2015 Apr 29;(4):CD010458

[119] Leary KJ, Riel MA, Roy MJ, Cantilena LR, Bi D, Brater DC, et al. A randomized, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. Am J Trop Med Hyg. 2009. Aug;81(2):356-62

TERM OF REFERENCE 6 – How other governments have responded to claims regarding Quinoline antimalarials

215. As mentioned earlier, Defence has had arguably the most conservative approach to the prescription of mefloquine of all allied militaries. Government inquiries that have examined the use of mefloquine in their military forces in both United Kingdom (UK) and Canada in recent years have referenced the fact that Australian Defence policy is more conservative than that of their militaries, both in using mefloquine as a third line antimalarial and also in enforcing more rigid prescribing practices.

216. A list of international and military guidelines for prevention of malaria is provided at Annex X. No governments have examined the use of tafenoquine as it is has not been registered for use in any country.

United Kingdom (UK)

217. The House of Commons Defence Committee conducted an Inquiry into the use of mefloquine in its armed forces and produced its final report, *An Acceptable risk? The use of Lariam for military personnel* on 10 May 2016. [120] In oral evidence to this committee, The Right Honourable Mark Lancaster MP, Minister for Defence Personnel, Welfare and Veterans, stated that there was "no single antimalarial that is effective for all the various and different strains, and nor is there a single antimalarial that is 100% effective or does not have any side effects" [121].

218. The UK Surgeon General, Vice Admiral Walker, explained to the Committee that the assessment of which drug to prescribe was based on a variety of factors, including "the person's ability to take the drug and their geographical location". The choice of which drug was used depended on the region to which personnel were being deployed and the individual's medical history, such as past history of side effects or contra-indications to the drug. He did note, however, that there was "no geographical area" where Lariam was "absolutely essential"[122].

219. During this inquiry Dr Nevin gave evidence that the ADF had long "de-prioritised" the use of mefloquine on the basis of its known neurological effects and used it as a "third-line" drug, or, like the US Armed Forces, a 'drug of last resort', for use "exclusively by those rare service members who cannot tolerate these two safer and equally effective alternatives"[123].

220. In terms of the requirement for research, the Ministry of Defence (MoD) highlighted that, while, there had been a number of studies into mefloquine in respect of civilian travellers, conducting studies of a similar scale on Service Personnel would be "unfeasible". Instead, it would continue to rely on the expert advice of the UK Advisory Committee on Malaria Prevention (ACMP) and international bodies such as the WHO and the CDC.[124]

[120] House of Commons Defence Committee. *An Acceptable risk? The use of Lariam for military personnel*. Fourth Report of Session 2015 – 2016, 10 May 2016
[121] Ibid, p 10
[122] Ibid, p 10-11
[123] Ibid, p 27
[124] Ibid, p 24

221. The Committee concluded: "The Ministry of Defence has a duty of care to protect military personnel on operations overseas. It includes ensuring that they are adequately inoculated against disease. This will never be without the risk of detrimental side effects, and we understand that the MoD must balance those risks against the health of our Armed Forces. However, in the case of malaria, we conclude that the MoD's current policy has got that balance wrong." [125] It was concluded by the Committee that the MoD should designate mefloquine as a 'drug of last resort' and that prescribing it should be restricted by the following conditions:

a. "Only to those who are unable to tolerate any of the available alternatives";

b. "Only after a face-to-face Individual Risk Assessment has been conducted"; and

c. "Only after the patient has been made aware of the alternatives and has been given the choice between Lariam and another suitable antimalarial drug."[126]

222. This guidance is consistent with Australian Defence policy, both current and historic.

223. In testimony to the Inquiry, Minister Lancaster, issued an apology to the "limited number" of former or current service personnel who did not have an individual risk assessment prior to receiving mefloquine.[127] It should be noted that he did not issue a blanket apology to all individuals who had received the drug.

Canada

224. On 29 September 2016, the House of Commons Standing Committee on Veterans Affairs passed a motion to undertake "a study on mental health focused on improving the transitional support between Canadian Armed Forces and Veterans Affairs". This study also included Mefloquine and its impact on the Mental Health of Canadian Military personnel and Veterans. The report of the Inquiry was published in June 2017[128].

225. During this Inquiry Brigadier-General McKay, Surgeon General of the Canadian Armed Forces, maintained that mefloquine should continue to be offered along with the other antimalarials, and emphasized that the rare instances of serious cases should not prevent other military personnel from benefiting from the drug. [129] He was also critical of the negative publicity the drug has received:

It's important to make sure that we consider all the available evidence and not rely on small bits of information, small groups of scientists who have opinions and theories, or jump to conclusions that might remove what has been recommended by the world experts as a useful antimalaria medication…We are also aware of the assertions of some regarding their theories that mefloquine might cause long-standing neurological damage and mental health issues, which they themselves suggest requires more research to support. Our assessment of their assertions, at this time, is that they are not sufficiently supported through direct scientific evidence for us to remove mefloquine as an option for patients to protect themselves from malarial infection, particularly if they have used it safely in the past.[130]

226. The review heard that Canadian service members deployed to at-risk areas had a choice of medications and that their informed consent is now clearly required if they choose mefloquine.

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[125] Ibid, p 32
[126] Ibid, p 33
[127] Ibid, p 30
[128] Ellis NR (Chair). *Mental Health of Canadian Veterans: A Family Purpose*. Report of the Standing Committee on Veterans Affairs, House of Commons Canada, June 2017.
[129] Ibid, p 27.
[130] Ibid, p 27.

This was not always the case in the past. Few now choose to take it and those who do must test its effects before they are deployed. They heard that only a minority of users experience serious enough effects that their mefloquine has to be replaced with a different drug and, although a warning about the long term effects is merited, there are still too few cases to outweigh the benefits of the drug.[131]

227. The Report made two recommendations regarding mefloquine related matters:

a. "That Veterans Affairs Canada reach out to members of the Canadian Armed Forces who served in Somalia, Rwanda, or other deployments in that time period, to ensure each is receiving the mental and physical health services and support, as well as Veterans Affairs Canada's benefits and programs to which they are entitled for their service."[132]

b. "That Veterans Affairs Canada cooperate with any institution concerned in any research program that would study the effects of mefloquine."[133]

228. During the same timeframe as the Inquiry, the Surgeon General of the Canadian Armed Forces conducted a review into the operational use of mefloquine, producing a Task Force Report[134]. The report stated that the Canadian Clinical Practice Guidelines for malaria prevention were consistent with other national and other international guidelines, and that mefloquine is a suitable antimalarial option in most endemic areas where doxycycline and atovaquone/proguanil are also considered as suitable choices.

229. The report did, however, recommended a change to the Canadian Armed Forces policy on malaria prevention, such that atovaquone/proguanil and doxycycline would be used as preferred antimalarial for prevention depending on resistance patterns. It was recommended that mefloquine was viewed as a less preferred option, when other alternatives were unsuitable or a person had previously tolerated it. Again this is consistent with Australian Defence policy.

United States

230. Defence is not aware of any recent US government discussions or hearings regarding mefloquine, although there have been recently been calls by several Veterans' agencies for Congressional hearings[135].

231. The Office of Secretary of Defence published a 2009 policy advising that doxycycline was the antimalarial of first choice, followed by atovaquone/proguanil, and that mefloquine use was restricted to only those personnel with contraindications to the other antimalarials[136], which is consistent with ADF policy. It further warned that it should be used cautiously in persons with a history of Traumatic Brain Injury or Post Traumatic Stress Disorder (PTSD) and other psychiatric diagnoses, such as depression, schizophrenia, and anxiety disorders.

232. Current US policy is that mefloquine "should be reserved for individuals with intolerance or contraindications to both first-line medications."[137] While the US Special Forces did

[131]Ibid, p 27.
[132] Ibid, p 26.
[133] Ibid, p 30.
[134] National Defence and the Canadian Armed Forces. *Surgeon General Taskforce Report on Mefloquine*. June 2017. Available at http://www.forces.gc.ca/en/about-reports-pubs-health/surg-gen-rpt-mefloquine.page
[135] MSN News. *Antimalarial drug prompts plea to Congress*, website, 19 June 2018. Available at: https://www.msn.com/en-us/news/politics/antimalarial-drug-prompts-plea-to-congress/ar-AAz1N2w
[136] Assistant Secretary of Defence for Health Affairs. Policy Memorandum: Policy Guidance on the use of mefloquine (Lariam™) for Malaria Prophylaxis 4 September 2009 . Available at: http://www.lariaminfo.org/pdfs/policy-memo-secy-defense%20malaria-prophylaxis.pdf
[137] Assistant Secretary of Defence for Health Affairs. Memorandum: Guidance on Medications for Prophylaxis of Malaria 15 April 2013.

temporarily cease using mefloquine in 2013[138], it is understood by Defence that they are also covered under the above policy.

Ireland

233. Mefloquine remains the first line antimalarial of the Irish Defence Force, particularly for deployments in sub-Saharan Africa.[139] The focus of local advocates has been to have it instead designated a "drug of last resort" [140], as is the policy in Defence. This is despite the fact that the commercial brand of mefloquine, Lariam™, was withdrawn from sale in Ireland in July 2016[141]. The pharmaceutical company said the decision followed a routine review of the products and was not related to the legal actions and that Lariam™ was still on the market in 16 other European countries[142]

234. No specific parliamentary inquiry into the use of mefloquine in the Irish Defence Force has been undertaken, however, the matter has been frequently raised in the Irish legislature. The government's response has been that

> *…fundamentally the choice of malaria chemoprophylaxis for use in the Defence Forces is a medical matter that should be decided by qualified medical professionals. In the Defence Forces these are decisions for highly qualified Medical Officers, having regard to the specific circumstances of the mission and the individual member of the Defence Forces.*[143]

235. A number of current and former serving members of the Irish Defence Force have submitted claims against the Defence Force. The Minister of State at the Department of Defence, Deputy Paul Kehoe, stated on 27 June 2017 that a total of 55 claims against the State had been received[144]. A claim was settled on 30th November 2017 without admission of liability[145]. The other cases are still pending.

Germany

236. On 19 January 2017 the Surgeon General of the German Armed Forces wrote a letter to the Canadian Surgeon General, which was copied to SGADF, regarding their use of mefloquine[146]. The letter outlined that, while the prescription practices of their medical officers had always been cautious, mefloquine had only become the third-line preventive antimalarial in 2013 on the advice of the German Society of Tropical Medicine and International Health and

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[138] Associated Press. Elite Army units to stop taking anti-malarial drug. CBS website, 19 September 2013. Available at:: https://www.cbsnews.com/news/elite-army-units-to-stop-taking-anti-malarial-drug/
[139] House of Oireachtas (Ireland). *Statement by Deputy Paul Kehoe, Minister of State at the Department of Defence to the Oireachtas Éireann*, 28 June 2017. Available at: https://www.oireachtas.ie/en/debates/debate/dail/2017-06-28/35/?highlight%5B0%5D=mefloquine
[140] Duffy R. Giving anti-malaria drug Lariam to Irish troops "beggars belief", says support group. The Journal, 19 Oct 2018. http://www.thejournal.ie/defence-forces-lariam-3034728-Oct2016/
[141] Raidió Teilifís Éireann. Controversial drug Lariam removed from sale. Raidió Teilifís Éireann website, 16 Sep 2016: https://www.rte.ie/news/2016/0915/816884-lariam/
[142] ibid
[143] House of Oireachtas (Ireland). *Statement by Deputy Paul Kehoe, Minister of State at the Department of Defence to the Oireachtas Éireann*, 24 January 2018. Available at: https://www.oireachtas.ie/en/debates/question/2018-01-24/16/?highlight%5B0%5D=mefloquine
[144] House of Oireachtas (Ireland). *Statement by Deputy Paul Kehoe, Minister of State at the Department of Defence to the Oireachtas Éireann*, 28 June 2017. Available at: https://www.oireachtas.ie/en/debates/debate/dail/2017-06-28/35/?highlight%5B0%5D=mefloquine
[145] House of Oireachtas (Ireland). *Statement by Deputy Paul Kehoe, Minister of State at the Department of Defence to the Oireachtas Éireann*, 24 January 2018.
[146] Lieutenant General M Temple, Official correspondence to Brigadier General HC MacKay, 19 January 2017.

when a new manufacturer's 'black box' warning was added[147]. The letter stated that the German Armed Forces have not noticed any severe side effects or permanent central nervous problems. In late 2016, the mefloquine manufacturer Roche withdrew Lariam™ from the German market (presumably for similar reasons as in paragraph 233), which became the catalyst for the German Ministry of Defense to order the cessation of use of mefloquine within German military personnel.

North Atlantic Treaty Organisation (NATO)

237. The Committee of the Chiefs of Military Medical Services in NATO (COMEDS) is NATO's senior body on military health matters. It aims to improve coordination, standardisation and interoperability in military medicine and the exchange of information between NATO member and partner nations. The ADF is an active member of COMEDS.

238. In response to concerns raised in many nations about the use of mefoquine, the Force Health Protection Working Group of COMEDS was asked to review the matter. The working group has recommended that the use of mefloquine is still justified when prescribed in line with national prescribing guidelines and the standard product information. The recommendation will enter the ratification process by COMEDS within the next few weeks to months.

[147] An FDA boxed warning, also known as a 'black box' warning appears on a prescription drug's label. It is the strictest warning used by the FDA and is designed to call attention to serious or life-threatening risks.

TERM OF REFERENCE 7 – Related Matters

239. For the past few years, a number of individuals have sought recognition that their current health complaints have been caused by, or are related to, past use of antimalarial medications administered by Defence. This is despite there being no clear evidence that this is the case. The advocates have compared use of these antimalarials with other past medication and/or chemical related controversies in an attempt to magnify concerns and imply wrong doing, particularly in relation to the clinical studies undertaken by Defence in the late 1990s and early 2000s. Personal attacks have also been made on social media against on a number of individuals in both Defence and broader government.

240. Defence recognises that many individuals involved in making these claims are concerned about the effect that taking antimalarials may have had on their long term health problems. Some of these individuals have advised that they have been diagnosed with mental health conditions but are questioning whether these diagnoses are correct. Most of these individuals are former serving members and, while some appear to be receiving services through DVA, many are perhaps not. This is particularly concerning because all current and former serving members are automatically eligible to access mental health care no matter the cause of their condition, either within Defence or under the non-liability health care arrangements administered through DVA. Additionally, they and their families can access care though the VVCS.

241. Perhaps due to the stigma associated with mental illness, these individuals may be seeking a specific cause (preferably a physical one), alternative diagnosis or explanation of their condition that may be less stigmatising and easier for them and others to accept.

242. Research and experience are increasingly showing that there can be physical, social, environmental and psychological causes for mental illness. Furthermore, the relationship between physical and mental illness is complex and individuals can experience both types of illness at the same time.

243. There has been much opinion expressed that this blurring of the lines between physical and mental health, and particularly a perceived overlap of symptoms between PTSD and the alleged long term health effects of antimalarial drugs, has led to some military personnel being incorrectly diagnosed[148]. Suggestions have also been made that the high rates of PTSD seen in ADF personnel who deployed to Timor-Leste are attributable to these antimalarials on the assumption that these operations did not expose ADF personnel to serious combat operations, and therefore to trauma, when compared with operations in Afghanistan[149].

244. This would appear an over-simplification of a complex issue, particularly as a proportion of those who served in Timor-Leste later went on to deploy to the Middle East Area of Operations. As the Canadian Committee noted: "…some veterans have difficulty accepting a diagnosis of post-traumatic stress or some other mental health disorder. PTSD has been recognized for decades, while the long term adverse effects of mefloquine have yet to be determined. While in some cases one may have been misdiagnosed as the other, it should not lead

[148] Nevin R, *Mefloquine and post-traumatic stress disorder*, in Ritchie E (ed.), *Forensic and Ethical Issues in Military Behavioural Health*, Borden Institute, Surgeon General U.S. Army, Falls Church, 2014

[149] International Mefloquine Veterans' Alliance. *PTSD as a "Diagnosis of Convenience": Mefloquine, Tafenoquine and the Prevalence of Neuropsychiatric Disorders in ADF Veterans of East Timor and Bougainville*. International Mefloquine Veterans' Alliance website, 11 July 2016. Available at: https://imvalliance.org/2016/07/11/ptsd-as-a-diagnosis-of-convenience-mefloquine-tafenoquine-and-the-prevalence-of-neuropsychiatric-disorders-in-adf-veterans-of-east-timor-and-bougainville/

to a sound, empirically-based diagnosis being set aside because an alternative one would be more easily accepted. [150]"

Public Health Concerns

245. Defence is increasingly concerned about the possible detrimental health effects that the claims by advocates may be having on vulnerable people who could, as a consequence, delay seeking appropriate treatment. For those who do have a mental health problem or have been diagnosed with a mental illness, the belief that there may be a physical cause, or that they may have been misdiagnosed could be barrier to seeking appropriate care, or may result in them disengaging from their current health providers. Such an outcome is deeply concerning, given that care for current serving and ex-serving ADF members and their families is freely available.

246. It is at best extremely difficult and at worst nearly impossible to prove that current health problems were caused by the administration of an antimalarial 18 years previously as opposed to the numerous other affronts, both physical and mental, that service personnel are exposed to over their lifetime, before, during and after service. In many cases this includes exposure to traumatic events and experiences. As Dr Ian Gardner, DVA Principal Medical Advisor stated at a Senate Estimates Hearing on 1 March 2017

There is a problem, here, for veterans. The problem is that many of these veterans believe that all of life's current problems are due to having taken mefloquine tablets 20 years ago[151].

247. Also, as explained above, it is generally very difficult to separate neurocognitive (brain) issues from mental health issues, as neurocognitive injuries can result in mental health problems and vice versa. There is currently no scientifically accepted way to definitively attribute long term neurological symptoms to past antimalarial use.

248. Even if such a diagnosis could be made this in itself would be unlikely to change the approach to managing the condition. There is no 'one size fits all' treatment that applies for any health condition, and best practice requires all problems to be managed on a case by case basis driven by the symptoms with which the individual presents. Linking of current symptoms to previous antimalarial use, as the cause, will not necessary dramatically change the prognosis, or the available evidence based interventions used to address and relieve the symptoms.

249. One of Defence's biggest concerns is that the publicity surrounding this issue has resulted in significant stress for many individuals. Approximately 25% of individuals who have emailed the Defence adf.malaria@defence.gov.au mailbox in search of their study records or confirmation of participation were not in the studies at all. Of those who were in an antimalarial study, about 7% took the standard antimalarial as a comparator. Several distressed families have asked whether their unwell or deceased child or spouse participated in the studies, and in many cases they had not.

250. While the study records are remarkably accurate given they were held in paper form for over 18 years, they are highly technical and often difficult to interpret for 'lay' individuals. This is why each study record is accompanied by a covering letter to help those requesting the information to decipher the documentation. Several individuals have found them difficult to understand even with this letter, and this has led to more angst, and many more email requests seeking assistance.

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[150] Ellis NR (Chair). *Mental Health of Canadian Veterans: A Family Purpose*. Report of the Standing Committee on Veterans Affairs, House of Commons Canada, June 2017. P 28-29

[151] Dr Ian Gardner, Principal Medical Advisor, The Department of Veterans' Affairs. Quoted in Foreign Affairs, Defence and Trade Legislation Committee Senate Estimates, Official Hansard for Wednesday 1 March 2017 - Pages 173-178

251. In addition, a number of currently healthy individuals, both current and former serving, have questioned Defence health staff as to whether they will suddenly become affected by drugs they took over 18 years ago, even though this is not biologically plausible.

252. Most worryingly, it is not unimaginable that some individuals may have delayed seeking treatment for mental health concerns while waiting for a specific outreach program. This is despite the consistent messages from Defence and DVA that help is available for all current and former serving members through the mechanisms described elsewhere.

253. The issues raised above are highly concerning from a public health perspective and, as a result, it could be argued that the claims made by advocates may have inadvertently caused more harm than good. Defence's concerns about these potential harmful effects are why Defence has focused on assisting and advising individuals to seek help through the means freely available to them and provided either by Defence or DVA.

CONCLUSION

254. Defence has continuously balanced the risks associated with antimalarial medications with the force health protection needs of its personnel in order to ensure ADF members are maximally protected from known and potentially fatal threats in malarious areas. Defence has been conservative in its use of mefloquine despite the drug's operational advantages over doxycycline. In fact it has been world leading in this regard and this has been acknowledged by international advocates.

255. As has been shown, there is no antimalarial medication that offers 100% protection against malaria, nor are any drugs completely free from side effects. Defence has therefore had to push the boundaries of knowledge to ensure that our personnel are given medications that are safe and effective against malaria as the parasite continues to evolve. In doing so, Defence has conducted ethical, legal and professional clinical studies on ADF members with the full and informed consent of these members. It has also monitored these individuals during and after the studies, and for the rest of their service careers.

256. Defence has always acknowledged that a small number of people can develop long term neuropsychiatric effects from mefloquine use, however, such cases are thought to be rare. Defence has not found any clear evidence that tafenoquine also causes these effects. This does not mean that Defence will just accept the common wisdom and assume that no problem will be found, as is evidenced by the research that has been commissioned with DVA.

257. Tafenoquine is currently being considered for registration, both in Australia and in the US. Defence has confidence in the regulatory processes of the TGA and will consider the use of tafenoquine if it is registered in this country.

258. Defence's response to concerns over the past few years has been comprehensive and thorough, and at its heart has been the concern for the health and wellbeing of all current and former serving members. Help is available to those individuals who are having health problems, be it through on-base garrison health facilities, local GPs, VVCS or DVA. Defence nevertheless understands that some veterans have trouble taking the first step. That is why Defence remains supportive of DVA outreach activities.

259. For these reasons, Defence will:

a. Continue to update its antimalarial policy on a regular basis as evidence regarding safety, efficacy and drug resistance evolve.

b. Examine, with DVA, the outcomes of the research at UQ to determine if further research or intervention is required, and encourage and facilitate future requests for research that have scientific merit and are ethically sound

c. Consider whether, if registered in Australia, tafenoquine warrants inclusion in Defence's malaria policy, and if this will in turn negate the requirement to retain mefloquine as a third-line antimalarial.

d. Continue to assist DVA in veteran outreach activities.

ANNEXES

Annex A – Letters of Appreciation for ADFMIDI's work

Annex B – Product information for Antimalarials used by Defence

Annex C – Social media campaign to report tafenoquine adverse events

Annex D – Letter from the US Army to Dr Remington Nevin

Annex E - Numbers of ADF personnel who took mefloquine and Tafenoquine during the antimalarial studies, and numbers who have been prescribed mefloquine since 2001.

Annex F – Mefloquine Study – Consent Forms and Information Sheets

Annex G – Prevention Study – Consent Form and Information Sheet

Annex H – Eradication Study - Consent Forms and Information Sheets

Annex I – Draft Copy of Letter sent to Participants who had taken Tafenoquine – Vortex Keratopathy.

Annex J – Overview of testing for new medications – Clinical studies

Annex K – Literature Review for Joint Health Command - Neuropsychiatric effects of Mefloquine – March 2016 – GPCAPT Alexander C McFarlane AO

Annex L – Defgram 42/16 – Mefloquine Use in the ADF

Annex M – Mefloquine Management Guidelines 09 June 2016

Annex N - Letter from RADM Robyn Walker to Repatriation Medical Authority April 2015

Annex O – Letter from AVM Smart to RMA April 2016

Annex P – Correspondence from RMA: 24 June 2016

Annex Q – Letter to COMCARE regarding Mefloquine Inquiry - 13 April 16

Annex R – Summary of the Evolution of Defence Malaria Policies

Annex S - Defence Health Policy Directive – Malaria 2000

Annex T – Current Health policy (Defence Health Manual) on Malaria (2013)

Annex U – Defence Health Material Manual – Chapter 11 – Governance

Annex V - Adverse Event reporting in AMI Studies 1999-2002

Annex W – Published tafenoquine studies

Annex X – International and military guidelines on malaria prevention

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ANNEX A

LETTERS OF APPRECIATION FOR ADFMIDI'S WORK

DEPARTMENT OF DEFENCE
AUSTRALIAN EMBASSY HANOI

Office of the Australian Defence Attaché,
Australian Embassy Hanoi, 8 Dao Tan Street, HANOI, VIETNAM

11 July 2012

Professor Dennis Shanks
Director
Australian Army Malaria Institute

LETTER OF APPRECIATION - AUSTRALIAN ARMY MALARIA INSTITUTE CONTRIBUTION TO AUSTRALIAN-VIETNAM DEFENCE ENGAGEMENT

Dear Professor Shanks,

This letter is to express my appreciation for the contribution made by the Australian Army Malaria Institute (AMI) to the development of defence relations between Australia and Vietnam. While July 2012 marks the conclusion of International Policy (IP) Division's funding for the projects undertaken by AMI in Vietnam, AMI's work in Vietnam over a twelve year period will have an enduring legacy.

The bilateral defence relationship with Vietnam has progressed strongly since the establishment of the Defence Attaché's office in Hanoi in 1999. The projects run by AMI in cooperation with the Vietnam People's Army (VPA) were pivotal in initiating and developing our defence engagement and taking us to where we are now. The two projects; the Vietnam Australian Defence Malaria Project from 2000 to 2012, and the Vietnam Australian Dengue Project from 2004 to 2012, have achieved their objectives from both the defence engagement perspective, as well as delivering substantive results in the field of medical research, capacity building, training and technology transfer.

AMI's success in establishing a close working relationship with the VPA Military Medicine Department and associated hospitals and units is clearly evident in my daily dealings with the VPA. The value of AMI's work has been commented upon by the Vietnamese Defence Minister in discussion with our Ambassador, and by Vice Defence Ministers and other senior officials. Through training, sponsorship and mentoring, AMI has also created a community of VPA medical officers who value their association with Australia and Defence.

Although IP Division funding for AMI's projects ceased in mid 2012, this is by no means a reflection on the continued relevance of these projects. Defence engagement with Vietnam is evolving to meet new challenges and priorities in a time of funding constraint. Core Defence engagement priorities are now focused on preparing the VPA for future UN peace keeping operations, and on cooperation on maritime security and countering non-traditional threats.

I have been advised that IP Division has no objections to AMI continuing its work in Vietnam, albeit with other sources of funding. I also understand that AMI's work in Vietnam may continue under a new cooperative arrangement with the US Navy Medical research Unit No 2

(NMRU2). The VPA have indicated their strong preference that AMI be involved in any NMRU2 continuance of AMI programs and I sincerely hope that this proves to be the case.

Matthew Dudley, CSC
Group Captain
Defence Attaché
Australian Embassy Hanoi

EIJKMAN INSTITUTE
for molecular biology

Eijkman-Oxford Clinical Research Unit

Ref. No.: EOCRU/200/210/Vol.1/050 7 August 2012

COL Craig Schramm
Director Future Health Capability
Joint Health Command CP2-6-011
Campbell Park Offices
PO Box 7911
Canberra BC ACT 2610
AUSTRALIA

Dear COL Schramm:

This unsolicited letter communicates my considered views regarding the tremendous value of the Australian Army Malaria Institute. The actual costs of running the Institute are of course unknown to me, and shrewd application of precious dollars and cents is not what I have in mind in expressing "*tremendous value*".

A warship afloat near potentially hostile shores is indeed a very expensive venture. It is also a tremendous value. It demonstrates military capacity and political will, and thereby discourages bellicose actions. Its value in preventing confrontation is priceless, even more so in the event of confrontation. AMI may be compared to such a warship at patrol along the shores of a threat, and a very serious one - malaria. This infection has slain more soldiers at war than the combined bullets and bombs of the enemy. Malaria is not in retreat in the face of modern medicine, but is resurgent, and it comes equipped with resistance to our best weapons.

Only the Australian Defense Forces can assess the likelihood and extent of their exposure to this threat, but this letter implores not underestimating that threat or the value of AMI as a strategic asset in dealing with it. AMI can prevent confrontation with that enemy, and strike decisively when it does occur. The necessary expertise with malaria as a problem of military medicine does not come incidentally. It cannot be garnered from the civilian workforce any more than a freighter can be made into an effective combatant warship. When the ADF need expertise in malaria, it cannot be drafted, hired, or otherwise conjured – it is absent, and the forces exposed to malaria will be vulnerable. AMI is a *tremendous value* in ensuring that never materializes.

Setting aside the proud traditions of the ADF in being a significant contributor to the march of progress against malaria, disengagement from that march, plainly speaking, is a poor value for Australian soldiers and Australia.

Sincerely yours,

J. Kevin Baird, Ph.D.
Captain, Medical Service Corps, United States Navy (ret)
Director

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12 December

COL Craig Schramm, Chair of AM1 Review
Director Future Health Capability, Joint Health Command CP2-6-0 1 1
Campbell Park Offices, PO Box 79 1 1
Canberra BC ACT 2610, Australia

Dear COL Schramm,

It is my pleasure to support the Army Medical Institute as you undertake a review of their accomplishments and importance in the context of military preparedness. I am a scientist who studies malaria, and my comments will focus on the key roles that my colleagues have played and should continue to play in that area.

I am the scientific Director of the WorldWide Antimalarial Resistance Network (WWARN), a Gates Foundation funded international effort to track antimalarial resistance. The scientists of AMI have worked collaboratively with WWARN, and Drs. Edstein, Cheng and Shenks have been active participants, a reflection of their strong involvement and many contributions to the malaria community.

The most important assets of the AMI are the intellectual quality, high motivation and impressive productivity of the scientists who work there. They are major "players" in the malaria community. Their work is highly regarded and frequently forms the basis for policy decisions on antimalarial use in the region. The proximity of Australia to malarious regions allows them to work directly in the field, and they have made major contributions to my particular area of study, resistance to antimalarial drugs. This has been particularly true of the decades-long work in the development and testing of new antimalarials, a collaboration with the US Walter Reed Army Institute of Research that has included long term posting of US personnel to AMI.

In short, AMI is a world-class scientific institution. Its scientists have made major contributions to basic science and malaria control, and continue to have a central place in the very strong Australian scientific community.

Due to the strategic importance of Australia in Asia-Pacific region, Australian troops have been deployed repeatedly in areas endemic for malaria, even in recent years. Malaria will remain a threat in Asia for many years to come and this reality has kept tropical diseases high on the agenda of troop readiness and protection. AMI has the expertise and breadth to support the practical needs for protection of Australian personnel when deployed in malaria endemic regions. It is a key component of future health capability and the combination of high quality science and practical utility is a win for both the Australian Army and malaria research.

Please feel free to contact me if further information would be helpful in your assessment of the AMI.

Sincerely,

Carol Hopkins Sibley
Professor of Genome Sciences
Scientific Director, WWARN

UNSW@ADFA
CANBERRA • AUSTRALIA
School of Physical, Environmental and Mathematical Sciences

COL Craig Schramm
AMI Review Chair
Joint Health Command
Campbell Park Offices
Canberra, ACT, 2610

14 August, 2012

Dear COL Schramm,

I am writing in support of the Australian Army Malaria Institute (AMI). I am an academic at the Australian Defence Force Academy (ADFA) in Canberra. Over the last few years my collaborators and I have been developing a family of novel metal-based compounds, called dinuclear ruthenium complexes, as antimicrobial agents. As we believed that these compounds might possess antimalarial activity, we contacted the Department of Drug Evaluation at AMI to see whether they could assist us in assessing the complexes as potential antimalarial agents. We are now actively collaborating with AMI, and believe that one of the ruthenium complexes shows a great deal of promise, as it exhibits very good *in vitro* activity against the malaria parasites, with low toxicity towards liver and kidney human cell lines. The ruthenium compounds are also active against both drug-sensitive and drug-resistant malaria strains, *in vitro*.

I would particularly like to stress, that without the Department of Drug Evaluation expertise in this project (that is, in addition to carrying out the necessary *in vitro* biological assays) we would not have a potential new antimalarial compound worthy of further investigations in animal models. As an indication of the importance of the collaborative project, ADFA provided funding for one of my PhD students to spend several weeks working at the Department of Drug Evaluation in 2011, where she gained valuable insight into the various strategies used in antimalarial drug discovery. Furthermore, if we can succeed in demonstrating good *in vivo* potency against rodent malaria, we plan to apply to ADFA to obtain defence related research funding and funds from external agencies, such as the Medicines for Malaria Venture, to further this work.

As you no doubt know, malaria is a significant health problem for the ADF and the wider world community. Given the increasing incidence and spread of drug-resistant malaria strains in operational areas of interest to the ADF, such as the Asia-Pacific region, it is important that new antimalarial drugs be developed. I have read that one of the problems with R&D for malaria is the potential low economic return on the investment – malaria is considered a poor country disease. However, for the ADF it is essential that we have the best and safest chemotherapeutic agents available to ensure that our military personnel are fully operational to carry out their mission without the adverse impact of malaria. I believe that it is highly appropriate that the

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Cricos Provider Number: 00100G

ADO funds an institute, such as the AMI, to enable the development of new medicines for a disease that is a significant issue for ADF personnel and the worldwide community. The existence of AMI, a centre of excellence in vector-borne diseases of military importance, allows academics like myself to access experts in the field of malaria chemotherapy and drug evaluation. This adds considerably to our research efforts, but also allows the ADO to utilise the expertise, personnel and infrastructure within Australian universities and research centres to help develop measures to protect and treat military personnel from malaria.

In summary, I strongly believe that AMI is extremely relevant and with the continuing spread of antimalarial drug resistant strains of malaria the institute will become more relevant to the ADO and the broader Australian community.

Yours sincerely,

A/Prof Grant Collins
School of PEMS
ADFA

Dr Ian Howie-Willis Consultant Historian

16 August 2012

The Chair of the Army Malaria Institute Review
c/o Colonel Craig Schramm
Director of Future Health Capability
Joint Health Command
CP2-6-011
Campbell Park Offices
PO Box 7911
Canberra BC
ACT 2610

Dear Sir

Re: Review of the Army Malaria Institute

I write to make comment on the Army Malaria Institute (AMI) in relation to the AMI review which you are to conduct.

My reason for doing so is that I am an interested but independent observer of the AMI in my capacity as an historian with a particular interest in the history of the Australian Army's long experience with malaria.

This interest arises from my current historical research project, which is being supported by funding awarded to me in 2011 under the Army History Research Grants scheme. This project requires me to write a book on the history of the Army's protracted struggle to reduce the impact of malaria on its personnel and in particular on its front-line combat troops.

The book, which I hope to have completed and published by 2014, will have the title ***An Unending War: The Australian Army's Continuing Struggle Against Malaria***. The book stems from, and will be an extension of, the research I carried out for my most recent book of military history — *A Medical Emergency: Major General 'Ginger' Burston and the Army Medical Service in World War II* (Big Sky Publishing, Sydney, 2012), which was also supported by an Army History Research Grant..

The Australian Army's on-going struggle against malaria may be summarized as follows:

- Australia's military experience of malaria predates the establishment of the Australian Army. It began with the NSW Sudan Contingent in 1885, many members of which suffered fevers, the symptoms of which indicate that it was certainly a form of malaria endemic in northern Africa. (At that stage the causes of malaria were still unknown.)

- Troops of the Australian colonial and subsequent Commonwealth contingents sent to the Boer War 1899–1902 also contracted malaria.

- During World War I malaria infected the ANZAC force on Gallipoli; however, it was during the desert campaigns of the Desert Mounted Corps that malarial infection rose to catastrophically epidemic proportions, causing the campaign against the Turks in Syria and Lebanon to have ground to a halt by the time of the Armistice.

- Malaria was the almost ubiquitous deadly enemy of Australian military personnel in World War II, a menace to troops fighting the campaigns in Egypt-Libya, Greece, Palestine, Syria, Malaya, New Guinea and Borneo. Malaria infection rates during the critical Papuan campaigns of 1942 rose to alarmingly high levels, with 12% of the fighting force hospitalized with malaria in any week of the war. Such extraordinarily high infection rates, which threatened to nullify the Allied effort, led to the establishment of the Land Headquarters Medical Research Unit (LHQ MRU) at Cairns in 1943. The LHQ MRU then undertook pioneering malaria research, the application of which succeeded in reducing the hospitalisation rate to below 1%, thus helping make the Allied victory possible.

- Malaria was again an issue of concern during the military involvements of the immediate post-war decades, for the British Commonwealth Occupation Force in Japan 1945–47 then in the Korean War 1950–53, the Malayan Emergency 1950–60 and Indonesia-Malaysia Confrontation 1962–66.

- During the Australian involvement in the Vietnam War 1962–73, malaria once more became such a major threat that in 1967 the 1 Malaria Research Laboratory (1MRL) was established to conduct research into the disease to minimize its adverse impact on Australia's military capability. (The name of the 1MRL changed to Army Malaria Research Unit in 1973 and then to Australian Army Malaria Institute (AMI) when relocated to Brisbane in 1996.)

- Malaria has subsequently been a concern in all the post-Vietnam involvements — the Gulf War (1991), East Timor (from 1999), Afghanistan (from 2001), Iraq (2003–11) and the lesser peace-keeping commitments in Cambodia, Rwanda, Somalia and the Solomons.

In short, in virtually all of Australia's military involvements since 1885, with the possible exception of the Western Front in World War I, malaria has always been a problem for the nation's Defence Forces. In at least three campaigns — Syria in World War I, Papua New Guinea in World War II and Vietnam in the 1960s–70s — malaria proved disastrous.

In view of this historical experience, I submit that the continued support of the Australian Defence Force (ADF) for the AMI and its programs is vital.

My strong belief here, however, arises not so much from the ADF's historical experience of malaria but from certain present-time realities which are elaborated in the following numbered points:

1. There might be no present threat of major overseas wars involving Australia as a combatant, nor any need for Australia to commit its military personnel to new peace-keeping operations abroad in the near future. Historical experience, however, suggests that this will not always be the case. Thus, in the past decade Australian troops have been committed to wars and peace-keeping operations in at least four nations — East Timor, Afghanistan, Iraq and the Solomons — all of which are highly malarious and have therefore hazarded the health and military effectiveness of the forces sent there. Two of these commitments have proved long-term and on-going.

2. When next the Australian Defence Force (ADF) is deployed to malarious regions overseas, as seems likely if post-World War II Australian military history is any guide, some specialised agency must be standing by already equipped to ensure that ADF personnel are protected against malaria. The AMI, which now has 45 years' experience in military-oriented malaria research and is at the forefront of this field, is the sole agency capable of fulfilling that expectation.

3. A highly pertinent consideration in relation to point 2 is the question of which agency might be entrusted with the heavy responsibility of keeping Australian military personnel malaria-

free if the AMI could no longer play its appointed role through having been down-sized, scaled back, denied the necessary resources and/or otherwise impeded in fulfilling its historic mission.

4. The obvious answer to the question just posed in point 3 is one or more of the civilian medical research institutes interested in malaria. These include the Walter and Eliza Hall Institute in Melbourne, the Queensland Institute of Medical Eesearch in Brisbane and university-based tropical medicine centres such as the Australian Institute of Tropical Health and Medicine at James Cook University in Townsville and the School of Public Health and Tropical Medicine at the University of Sydney. The difficulty with the civilian and university-based research centres, however, is that:

   (a) their programs of research do not necessarily relate to specific Army need;

   (b) they do not necessarily focus, as AMI research must perforce do, on prophylaxis for and the treatment of troops deployed to exotic and often remote and malarious places overseas;

   (c) they are not under ADF control and need not therefore accept ADF research priorities;

   (d) if they were contracted to undertake the kind of ADF-oriented research presently the responsibility of the AMI, they would expect generous resourcing which could well exceed that of the AMI and would therefore be a heavier burden on the ADF, the government and taxpayers;

   (e) being civilian institutions, if they were contracted to undertake ADF-sponsored research they might reasonably expect to come under attack from various agitators — e.g. anti-war activists and animal liberationists — with radical, anti-military agenda to pursue.

5. The present global situation with malaria is that, in the wake of the World Health Organisation's failed Malaria Eradication Program of the 1950s and early 1960s, the disease is now resurgent worldwide. This situation has come about through a complex set of historical, political and socio-economic factors that render its control problematic. Such factors include:

   (a) the emergence of more virulent and drug-resistant strains of the *Plasmodium* parasites;

   (b) the evolutionary tendency of the anopheline mosquito vectors to acquire immunity to particular insecticides;

   (c) prohibitions on the use of the DDT-based insecticides that had been effective in eradicating the vectors but had unwanted environmental side-effects;

   (d) the inability of governments in many under-developed nations to mount and sustain effective anti-malaria programs and to fund prophylaxis for their citizens;

   (e) endemic poverty and malnutrition exacerbated by rapid population growth, which militates against people in poor regions of the world taking effective personal anti-malarial precautions;

   (f) migration patterns which have resulted in malaria gaining hold in previously malaria-free regions;

(g) environmental changes that have encouraged the spread of anopheline vectors, including dam-building, deforestation, siltation and altered stream flows resulting in increased flooding in low-lying areas.

6. In view of the factors enumerated in point 5 above, there is a strong probability that ADF personnel deployed overseas in future military operations, especially to under-developed, malarious nations and/or those with unstable political regimes, would be at increased risk of malaria.

7. Here it is worth remembering that, depending on the type of malaria contracted, the disease is often severely debilitating and potentially fatal. Controlling it requires increasingly sophisticated pharmacology and the continual development of new combinations of drugs to combat the parasites' evolutionary tendency to acquire resistance to drugs which formerly were toxic to it.

8. For ADF personnel on active service generally and for combat troops in war zones in particular, malaria and dengue fever are a threat at least as great as hostile armed opposition. One former ADF Surgeon-General* has stated the situation nicely by observing that *"troops shivering, sweating and shaking with malarial fever cannot shoot straight, let alone fight"*. A similar comment would apply to dengue fever as well.

9. The AMI's capacity to undertake the relevant parasitological, entomological, immunological and pharmacological investigation has lifted it to the forefront of research on malaria and other vector-borne diseases. If its activities were to be scaled back, that would inevitably impact adversely on the health and welfare of ADF personnel deployed overseas. The ADF management, the Defence Department and the Government would accordingly be obliged to find workable, effective and credible alternatives to the AMI research programs if these were to be curtailed.

10. There would, of course, be political ramifications for the ADF, Defence Department and Government in ADF personnel being deployed to malarious regions if inadequately protected against malaria through ignorance of the latest trends in effective prophylaxis. Few elected governments would wish to be seen to be placing ADF lives at risk by having disabled an effective agency such as the AMI. The AMI's achievement speaks for itself — an unparalleled record of safeguarding ADF personnel against tropical diseases across a continuous 45-year time-span.

I will conclude this submission with some pertinent observations on the Allied Armies' experience of malaria in Papua New Guinea in World War II. One significant factor in the eventual Allied victory was the successful application of the ground-breaking malaria research undertaken by the LHQ Medical Research Unit in Cairns 1943–46. By contrast, the Japanese, whose anti-malaria effort was at best haphazard, inconsistent and spasmodic, suffered huge mortality from malaria. For the Japanese, malaria perhaps proved a more lethal foe than the Allied armies, navies and air forces combined. Through the LHQ MRU, the Allies tackled malaria scientifically, systematically, thoroughly and effectively. The Japanese did not and in consequence lost the war.

The World War II strategic experience of successfully combating malaria is both instructive and relevant to ADF health planning seven decades later in the early 21st century. The AMI, a worthy successor to the LHQ MRU, still has a key role to play in protecting ADF personnel against vector-borne diseases. I submit that its ability to do so should not be constrained by short-sighted cost-cutting, expedient and ill-advised restructuring or internal and self-serving ADF politicking, none of which gives priority to soldiers serving on active duty.

---

* Major-General Professor John H. Pearn.

Finally, I submit that what one government or set of defence bureaucrats or senior ADF management team might choose to dismantle, later governments, bureaucrats and ADF managers will subsequently be obliged to re-erect when the need inevitably arises. Almost inevitably, too, the cost of re-erection, both in terms of finance and regaining lost expertise, will be appreciably higher than having maintained the amenity that was dismantled.

In conclusion, I would direct your attention to what might best be called "the verdict of history". Medical and military historians of the future may be relied on to take particular interest in the review you are conducting, the report that flows from the review, the action taken by the ADF and/or the government to implement the review recommendations and the impact of such action upon ADF capability. And here I would point out that the favourable verdict of history on the World War II Prime Minister, John Curtin, and his Army Commander-in-Chief, Field Marshal Sir Thomas Blamey, arises in part from their effective leadership in establishing the LHQ Medical Research Unit and then in providing it with the necessary resources to defeat malaria before it could defeat the Allied forces in Papua New Guinea.

Yours sincerely

Dr Ian Howie-Willis
Consultant Historian

WORLD HEALTH ORGANIZATION **ORGANISATION MONDIALE DE LA SANTE**

REGIONAL OFFICE FOR THE WESTERN PACIFIC **BUREAU REGIONAL DU PACIFIQUE OCCIDENTAL**

United Nations Avenue, P.O. Box 2932, 1000 Manila, Philippines

In reply please refer to:
Prière de rappeler la référence:

Col Craig Schramm
The Australian Army Malaria Institute
Review Chair
Director, Future Health Capability
Joint Health Command CP2-6-011
Campbell Park Offices, P.O. Box 7911
Canberra BC ACT 2610, Australia

17 August 2012

Dear Col Schramm,

The World Health Organization considers the Australian Army Malaria Institute a vital player in the field of malaria control in the Asia Pacific Region. The Institute has been a WHO Collaborating Centre for malaria since 1998, and, in a longstanding and fruitful relationship, has been an active partner in both training and research.

Over the years, the Institute has contributed substantially to improving malaria diagnosis in the Region, including the establishment of a product-testing programme and the lot testing of malaria rapid diagnostic tests. Through its involvement in malaria microscopy, the Institute has provided important support for the WHO external competency assessment scheme, which has been ongoing since 2002 throughout the Asia Pacific Region. The Institute's expertise is now an integral part of the WHO Quality Assurance Manual on Malaria Microscopy.

The Institute is also a key partner in the Pacific Malaria Initiative, focusing on intensified malaria control and elimination in Solomon Islands and Vanuatu, particularly in the fields of evaluation and research. This includes significant support in the development and conduct of malaria indicator surveys and entomological research. Importantly, the Institute is also a key partner in antimalarial drug issues, as well as in vivax malaria research.

The World Health Organization maintains that continued collaboration with high-capability partners such as the Australian Army Malaria Institute is critically important in WHO's fight against vectorborne diseases in the Asia Pacific Region.

Best regards,

Dr John Ehrenberg
Director
Combating Communicable Diseases

Telephone: (632)528 8001 Facsimile: (632)521 1036, (632)526 0279, (632)526 0362 E-mail: postmaster@wpro.who.int Website: http://www.wpro.who.int

Schramm, Craig COL

From:
Sent: Saturday, 18 August 2012 9:16 AM
To: Schramm, Craig COL
Subject: The Army Malaria Institute
Attachments: Col Schramm re AMI Aug 2012.pdf

Dear Colonel Schramm,

The Army Malaria Institute

I write to convey my strongest support and appreciation for the exceptional work of the Army Malaria Institute in Brisbane.

I have worked on malaria in many different roles and capacities since 1965. I have long been aware of the exceptional role of the Army Malaria Institute in Brisbane. Over the past 6 years, I have chaired and guided, on behalf of AusAID and the Australian Government, the Pacific Malaria Initiative (PacMI) and the Asia Pacific Malaria Elimination Network (APMEN). Both of these Initiatives, mainly financed by Australia, have had rapid and exceptional impact in driving down malaria across the Asia Pacific region. A dozen countries in the region have now set their sights on the complete elimination of malaria and are making rapid progress in this direction. This would not have been possible without the many contributions of the Army Malaria Institute. The role of the Army Malaria Institute to both PacMI and APMEN has been second to none.

Australia's leadership in the fight against malaria in the Asia Pacific region is exceptional, highly appreciated in the region, and widely recognized worldwide. Symbolizing this leadership role, Senator Bob Carr is hosting a major international event in Sydney on October 31-November 2 under the banner Malaria 2012. The Army Malaria Institute will play a major role in this event.

From the global perspective, the country with the largest and most impactful malaria capacity within its military is the United States. In my estimation, Australia comes in clear second place. This is quite remarkable and means that Australia is punching well above its weight in malaria. This has big impact and is much appreciated internationally, especially in the Asia Pacific region.

Finally, as you will be well aware, Australia's role in fighting malaria in the Asia Pacific region is strongly in the interest of Australia. This is not only for reasons of regional politics and mutually beneficial relationships, but also because of Australia's self-interest in limiting the constant reintroduction of malaria into areas of northern Queensland which still have the potential for malaria transmission to be re-established. The Army Malaria Institute, with its strategic location in Brisbane, plays a major role in defending Australia from the re-establishment of endemic malaria.
I hope you will find these reflections and opinions of use as you take forward your review. Please do not hesitate to contact me if I can offer any further information or clarification.

With very best regards.

Yours sincerely,

Richard Feachem

Sir Richard Feachem, KBE, FREng, DSc(Med), PhD
Director, The Global Health Group
Professor of Global Health
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UCSF GLOBAL HEALTH SCIENCES
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August 16, 2012

Colonel Craig Schramm
AMI Review Chair
Campbell Park Offices
PO Box 7911
Canberra BC ACT 2610
Australia

Dear Colonel Schramm,

The Army Malaria Institute

I write to convey my strongest support and appreciation for the exceptional work of the Army Malaria Institute in Brisbane.

I have worked on malaria in many different roles and capacities since 1965. I have long been aware of the exceptional role of the Army Malaria Institute in Brisbane. Over the past 6 years, I have chaired and guided, on behalf of AusAID and the Australian Government, the Pacific Malaria Initiative (PacMI) and the Asia Pacific Malaria Elimination Network (APMEN). Both of these Initiatives, mainly financed by Australia, have had rapid and exceptional impact in driving down malaria across the Asia Pacific region. A dozen countries in the region have now set their sights on the complete elimination of malaria and are making rapid progress in this direction. This would not have been possible without the many contributions of the Army Malaria Institute. The role of the Army Malaria Institute to both PacMI and APMEN has been second to none.

Australia's leadership in the fight against malaria in the Asia Pacific region is exceptional, highly appreciated in the region, and widely recognized worldwide. Symbolizing this leadership role, Senator Bob Carr is hosting a major international event in Sydney on October 31-November 2 under the banner Malaria 2012. The Army Malaria Institute will play a major role in this event.

From the global perspective, the country with the largest and most impactful malaria capacity within its military is the United States. In my estimation, Australia comes in clear second place. This is quite remarkable and means that Australia is punching well above its weight in malaria. This has big impact and is much appreciated internationally, especially in the Asia Pacific region.

UCSF
University of California
San Francisco

Finally, as you will be well aware, Australia's role in fighting malaria in the Asia Pacific region is strongly in the interest of Australia. This is not only for reasons of regional politics and mutually beneficial relationships, but also because of Australia's self-interest in limiting the constant reintroduction of malaria into areas of northern Queensland which still have the potential for malaria transmission to be re-established. The Army Malaria Institute, with its strategic location in Brisbane, plays a major role in defending Australia from the re-establishment of endemic malaria.

I hope you will find these reflections and opinions of use as you take forward your review. Please do not hesitate to contact me if I can offer any further information or clarification.

With very best regards.

Yours sincerely,

Sir Richard Feachem, KBE, FREng, DSc(Med), PhD
Director, The Global Health Group
Chair, Asia Pacific Malaria Elimination Network
Professor of Global Health

Eskitis Institute
Nathan Campus, Griffith University,
Brisbane, Queensland 4111,
Australia

Dr. Rohan A. Davis
Group Leader
Natural Products Chemistry

23 August 2012

AM1 Review Chair
Colonel Craig Schramm (Director Future Health Capability
Joint Health Command CP2-6-0 11
Campbell Park Offices, PO Box 7911
Canberra BC ACT 2610 Australia

Dear Colonel Schramm.

I am writing this letter in support of the research being conducted at the Australian Army Malaria Research Institute in Brisbane, Queensland.

I have collaborated with Michael Edstein and his team at AAMI since 2007. Our research is focused on the identification of potent antimalarial small molecules from nature. To date we have successfully identified several potential lead candidates and are currently optimizing one lead series for pre-clinical drugs trials in the next 2 years. The grants that I have co-written with AAMI include:

1) Medicines for Malaria Venture – project grant ($282K **2007**, $539K **2008**, $716K **2009**)
Ronald J. Quinn, Rohan Davis, Vicky Avery, Susan Charman, William Charman, Michael Good, Katherine Andrews, Michael Edstein
Project title: "Lead generation *via* HTS of malaria targets against a large natural product extract library"

2) NHMRC project grant (APP1024314) ($156K **2012**, $221K **2013**, $216K **2014**)
Rohan Davis, Mark Coster, Kathy Andrews, Michael Edstein, Susan Charman
Project title: "Evaluation of novel pyrrolo/iminoquinone antimalarial compounds"

Without the intellectual input and on-going research support offered by the world-renowned malaria team at the AAMI there is no doubt in my mind that the above listed applications would not have been successful. My continued collaboration with the group is essential for the NHMRC project grant success.

I hope the up-coming review of the AAMI has positive outcomes, and that this world-class research institute can continue to contribute to the fight against malaria and other vector-borne diseases that are of both military and public health importance.

Yours sincerely,

Rohan A. Davis

MMV
Medicines for Malaria Venture

27 August 2012

Colonel Craig Schramm
Director Future Health Capability
Joint Health Command CP2-6-011
Campbell Park Offices
PO Box 7911
Canberra BC ACT 2610
Austral

Dear Colonel Schramm

Ref: Letter of support for Australian Army Malaria Institute

In light of the forthcoming review of the Army Malaria Institute (AMI) in Brisbane, Medicines for Malaria Venture (MMV) would like to express its full support for this institution and endorse the appropriateness of its mission and the quality and relevance of its research in combating vector-borne diseases of military importance.

The Institute is a highly valued collaborator with MMV's partners in both Australia and globally. Its focus on clinical and translational research fills a critical gap in the development of new drugs to protect against malaria and other vector-borne diseases.

In the past ten years there has been considerable progress made in the development of new anti-malarial medicines, but increasing drug resistance threatening public health in AsiaPacific amplifies the need to intensify research and development activities. This is increasingly being recognized by MMV's partners in AsiaPacific.

The institute provides important regional engagement with military organisations to control vector-borne diseases more effectively, therefore contributing to regional control efforts.

The focus of its research, particularly on areas such as malaria chemoprophylaxis, diagnosis, drug evaluation and resistance, personal protection, and elimination of the disease, has been central to global efforts to discover and develop new antimalarials. AMI's clinical evaluation of tafenoquine (a long-acting primaquine analogue), which is being co-developed with MMV and GlaxoSmithKline as the next generation drug for the radical cure of *P. vivax* malaria, has been instrumental in bringing the molecule closer to regulatory submission.

We believe the academic achievements of AMI are effectively measured through the publications of its staff, which currently stands at over 300 articles on infectious disease topics. Together with its extensive network of collaborators, national and international, AMI demonstrates its strong capability as a key player in the global move to combat vector-borne diseases that are of critical importance both to the military and wider public health community.

Sincerely,

Dr David Reddy, CEO

International Center Cointrin Entrance G, 3rd floor Route de Pré-Bois 20 PO Box 1826 CH-1215 Geneva 15 Switzerland
Tel: +41 22 799 4060 Fax: +41 22 799 4061 www.mmv.org

World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Tel. direct:
Fax direct:
E-mail :

In reply please refer to:

Your reference:

COL Schramm
Head, Review Committee
Australian Army Malaria Institute
Campbell Park Offices
P.O.Box 7811
Canberra BC ACT
Australie

19 September 2012

Dear Colonel Schramm,

It is pleasure for me to refer to the very fruitful collaboration and support that the Australian Army Malaria Institute provides to the work of the World Health Organization (WHO), in relation to both global activities coordinated by WHO's Global Malaria Programme (GMP) as well as several important initiatives of the Regional Office for the Western Pacific. As you certainly know, the Australian Army Malaria Institute has been recently re-designated for four years as WHO Collaborating Center for Malaria on the basis of its excellent contributions to WHO's work in multiple technical areas.

This work spans over basic and applied research, focussing on multiple aspects of the malaria parasites and its vectors. This includes in particular, studies on mechanisms of artemisinin resistance; evaluation of new genotyping to distinguish recrudescence's from new infections; measurements of antimalarial drug concentrations from samples obtained from multiple groups, research on RDT diagnostic performance as part of WHO Product Testing of malaria RDTs, PCR validation of malaria species in samples collected, malaria surveys, and slide banks. The centre provides invaluable support to national health authorities in endemic countries in the development of quality management systems for malaria RDTs and the management of training and accreditation workshops for malaria microscopists in numerous countries, including accreditation workshops in 12 countries in the last year and courses on external competency assessment in eight countries in the same period. The microscopy accreditation approaches developed as part of these activities have become WHO global standards for quality assurance of malaria microscopy and have been also adopted and introduced in other regions, including the South East Asian and the African regions. The presence of senior malaria experts from the institute at multiple WHO expert consultations, is also an asset for the Organisation and a valid contribution that this WHOCC brings to global public health.

./...

Overall, the expertise, resources and services of the Australian Army Malaria Institute give invaluable support to WHO's work in the fight against malaria, with a key presence in several global and regional initiatives which have major public health relevance today and for the several years to come.

We sincerely appreciate the support that the Institute continues to provide in malaria research and training, and we hope this could be continued and even expanded in the near future.

Yours sincerely,

Dr Robert Newman
Director
Global Malaria Programme

INSTITUTE FOR GLYCOMICS

Prof. Michael F Good AO MD PhD FTSE
Australia Fellow

www.griffith.edu.au

G26/4.18 Gold Coast Campus,
Griffith University, QLD 4222, Australia

20 September 2012

Dr. Dennis Shanks
Professor and Director,
Australian Army Malaria Institute
Building K10
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4051

Dear Dennis,

I understand that the Australian Army Malaria Institute is undergoing a formal review and if the opportunity arises I would like you to provide my thoughts to the committee of review.

My own association with AAMI goes back to when Dr. Karl Rieckmann was the Director. My own research in malaria at that time had a heavy focus on sporozoite immunity and vaccine research and I was very aware of Dr. Rieckmann's substantial contributions to the field, being one of the first to deliberately inoculate volunteers with irradiated sporozoites to measure immunity. Dr. Rieckmann provided me with good advice and encouragement after I returned from the USA.

After I became Director of QIMR, Dr. Qin Chen had moved from QIMR to AAMI and I again became associated with AAMI to help establish a QIMR Lab at AAMI. I believe that this was very beneficial to both QIMR and to AAMI. Other QIMR personnel have moved to AAMI since that time while maintaining close links with QIMR.

About 8 years ago, I had a direct collaboration with AAMI via Dr. Mike Edstein. We had previously published a paper in *The Lancet* demonstrating that exposure of humans to low doses of *P. falciparum*-infected red cells led to a strong T cell response and apparent protection from subsequent malaria. Mike Edstein subsequently demonstrated that the drug that we were using to treat malaria in the volunteers in our study had a slower metabolism than previously thought and this brought into consideration the possibility that the apparent protection that we had observed may have been mediated, at least in part, by residual drug. Mike and I subsequently wrote a paper on the topic and published it in *Antimicrobial Agents and Chemotherapy* in 2005.

More recently, I have re-established a very significant collaboration with Mike Edstein to test in *Aotus* monkeys a prototype malaria vaccine that we have developed. AAMI holds the only *Aotus* colony in Australia. Furthermore, after visiting a number of non-human primate colonies overseas I can attest that the AAMI facility is absolutely world class in terms of not just the scientific program but also in terms of animal welfare. We plan to use the facility within the next 6 months to test our vaccine. There are other primate colonies in Australia (including a Rhesus facility and a Baboon facility in Sydney), but these primates cannot be infected with the major human parasite, *P. falciparum*; thus AAMI has an incredibly valuable resource that is of enormous benefit to Australian research. While my own work is in the field of vaccines, the Army uses the facility for much drug development work for malaria. It goes without saying that as drug resistance of falciparum malaria parasites is increasing rapidly, the value of a facility to screen new drugs is very significant.

I know a number of the individuals who work at AAMI and I can personally attest to their very high international standing. As a result of their efforts and the efforts of those who have gone before them AAMI has a stellar international profile and is a facility of which Australia cannot only be proud, but of which Australia has a great need.

Yours sincerely

Prof. Michael F Good AO
Australia Fellow

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AUSTRALIA

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Professor Peter A Leggat
MD, PhD, DrPH, FAFPHM, FFPH RCP(UK), FACAsM, FACTM, FACRRM, FFTM FFEWM ACTM, FFTM RCPSG, FACE, FSIA, FAICD, FRGS, ACPHM CMSA, Hon FACTM
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26 September 2012

AMI Review Chair COL Craig Schramm
Director, Future Health Capability
Joint Health Command CP2-6-011
Campbell Park Offices
PO Box 7911
Canberra BC ACT 2610 Australia)

Dear COL Schramm,

Re: The Australian Army Malaria Institute

I write in my capacity as Director of the Anton Breinl Centre for Public Health and Tropical Medicine at James Cook University in response to a call for submissions concerning the review of the Australian Army Malaria Institute (AMI). Our Centre is one of the largest providers of postgraduate training in the Australasian region for public health and tropical medicine and we have maintained a close association with the AMI over many years.

The work of the AMI has been recognised internationally with conferral of World Health Organization Collaborating Centre status in the field of Malaria. This is noteworthy recognition for an organisation tackling a significant global health problem and a major problem for our region and for international deployments. The expertise of the Institute is broader than malaria however and there has been considerable involvement in translational research in other infectious disease areas with particular relevance to the tropics.

One of the reasons for the success of the AMI has been the strong multidisciplinary team operating out of the Institute that can, for example, examine issues relevant to vector biology, laboratory science or clinical practice. AMI has established strong links to relevant research groups working here and abroad. It has developed strong collaboration with universities supporting the Centre for Military and Veteran's Health, including the University of Queensland.

The record of the AMI is impeccable as are the credentials of its research leaders. I see considerable merit for the AMI in continuing to work with institutions such as the University of Queensland and ourselves, as this provides strong synergies in responding to issues arising from deployments.

Yours faithfully

Professor Peter A. Leggat
Director, Anton Breinl Centre
& Deputy Head (Campus Head)
School of Public Health, Tropical Medicine and Rehabilitation Sciences
Faculty of Medicine, Health and Molecular Sciences
James Cook University

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
F. EDWARD HEBERT SCHOOL OF MEDICINE
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799
http://www.usuhs.mil

October 4, 2012

Office of the Dean

COL Craig Schramm
Director, Future Health Capability
Joint Health Command CP2-6-011
Campbell Park Offices
P.O. Box 7911
Canberra BC ACT 2610
Australia

Ref: AMI Review

Dear COL Schramm:

I am writing to provide hopefully useful input into your review of the status of the Australian Army Malaria Institute (AMI). Over my more than 20-year US Army medical career, I've worked closely with the professionals assigned to the AMI and more recently, have had the opportunity to assign some of my own officers there for mutual benefit.

The US Army medical research mission, worldwide, is focused on the identification of new disease threats to our deployed forces and on the development of effective countermeasures (like drugs, vaccines, and diagnostic techniques) against these threats. In so many ways, this mission is very much aligned with that of the AMI. For much of my research career, I have worked in malaria vaccine development. To say that the AMI team has contributed in multiple important ways to the larger military malaria research mission—one of the top priorities for the US Army—would be an understatement. Further, AMI's expertise in the scientific assessment of vector-borne disease in general and the ability to properly frame these diseases in the proper public health and military context is incredibly remarkable. While many countries and their militaries are carefully considering how best to apply limited funds in support of the greatest good, one only needs to be reminded of potentially catastrophic outbreaks like that of SARS and the potential for more of the same in the future where the capability of an organization like the AMI is an important asset for both public/military health but also for national security.

When I commanded the Walter Reed Army Institute of Research (WRAIR), the US Department of Defense's largest and most diverse medical research laboratory, I witnessed first-hand the excellence and breadth of capabilities of the AMI staff, so much so that I continued to endorse the assignment of suitable exchange officers from my staff to the AMI where they had incredible opportunities to conduct militarily-relevant medical research responsive to the needs of both of our countries. The ties between the AMI, the WRAIR, and our research facility in Thailand, the

Armed Forces Research Institute for the Medical Sciences (AFRIMS) are extensive and AMI's status as the only WHO Collaborating Center in the entire South Pacific Region is a real enabler.

For its small size, the AMI is a powerhouse of military-focused medical/scientific knowledge and experience and is an important capability for the Australian Defense Organization. As a senior military clinician and as one who has worked closely with the AMI staff over the years, my hope is that your review will prove to be a positive one for the AMI. If you desire additional input from me or from others within the US Army's medical establishment, please let me know. I may be contacted by phone at and via e-mail at:

I look forward to a positive review.

Sincerely,

KESTER.KENT.EDWARD.1045853027

Digitally signed by KESTER.KENT.EDWARD.1045853027
DN: c=US, o=U.S. Government, ou=DoD, ou=PKI, ou=USA, cn=KESTER.KENT.EDWARD.1045853027
Date: 2012.10.04 11:42:02 -04'00'

Kent E. Kester, MD, FACP, FIDSA
Colonel, US Army
Associate Dean for Clinical Research and
Consultant to the Army Surgeon General
in Infectious Diseases and in Medical Research
and Development

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MD 21702-5012

OCT 2 3 2012

Office of the Commanding General

Colonel Craig Schramm, AMI Review Chair
Director, Future Health Capability Joint Health Command CP2-6-011
Campbell Park Offices
PO Box 7911
Canberra BC ACT 2610, Australia

Dear Colonel Schramm:

It is my understanding that the Australian Army Malaria Institute (AMI) is in the process of undergoing a review of its mission, current capabilities, and future role within the Australian Defense Organization (ADO). The US Army Medical Research and Materiel Command, specifically the US Army Medical Materiel Development Activity (USAMMDA), Pharmaceutical Systems Project Management Office, fully recognizes the exceptional work that has been done by the AMI in research on vector-borne infectious diseases, and in the development of vaccines for Dengue and Japanese Encephalitis and drugs for malaria treatment and prophylaxis. The USAMMDA has heavily relied on the AMI studies in filings for licensing of products with the Food and Drug Administration (FDA) in the past, and expect to continue to do so in the future.

I would like to express to the review committee the importance of AMI's continued contribution in the coming years as the challenges from vector-borne diseases are unlikely to diminish given the increasing participation of developing economies ravaged by malaria and other vector-borne diseases in the global market place. The potential for vector-borne diseases to expand under such circumstances cannot be ignored as our world becomes smaller.

Without the effort of AMI in the past several years in designing and implementing field studies to test the efficacy of new candidate prophylactic drugs, it is doubtful that the next generation of prophylactic candidate drugs would have been available as viable products with reasonable prospects for licensing in the US and elsewhere.

There is a common interest between our organizations' missions in protecting active duty service members deployed to malaria endemic areas. Both of our respective organizations have contributed in the past to the monitoring and evaluation of emerging drug resistance, the testing of new candidate antimalarial drugs, and the development of new chemoprophylaxis, and we are counting on AMI to continue to do so in the future. The synergy accrued from our mutual and parallel efforts should continue, not only for the benefit of our service members, but to enhance stability in emerging

economies. Our work contributes in no small measure to the global political stability that is an integral part and an essential component of the security of both our nations, given the fact that we have been closely allied in international peacekeeping efforts and will undoubtedly continue to do so in the future.

Malaria will undoubtedly continue to develop resistance to the currently available drugs. The question that we in the US and you in Australia need to continue to address is whether we will give up on the efforts to keep ahead of the disease or whether we will be fully engaged in developing new products.

We sincerely believe that continued support by the ADO for the mission of AMI is essential for future development of new prophylactic antimalarial drugs and vaccines. In fact, without such continued effort, it is doubtful that new prophylactic antimalarial drugs, such as Tafenoquine, will ever be licensed in the US or anywhere else. In the pursuit of this effort, a team representing USAMMDA visited AMI in recent months to coordinate the development of Tafenoquine as we intend to facilitate the licensing of this drug in both places, Australia and the US, within the next five years. To this end, studies done by AMI in the past several years will be essential for USAMMDA's filing with the FDA, and studies funded by us will similarly be critical for the filing package, which will be submitted to the Therapeutic Goods Administration in Australia.

We urge the review board to continue to support AMI in the coming years and look forward to a closer collaboration between our organizations in the realization that, under a resource constraint environment, collaboration will become even more essential if we hope to achieve our common goals of protecting our service members from vector-borne diseases as we deploy them to endemic areas.

Sincerely,

James K. Gilman
Major General, Medical Corps
Commanding General

ANNEX B

PRODUCT INFORMATION FOR ANTIMALARIALS USED BY DEFENCE

DORYX® CAPSULES

NAME OF THE MEDICINE

Doxycycline hyclate (hydrochloride)

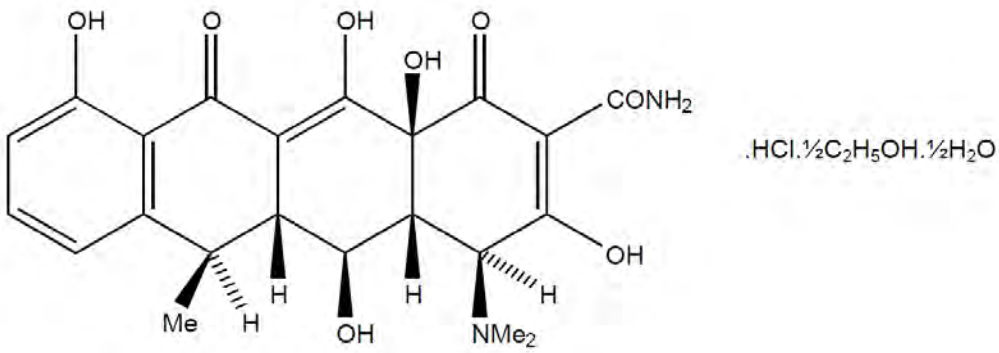
DESCRIPTION

Doxycycline is a broad spectrum antibiotic synthetically derived from oxytetracycline. The chemical designation of this light-yellow crystalline powder is 6-deoxy-5-oxytetracycline. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

The chemical structure of doxycycline hydrochloride is shown below:

Molecular Formula: $C_{22}H_{24}N_2O_8.HCl,½[C_2H_5OH.H_2O]$

MW: 512.9



CAS No: 24390-14-5

Doryx® capsules contain modified release pellets of doxycycline hyclate (hydrochloride). The capsule contains pellets which are coated so as to retard but not prevent release in acid media. Excipients include lactose, cellulose, povidone, hydroxypropyl methylcellulose phthalate, hypromellose, diethyl phthalate, gelatin, shellac, carbon black, wheat starch, magnesium stearate andhyprolose.

PHARMACOLOGY

Doxycycline is virtually completely absorbed after oral administration. Its absorption is not significantly affected by the presence of food or milk. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function (creatinine clearance above 75 mL/min). This percentage may fall as low as 1 to 5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half life of doxycycline range (18 to 22 hours) in individuals with normal and impaired renal function.

The proportion of drug that is not eliminated within urine is mainly excreted in the faeces. More than 90% of an oral dose of doxycycline is eliminated from the body within 72 hours of drug administration. The metabolism of doxycycline in the human body has not been investigated. *In vitro* serum protein binding of doxycycline varies from 23 to 93%.

Haemodialysis does not alter serum half life.

INDICATIONS

Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram positive and gram negative organisms.

NOTE: THE 50 mg CAPSULE IS NOT A PAEDIATRIC FORMULATION.

Doryx® is indicated in the treatment of infections caused by the following micro-organisms:

Mycoplasma pneumoniae: primary atypical pneumonia

Rickettsiae: Queensland tick typhus, typhus fever and Q fever

Agents of psittacosis

Calymmatobacterium (Donovania) granulomitis: granuloma inguinale

Agents of lymphogranuloma venereum

Borreliae: relapsing fever

Chlamydia trachomatis

Doryx® is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may be treated with oral Doryx® alone, or in combination with topical agents.

Doryx® is indicated in the treatment of infections caused by the following gram negative micro-organisms:

Vibrio species: cholera

Brucella species: brucellosis (in conjunction with streptomycin)

Yersinia pestis: plague

Francisella tularensis: tularemia

Bartonella bacilliformis: Bartonellosis

Bacteroides species

When penicillin is contraindicated, doxycycline is an alternative medicine in the treatment of infections due to:

Treponema pallidum: syphilis

Treponema pertenue: yaws

Neisseria gonorrhoea: gonorrhoea (see **DOSAGE AND ADMINISTRATION**)

Doryx® is not the medicine of choice in the treatment of any type of Staphylococcal infection or infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus faecalis*, or any type of enteric bacteria because many strains of

these organisms have been shown to be resistant to doxycycline. Doxycycline should not be used in these infections unless the organism has been shown to be sensitive. For upper respiratory tract infections due to group A beta-haemolytic streptococci (including prophylaxis of rheumatic fever) penicillin is the usual medicine of choice.

Doxycycline is active against both pre-erythroycitic and asexual bloodstages of *Plasmodium falciparum.* The tetracyclines are only partially active against the pre-erythrocytic stages of *Plasmodium vivax* and protection depends on drug suppression of the blood stages. Doxycycline has no activity against the relapsing forms (hypnozoites) of *Plasmodium vivax.*

Doxycycline is indicated, in adults and children older than 10 years, as chemoprophylaxis for malaria caused by *Plasmodium falciparum* and, in combination with other antimalarial agents, against malaria caused by *Plasmodium vivax.* Doxycycline is only able to suppress malaria caused by *P.vivax.* As there are relatively few locations where *P. vivax* does not co-exist to some extent with *P.falciparum*, it is recommended that doxycycline should be used routinely with other agents, for example chloroquine.

In acute intestinal amoebiasis Doryx® may be a useful adjunct to amoebicides.

In severe acne Doryx® may be a useful adjunctive therapy.

Susceptibility Testing

The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross resistance among them is common. Micro-organisms may be considered susceptible if the MIC (minimum inhibitory concentration) is less than 1.0 mcg/ml and intermediate if the MIC is 1.0 to 5.0 mcg/ml.

Susceptibility plate testing: A tetracycline disc may be used to determine microbial susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg tetracycline disc should give a zone of at least 19 mm when tested against a tetracycline-susceptible bacterial strain.

CONTRAINDICATIONS

This medicine is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any of the excipients of Doryx® capsules.

Use in pregnancy (16 weeks post conception) and use in lactation are contraindicated (see **PRECAUTIONS**).

Rare cases of benign intracranial hypertension have been reported after tetracyclines and after vitamin A or retinoids such as isotretinoin and etretinate. Concomitant treatment of tetracyclines with vitamin A or retinoids is therefore contraindicated (see **ADVERSE EFFECTS**)

PRECAUTIONS

If Doryx® capsules are ingested in an incorrect manner there is a risk of adhesion of the capsule to oesophagus. If this happens, oesophageal injury may occur. Dysphagia, retrosternal pain, new or worsening heartburn are possible symptoms of such injury. In order to avoid oesophageal injury, Doryx® capsules must be ingested with at least 100 mL of fluid

(half a glass) and the patient must remain upright for at least 30 minutes. Administration in the morning is recommended rather than in the evening.

The use of the medicines of the tetracycline class including Doryx® during tooth development (latter half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long term use of the medicines but has been observed following repeated short term courses. Enamel hypoplasia has also been reported. Doryx® therefore, should not be used in this age group unless other medicines are not likely to be effective or are contraindicated.

Intracranial hypertension (IH) has been associated with the use of tetracyclines including doxycycline (see **CONTRAINDICATIONS** and **ADVERSE EFFECTS**). The use of tetracyclines in infants, even in the usual therapeutic doses, may cause increased intracranial pressure and bulging of the fontanelles. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Clinical manifestations include headache, blurred vision, diplopia and vision loss. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Discontinuation of therapy typically results in prompt return of the pressure to normal. However, since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilise.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline medicines, and treatment should be discontinued at the first evidence of skin erythema.

The anti-anabolic action of the tetracyclines may cause an increase in serum urea. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

The use of tetracyclines in infants, even in the usual therapeutic doses, may cause increased intracranial pressure and bulging of the fontanelles. Discontinuation of therapy results in prompt return of the pressure to normal.

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Antibiotic associated psuedomembranous colitis has been reported with many antibiotics including Doryx®. A toxin produced with *Clostridium difficile*, appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to medicine discontinuation alone. This may be sufficient in the early stages, although cholestyramine orally may help by binding the toxin in the colonic lumen. However in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Medicines which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition and should not be used.

Product Information

In venereal disease when co-existent syphilis is suspected, proper diagnostic measures including a dark field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

In long term therapy, periodic laboratory evaluation of organ systems, including haemopoietic, renal and hepatic studies should be performed.

Rarely oesophagitis and oesophageal ulceration have been reported in patients receiving doxycycline. Most of these patients took medication immediately before going to bed. Administration of adequate amounts of fluid with the antibiotic is recommended to reduce the risk of oesophageal irritation and ulceration. It also is recommended that the antibiotic be administered in the morning (rather than late night), where practical, in an attempt to avoid this adverse effect.

If gastric irritation occurs, it is recommended that Doryx® be given with food or milk. The absorption of Doryx® is not markedly influenced by simultaneous ingestion of food or milk.

Infections due to group A beta-haemolytic streptococci should be treated for at least 10 days.

Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

Use in Pregnancy
Category D

Tetracyclines are safe for use during the first 18 weeks of pregnancy, after which they cause discolouration of the baby's teeth.

During the period of mineralisation of teeth (the latter half of pregnancy, the neonatal period and the first 8 years of life) tetracyclines may induce hypoplasia of the enamel and discolouration of the teeth. Tetracyclines also accumulate in the growing skeleton. These products should be avoided during the latter half of pregnancy.

Large doses of tetracyclines have caused fatty necrosis of the liver in pregnant women, especially those with pyelonephritis.

Australian categorisation definition of Category D:

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Use in Lactation

Doxycycline is present in the milk of lactating women. It forms a stable calcium complex in bone-forming tissue and a decrease in the fibula growth has been observed in prematures. The use of medicines of the tetracycline class during tooth development may also cause permanent discolouration of the teeth. Doxycycline should not be given to nursing mothers.

Usage in Newborns, Infants and Children

(See **PRECAUTIONS** regarding use during tooth development.)

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the medicine was discontinued.

Product Information

INTERACTIONS WITH OTHER MEDICINES

Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Antacids containing aluminium, calcium, magnesium or bismuth salts and preparations containing iron impair absorption and should not be given to patients taking Doryx®.

Since bacteriostatic medicines may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

Plasma levels of doxycycline are reduced by the administration of barbiturates, anticonvulsants (phenytoin, carbamazepine), disodium hydrogen citrate, sodium bicarbonate, sodium lactate, acetazolamide and ethoxzolamide.

Concurrent use of doxycycline may render oral contraceptives less effective and breakthrough bleeding may occur. Unplanned pregnancy may occur with this combination. A barrier method of contraception should be used while taking Doryx® and for seven days following completion of the course of Doryx®.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Effects on Laboratory Tests

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

ADVERSE EFFECTS

Doryx® is generally well tolerated.

Cases of benign intracranial hypertension have been reported with tetracyclines. It has also occurred with concomitant vitamin A or retinoids such as isotretinoin and etretinate (see **CONTRAINDICATIONS**).

Due to Doryx®'s virtually complete absorption, side effects of the lower bowel, particularly diarrhoea, have been infrequent. The following adverse reactions have been observed in patients receiving doxycycline:

More Common Reactions

Dermatological: photosensitive dermatitis, erythematous rash, maculopapular rash, morbilliform rash, pustular rash, urticaria, onycholysis and discolouration of the nails.

Hypersensitivity Reactions: urticaria, exacerbation of systemic lupus erythematosus.

Gastrointestinal: nausea, anorexia, vomiting, dysphagia, diarrhoea, oesophagitis, oesophageal ulceration, abdominal pain, glossitis, black hairy tongue.

Hepatic: cholestatic hepatitis, fatty liver degeneration.

Renal: dose related increase in serum urea.

Musculoskeletal: tooth discolouration, enamel hypoplasia.

Other: Bulging fontanelles have been reported in young infants following full therapeutic dosage. This sign disappeared rapidly when the medicine was discontinued.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

Less Common Reactions

Gastrointestinal: enterocolitis (see **PRECAUTIONS**), inflammatory lesions (with monilial overgrowth) in the anogenital region, dyspepsia and pseudomembranous colitis (see **PRECAUTIONS**), *C.difficile* diarrhoea. Abnormal hepatic function has been reported rarely (<1/1000).

Skin: exfoliative dermatitis, Steven-Johnson syndrome, Toxic Epidermal Necrolysis (TEN).

Musculoskeletal: arthralgia, myalgia.

Genitourinary: acute renal failure.

Hypersensitivity Reactions: angioneurotic oedema, anaphylaxis, anaphylactic shock, anaphylactic reaction, pericarditis, anaphylactoid purpura, serum sickness, hypotension, dyspnoea, peripheral oedema, tachycardia.

Haematological and Reticuloendothelial: phlebitis associated with IV administration, leucopenia, thrombocytopenia, purpura, increase in prothrombin time, haemolytic anaemia, eosinophilia.

Nervous System: flushing, malaise, headache, confusion, taste loss; stupor, hypoaesthesia, paraesthesia, somnolence, benign intracranial hypertension in adults, increased intracranial pressure in infants. In relation to benign intracranial hypertension, symptoms included blurring of vision, scotomata and diplopia. Permanent visual loss has been reported.

Ocular: conjunctivitis, periorbital oedema.

Hearing/Vestibular: tinnitus.

Psychiatric: depression, anxiety, hallucination.

Respiratory: bronchospasm.

Rare Reactions

Dysphagia, retrosternal pain.

DOSAGE AND ADMINISTRATION

NOTE: THE 50 mg CAPSULE IS NOT A PAEDIATRIC FORMULATION.

Doryx® capsules must be ingested whole with at least 100 mL of liquid (half a glass), preferably in the morning when the patient can remain upright for at least 30 minutes. If gastric irritation occurs, Doryx® capsules can be taken with food or milk, since studies indicate that the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Administration of adequate amounts of fluid with the capsules and morning (rather than late night) dosage of the medicine, where practical, is recommended to reduce the risk of oesophageal irritation and ulceration. If gastric irritation occurs, it is recommended that

Product Information

Doryx® be given with food or milk. The absorption of Doryx® is not markedly influenced by simultaneous ingestion of food or milk. Antacids containing aluminium, calcium, magnesium or bismuth salts and preparations containing iron, impair absorption and should not be given to patients taking Doryx® (see **PRECAUTIONS**)

The usual dosage and frequency of administration of Doryx® differs from that of other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side-effects. Therapy should be continued at least 24 to 48 hours after symptoms and fever have subsided.

Tetracyclines are not the medicines of choice for the treatment of streptococcal infections (see **INDICATIONS**). However, when used, therapy should be continued for 10 days.

Adults and children over 8 years of age (and above 50 kg in weight): The usual dose of Doryx® is 200 mg on the first day of treatment (administered as 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract) 100 mg every 12 hours is recommended.

For treatment of severe acne, some efficacy has been demonstrated in some individuals at a dose of 50 mg/day over a period of 12 weeks. No data showing efficacy beyond 12 weeks have been submitted.

Malaria chemoprophylaxis: Doryx® 100 mg once a day; commencing 2 days prior to entering malarious areas, while in the malarious area and for 4 weeks after leaving the malarious area. A maximum of Doryx® 100 mg daily for 8 weeks is recommended, as safety after 8 weeks has not been clearly established (See **INDICATIONS** section about combination with other antimalarial agents for prophylaxis against *P.vivax*).

Acute uncomplicated gonococcal infections: 100 mg twice daily for 5 to 7 days. Resistance to tetracyclines is not uncommon amongst gonococci. The use of tetracyclines in the treatment of gonorrhoea should, therefore, be accompanied by monitoring efficacy.

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.

Louse-borne typhus has been successfully treated with a single oral dose of 100 mg or 200 mg according to severity.

For the prevention of scrub typhus: 200 mg as a single dose.

For children above 8 years of age without skeletal growth retardation but weighing less than 50 kg: The adult dose of 100 mg should be calculated on a weight basis of 2 mg/kg. (See **PRECAUTIONS** about **Use in children**).

Studies to date have indicated that administration of Doryx® at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

OVERDOSAGE

In case of overdose, immediately contact the Poisons Information Centre for advice (in Australia, call 13 11 26).

Product Information

PRESENTATION AND STORAGE CONDITIONS

Doryx® 100 mg: clear capsules marked Doryx 100, containing yellow pellets, available in a blister pack or bottles of 7 and 21.

Doryx® 50 mg: clear capsules marked Doryx 50, containing yellow pellets, available in a blister pack or bottle of 25.

Store below 25ºC.

NAME AND ADDRESS OF THE SPONSOR

Mayne Pharma International Pty Ltd
ABN 88 007 870 984
1538 Main North Road
Salisbury South SA 5106
Australia

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

25 October 1991

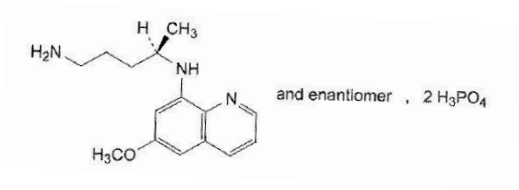
DATE OF MOST RECENT AMENDMENT

23 June 2017

PRODUCT INFORMATION

PRIMACIN® TABLETS

Name of the medicine
Primaquine phosphate



and enantiomer

$C_{15}H_{21}N_3O,2H_3PO_4$ 455.3

(4RS)-N^4-(6-Methoxyquinolin-8-yl)pentane-1,4-diamine bisphosphate

CAS Registry Number: 63-45-6

Description
Primaquine phosphate is an orange crystalline powder and melts at about 200°C with decomposition. It is soluble in water and practically insoluble in ethanol.

Primacin tablets contain lactose (53.6 mg), wheat starch, povidone, gelatin, glycerol, magnesium stearate and purified talc as excipients.

Pharmacology
Primaquine is an antimalarial agent. It is used as a schizontocide for the treatment of the hypnozoite stage (in the liver) of malaria. Primaquine is effective against exoerythrocytic stages of *Plasmodium vivax* and *Plasmodium ovale* and against the primary exoerythrocytic stages of *Plasmodium falciparum*. It is also effective against the sexual forms (gametocytes) of plasmodia, especially *P. falciparum*, disrupting transmission of the disease by eliminating the reservoir from which the mosquito carrier is infected. Primaquine is more active against tissue forms and gametes than asexual blood forms of plasmodia. The precise mechanism of action is not known. There is some *in vitro* evidence that some of the antiparasitic effect may be due to the binding and inhibition of entry of the parasite to the hepatoma cell.

Pharmacokinetics
Absorption
Primaquine is rapidly absorbed (T_{max} about 2 hours) from the gastrointestinal tract and the concentration of the drug in the body is dose dependent. Oral bioavailability studies (not performed with this product) shows that primaquine is rapidly and almost completely absorbed.

Distribution
It is widely distributed and the mean apparent Vd range across studies is 260 – 300 L. It is extensively

distributed in body issues.
Metabolism
Primaquine is rapidly metabolised after an oral dose, mainly by the liver, with an elimination half-life ranging from 4.3 to 7.4 hours. The principle metabolite is carboxyprimaquine which has a longer half-life and accumulates over a 14 day course of 15 mg primaquine/day.

Indications
- Prevention of relapses (radical cure) of malaria caused by *P. vivax* and *P. ovale.*
- Adjunctive therapy in the treatment of gametocytemia due to *P. falciparum* in patients resident in areas receptive to malaria.

Contraindications
- Hypersensitivity to primaquine or other 8-aminoquinolines
- Hypersensitivity to other ingredients in Primacin tablets
- Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Pregnant women
- Acutely ill patients with any serious systemic diseases characterised by a tendency to granulocytopenia, such as rheumatoid arthritis or lupus erythematosus
- Patients receiving concurrently other potentially haemolytic medicines or depressants of myeloid elements of the bone marrow

Precautions
Primaquine was first used as an anti-malarial agent in humans in the late 1940's and early 1950's. It has not been subject to the systematic long term safety testing in animals that would be expected of a drug developed more recently.

Haemolytic anaemia and G6PD deficiency
Primaquine may cause severe haemolytic anaemia in individuals with G6PD deficiency. Due to the risk of haemolytic anaemia in patients with G6PD deficiency, G6PD testing has to be performed prior to the administration of primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of haemolysis, and adequate medical support and follow-up to manage haemolytic risk should be available.

Primaquine should not be prescribed for patients with severe G6PD deficiency (see **Contraindications**).

There is limited evidence that adults with moderately reduced G6PD deficiency may be able to tolerate 45 mg once weekly for 8 weeks. In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. If primaquine administration is considered, baseline haematocrit and haemoglobin must be checked before treatment, and close haematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage haemolytic risk should be available.

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline haematocrit and haemoglobin must be checked before treatment and close haematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage haemolytic risk should be available.

Discontinue the use of primaquine phosphate promptly if signs suggestive of haemolytic anaemia occur (darkening of the urine, marked fall of haemoglobin or erythrocyte count).

Haemolytic reactions (moderate to severe) may occur in individuals with G6PD deficiency and in individuals with a family or personal history of favism. Areas of high prevalence of G6PD deficiency are Africa, Southern Europe, Mediterranean region, Middle East, South-East Asia and Oceania. People from these regions have a greater tendency to develop haemolytic anaemia while receiving primaquine and related drugs, due to a congenital deficiency of erythrocytic G6PD.

Methaemoglobinaemia and NADH methaemoglobin reductase deficiency
Primaquine may cause methaemoglobinaemia in individuals with NADH methaemoglobin reductase deficiency. Patients should be observed carefully and treatment stopped if signs of methaemoglobinaemia are observed.

Blood monitoring
Anaemia, methaemoglobinaemia and leukopenia have been observed following administration of large doses of primaquine. Primaquine taken at daily doses of 120 mg/day, higher than recommended for Primacin tablets, has been associated with neutropenia and agranulocytosis.

It is advisable to perform routine blood examinations, particularly blood cell counts and haemoglobin determinations, during therapy.

If primaquine phosphate is prescribed for an individual who has shown a previous idiosyncratic reaction to primaquine phosphate as manifested by haemolytic anaemia, methaemoglobinaemia or leukopenia, or for an individual with a family or personal history of haemolytic anaemia or NADH methaemoglobin reductase deficiency, the person should be observed closely.

In all patients, primaquine phosphate should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or leukocyte count occurs.

Potential prolongation of QT interval
Due to potential for QT prolongation, monitor electrocardiogram (ECG) when using primaquine in patients with cardiac disease, long QT syndrome, a history of ventricular arrhythmias, uncorrected hypokalaemia and/or hypomagnesaemia, or bradycardia (< 50 bpm) and during concomitant administration with QT interval prolonging agents.

Lactose intolerance
Primaquine tablets contain lactose as an excipient and should be used with caution in patients sensitive to lactose.

Use in pregnancy
Category D
Safe usage of primaquine phosphate in pregnancy has not been established. Primaquine is contraindicated in pregnant women. Even if a pregnant woman is G6PD normal, the fetus may not be.

Use in lactation
No studies have been carried out in relation to the safe use of primaquine during lactation. It is not known whether primaquine is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse effects in nursing infants from primaquine, a decision should be made whether to discontinue nursing or discontinue primaquine, taking into account the importance of primaquine to the mother.

Use in the elderly
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and

of concomitant disease or other therapy.

Interactions with other medicines

Because quinacrine hydrochloride appears to potentiate the toxicity of antimalarial compounds which are structurally related to primaquine, the use of quinacrine in patients receiving primaquine is contraindicated. Similarly, primaquine should not be administered to patients who have received quinacrine recently, as toxicity is increased.

The interaction of primaquine and proguanil has not been assessed *in vivo*. Other 8-aminoquinolines (pamaquine and pentaquine) administered with proguanil have resulted in 5 – 10 fold increases in 8-aminoquinoline concentration.

Drugs known to suppress bone marrow and drugs known to cause haemolysis should not be administered with primaquine.

Caution is advised of primaquine is used concomitantly with other medicines that prolong the QT interval.

Ketoconazole reduced metabolism of primaquine in an *in vitro* study using human liver microsomes. The effects of ketoconazole and other drugs metabolised by the cytochrome P450 system on primaquine metabolism have not been assessed *in vivo*.

Adverse effects

Gastrointestinal disorders

Common: abdominal cramps and pains, nausea, vomiting, epigastric distress. Gastrointestinal symptoms are dose related.

Blood and lymphatic system disorders

Haemolytic anaemia in individuals with G-6-PD deficiency or following administration of large doses of primaquine.

Methaemoglobinaemia in individuals with NADH methaemoglobin reductase deficiency or following administration of large doses of primaquine. Evidence of increased methaemoglobin concentration on laboratory testing may be observed more commonly.

Leukopenia has been observed following administration of large doses of primaquine. Neutropenia and agranulocytosis have been observed in subjects taking very high doses of primaquine (120 mg daily for 14 days).

Cardiac disorders

Cardiac arrhythmia, QT interval prolongation.

Nervous system disorders

Common: dizziness, headache.

Skin and subcutaneous disorders

Rash, pruritus.

Dosage and administration

Primaquine should be taken with food.

Radical treatment

(a) 15 mg daily for 14 days.
(b) Up to 30 mg daily for 14 days in areas where resistant malaria strains occur or where treatment has failed with lower doses.
(c) The WHO advises that the treatment period of 21 days should be employed to achieve *radical cure* in most of South East Asia and the Pacific regions. Other antimalarial agents may be used concomitantly.

(d) For patients with G6PD deficiency: up to 45 mg once weekly for 8 weeks with monitoring for the development of haemolysis.
(e) Paediatric dose: 0.3 mg/kg/day.
(f) For the reduction of gametocytes of *P. falciparum*: 45 mg as a single dose for adults and 0.7 to 1.0 mg/kg for children.

Overdosage

Symptoms of overdosage of primaquine phosphate include abdominal cramps, vomiting, burning epigastric distress, central nervous system and cardiovascular disturbances, including cardiac arrhythmia and QT interval prolongation, cyanosis, methaemoglobinaemia, moderate leukocytosis or leukopenia, and anaemia. The most striking symptoms are granulocytopenia and acute haemolytic anaemia in sensitive persons. Acute haemolysis occurs, but patients recover completely if the dosage is discontinued.

For all overdoses in general, the mainstay of treatment is supportive and symptomatic care.

Treatment may be conducted according to an acute oral overdose protocol, including use of activated charcoal. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Prompt measures should be taken to counteract depressant effects on the cardiovascular and respiratory systems.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

Presentation and storage conditions

Primacin tablets are round, flat, orange uncoated tablets containing 7.5 mg primaquine base as 13.2 mg primaquine phosphate.

HDPE bottles with PP child-resistant closure of 28 and 56 tablets

Store below 25°C.

Name and address of the sponsor

Boucher & Muir Pty Ltd
Level 9, 76 Berry Street
North Sydney NSW 2060

Poison Schedule of the medicine

Prescription Only Medicine – Schedule 4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

10 November 2014

Date of most recent amendment

27 February 2017

PRODUCT INFORMATION

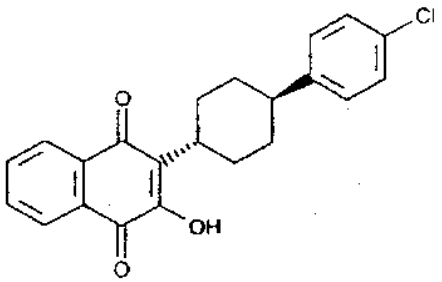
MALARONE® TABLETS (250/100)
MALARONE® JUNIOR TABLETS (62.5/25)

NAME OF THE MEDICINE: atovaquone and proguanil hydrochloride

DESCRIPTION:

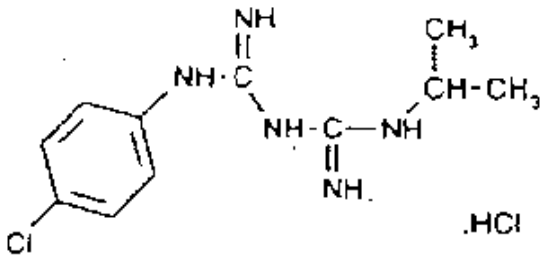
Malarone Tablets (250/100) and Malarone Junior Tablet (62.5/25) are fixed combination products containing atovaquone and proguanil hydrochloride. Each Malarone Tablet (250/100) contains atovaquone 250 mg and proguanil hydrochloride 100 mg. Each Malarone Junior Tablet (62.5/25) contains atovaquone 62.5 mg and proguanil hydrochloride 25 mg. Both tablets also contain: hydroxypropylcellulose, microcrystalline cellulose, povidone K30, sodium starch glycollate, macrogol 400, magnesium stearate, macrogol 8000, poloxamer 188 and pink colour concentrate OY-S-24972.

The chemical name of atovaquone is *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone. The molecular formula of atovaquone is $C_{22}H_{19}ClO_3$ and it has a molecular weight of 366.84. Atovaquone is virtually insoluble in water (less than 2×10^{-4} mg/mL) and slightly soluble (1.7 mg/mL) in 0.1 M sodium hydroxide. The CAS Registry Number is 95233-18-4. The structural formula is shown below:



Atovaquone

The chemical name of proguanil hydrochloride is 1-(4-chlorophenyl)-5-isopropyl-biguanide hydrochloride. The molecular formula of proguanil hydrochloride is $C_{11}H_{16}ClN_5.HCl$ and it has a molecular weight of 290.20. Proguanil hydrochloride is slightly soluble at 1 part in 110 parts of water and is sparingly soluble in alcohol (1 part in 40 parts of alcohol). The CAS Registry Number is 637-32-1. The structural formula is shown below:



Proguanil hydrochloride

PHARMACOLOGY:

Mode of Action
The constituents of Malarone, atovaquone and proguanil hydrochloride, interfere with two different pathways in the biosynthesis of pyrimidines, required for nucleic acid replication. The mechanism of action of atovaquone against *P. falciparum* is via inhibition of mitochondrial electron transport, at the level of the cytochrome bc_1 complex, and collapse of mitochondrial membrane potential. One mechanism of action of proguanil, via its metabolite cycloguanil, is inhibition of dihydrofolate reductase, which disrupts deoxythymidylate synthesis. Proguanil also has antimalarial activity independent of its metabolism to cycloguanil, and proguanil, but not cycloguanil, is able to potentiate the ability of atovaquone to collapse mictochondrial membrane potential in malaria parasites. This latter mechanism may explain the synergy seen when atovaquone and proguanil are used in combination, as in Malarone.

Microbiology
Atovaquone is active against *Plasmodium spp* (*in vitro* IC_{50} against *P. falciparum* 0.23-1.43 ng/mL).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC_{50} against various *P. falciparum* strains of 4-20 ng/mL). Some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 0.6-3.0 µg/mL.

In *in vitro* studies of *P. falciparum*, the combination of atovaquone and proguanil was shown to be synergistic. This enhanced efficacy was also demonstrated in clinical studies.

PHARMACOKINETICS:

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose. In clinical trials, trough levels of atovaquone, proguanil and cycloguanil in children (weighing 11-40 kg) are within the effective range observed in adults after adjusting for bodyweight.

Absorption
Atovaquone is a highly lipophilic compound with low aqueous solubility and poor oral bioavailability that varies with dose and diet.

Although there are no atovaquone bioavailability data in healthy subjects, in HIV-infected patients the absolute bioavailability of a 750 mg single dose of atovaquone tablets taken with food is 21% (90% CI: 17% - 27%).

Dietary fat taken with atovaquone increases the rate and extent of absorption. When taken with a standard breakfast containing 23 g of fat, AUC was increased 2-3 times and C_{max} 5 times compared with fasting. Patients are recommended to take Malarone tablets with food or a milky drink (see **DOSAGE AND ADMINISTRATION**).

Proguanil hydrochloride is rapidly and extensively absorbed regardless of food intake. Peak plasma concentrations occur between 2-4 hours after a single 200 mg dose. The absolute bioavailability is not known.

In a comparative bioavailability study in healthy adult volunteers, Malarone administered as a single dose was bioequivalent to separate tablets of atovaquone 250 mg and proguanil hydrochloride 100 mg given concomitantly. In healthy adult subjects treated for 3 days, the pharmacokinetics of atovaquone, and proguanil and its metabolite cycloguanil, were not modified when atovaquone and proguanil were given alone or in combination as Malarone.

Distribution:
Atovaquone is highly protein bound (>99%) but does not displace other highly protein bound drugs *in vitro*, indicating significant drug interactions arising from displacement are unlikely.

Following oral administration, the volume of distribution of atovaquone in adults and children is approximately 7 to 8 L/Kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults is 25 L/Kg. In children (weighing 11 - 40 kg), the volume of distribution is approximately 27 to 30 L/Kg.

In human plasma, the protein binding of atovaquone or proguanil was unaffected by the presence of the other drug.

Metabolism:
There is no evidence that atovaquone is metabolised. Greater than 90% of atovaquone is eliminated unchanged in the faeces with negligible excretion in urine.

Proguanil hydrochloride is partially metabolised to cycloguanil and 4-chlorophenyl biguanide with less than 40% being excreted unchanged in urine. These metabolites are also excreted in the urine. Conversion of proguanil to cycloguanil is mediated in the liver by cytochrome P450 3A4 and 2C19. Conversion of proguanil to cycloguanil may be reduced in some individuals, due to genetic polymorphism of the metabolising enzyme. During administration with Malarone, at the recommended doses, proguanil metabolism status appears to have no implications for treatment or prophylaxis of malaria.

Elimination:
The elimination half-life of atovaquone is about 2-3 days in adults and 1-2 days in children.

Following oral administration, the clearance of atovaquone in adults and children (weighing 40 kg) is approximately 0.04 to 0.05 L/h/Kg. In children (weighing 11 - 40 kg), the clearance is approximately 0.12 to 0.05 L/h/Kg, respectively.

Following oral administration, the clearance of proguanil in adults is 1.3 L/h/Kg. In children (11-40 kg body-weight) after adjusting for differences in body-weight, clearance is higher in an 11 kg child (0.12 L/h/kg) and decreases with increasing weight to 0.05 L/h/kg in a 40 kg child.

In both adults and children, the elimination half life for proguanil or cycloguanil is about 12-15 hours.

Pharmacokinetics in the elderly:
There is no clinically significant change in the average rate or extent of absorption of atovaquone or proguanil between elderly and young patients. Systemic availability of cyloguanil is higher in the elderly compared with young patients, but there is no clinically significant change in its elimination half-life (see **DOSAGE and ADMINISTRATION**).

Pharmacokinetics in renal impairment:
In patients with mild to moderate renal impairment, oral clearance and/or AUC data for atovaquone, proguanil and cycloguanil are within the range of values observed in patients with normal renal function. Atovaquone Cmax and AUC are reduced in patients with severe renal impairment. The elimination half lives for proguanil and cycloguanil are prolonged in patients with severe renal impairment with corresponding increases in AUC, resulting in the potential of drug accumulation with repeated dosing (see **DOSAGE and ADMINISTRATION, CONTRAINDICATIONS** and **PRECAUTIONS**).

Pharmacokinetics in hepatic impairment:
In patients with mild to moderate hepatic impairment, there is no clinically significant change in exposure to atovaquone compared with healthy patients. In patients with mild to moderate hepatic impairment there is an increase in proguanil AUC with no change in its elimination half life and there is a decrease in Cmax and AUC for cycloguanil. No data are available in patients with severe hepatic impairment. (See **DOSAGE and ADMINISTRATION,** and **PRECAUTIONS**).

CLINICAL TRIALS:

The safety and effectiveness of Malarone Tablets (250/100) and Malarone Junior Tablets (62.5/25) have been established in studies of up to 12 weeks in adult and paediatric subjects.

Prophylaxis of Malaria (individuals > 40 kg): The safety and efficacy of Malarone Tablets (250/100) in the prophylaxis of *P. falciparum* malaria was demonstrated in five randomised, double-blind clinical studies. Three placebo-controlled parallel group studies were conducted in residents of malaria-endemic areas (MALB2001, MALB3001 and MALB3003), and two active-controlled studies were conducted in non-immune travellers (MALB30010 and MALB30011).

There were 473 patients in placebo-controlled studies, 232 of whom received one Malarone Tablet (250/100) daily for 10-12 weeks of chemoprophylaxis, and 241 received placebo. Prevention of parasitaemia was the primary endpoint in the studies. Malarone had an overall efficacy of 97% (range 95-100%) for prevention of *P. falciparum* parasitaemia and an adverse event profile similar to placebo.

MALB3003 included 204 children (weighing 11-40 kg) who received a lower dose of Malarone or placebo based on body weight (see Prophylaxis of Malaria (individuals 11-40 kg)

There were 1975 patients in active controlled studies, 993 of whom received one Malarone Tablet (250/100) daily at the recommended dose (see **DOSAGE and ADMINISTRATION)**, 471 received mefloquine weekly (1 to 3 weeks before until 4 weeks after travel) and 511 patients received chloroquine weekly (1 week before until 4 weeks after travel) plus daily proguanil (1-2 days before until 4 weeks after travel). Frequency of adverse events was the primary endpoint and development of confirmed falciparum malaria within 60 days after leaving the malaria-endemic area was the secondary endpoint in the studies. No patients receiving Malarone or mefloquine contracted malaria (efficacy 100%), and 3 patients receiving chloroquine/proguanil contracted malaria (efficacy at least 70%). Patients receiving Malarone experienced fewer neuropsychiatric and gastrointestinal adverse reactions than patients receiving mefloquine and chloroquine/proguanil respectively.

Prophylaxis of Malaria (individuals 11-40 kg): The efficacy and safety Malarone Junior Tablets (62.5/25) in the prophylaxis of *P. falciparum* malaria in patients weighing 11-40 kg was demonstrated in two randomised, placebo-controlled, double blind studies of 12 week duration conducted in residents of malaria endemic areas. A total of 534 patients (11-40 kg) were enrolled in the studies, of which 264 received the recommended dose of Malarone Junior Tablets (62.5/25) based on body weight; 11-20 kg - 1 Junior tablet containing 62.5 mg atovaquone + 25 mg proguanil hydrochloride; 21-30 kg - 2 Junior tablets; 31-40 kg - 3 Junior tablets (MALB3003 and MAL30015).

In the combined data from the two studies (per-protocol population), only one of 238 patients (0.4%) in the Malarone group developed *P. falciparum* parasitaemia during chemoprophylaxis over 12 weeks, compared with 50 of 245 (20.4%) patients in the placebo group. The protective efficacy of Malarone was calculated to be 97.9% in this population.

The safety findings with regard to adverse events during chemosuppression showed no differences between Malarone and placebo.

The safety profile of Malarone was assessed in two active controlled studies in travelers to malaria endemic areas (Studies MAL30010 - mefloquine and MAL30012 - chloroquine/ proguanil). (See **Adverse Events)**. With respect to efficacy, in combined data from the two active-controlled studies (n=186; 93 in the Malarone group), there was no confirmed cases of *P. falciparum* during chemoprophylaxis or in follow-up to Day 60.

Treatment of Malaria: Eight clinical studies (5 controlled and 3 uncontrolled) were conducted in 1115 patients of atovaquone and/or proguanil hydrochloride administered for the treatment of falciparum malaria. Studies in children were conducted at doses of atovaquone and proguanil hydrochloride based on body weight; 466 patients (adults and children) received concurrent atovaquone and proguanil hydrochloride at the recommended dose (see **DOSAGE and ADMINISTRATION**).

The primary efficacy endpoint was the proportion of evaluable patients cured of acute malaria. Cure was defined by clearance of asexual parasitaemia within 7 days of initiation of treatment, without subsequent recrudescence during the 28 day follow-up period.

In the controlled clinical trials, the study population included only patients with uncomplicated falciparum malaria. The comparator was standard antimalarial therapy within the country in which the study was conducted. Treatment with combination of atovaquone and proguanil hydrochloride was curative in 98% of evaluable patients (combined result). The concurrent administration of atovaquone and proguanil hydrochloride was more efficacious in three studies and of equivalent efficacy in two trials as the respective comparator antimalarial regimen (Table 1).

Table 1. Summary of Controlled Clinical Studies

			Evaluable Patients		Cure Rate (%)	
Country	Age Range (years)	Comparator	ATOV and PROG	Comparator	ATOV and PROG	Comparator
Zambia	14-54	Pyrimethamine and Sulphadoxine	80	80	100	99
Thailand	15-63	Mefloquine Hydrochloride	79	79	100***	86
Gabon	15-80	Amodiaquine Hydrochloride	63	63	98**	81
Philippines	12-64	Chloroquine+, Pyrimethamine and Sulphadoxine	54	32	100*	88
Kenya	3-12	Halofantrine	81	83	94	90

ATOV - Atovaquone; PROG - Proguanil hydrochloride.
* p<0.05, **p<0.005, ***p<0.002 versus comparator.
+ Initially as monotherapy, followed by combination therapy.

In uncontrolled studies conducted in Thailand using the recommended dose of atovaquone and proguanil hydrochloride, the cure rate of malaria was 100% in adults (n=24, *P. falciparum*) and 100% in children (n=26, *P. falciparum*).

INDICATIONS:

Malarone is indicated for:

- Prophylaxis of *Plasmodium falciparum* malaria in adults and children ≥ 11 kg.
- Treatment of *Plasmodium falciparum* malaria in adults and children aged 3 years or older.

CONTRAINDICATIONS:

Malarone is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or to any component of the formulation.

Malarone is contraindicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30 mL/min).

PRECAUTIONS:

Malarone has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria including hyperparasitaemia, pulmonary oedema or renal failure.

Safety and efficacy of Malarone for the treatment and prophylaxis of malaria in paediatric patients who weigh less than 11 kg have not been established.

In the event of recrudescent infections due to *P. falciparum* or failure of chemoprophylaxis, patients should be treated with a different blood schizonticide.

Parasite relapse occurred commonly when *P. vivax* malaria was treated with Malarone alone. Travellers with intense exposure to *P. vivax* or *P. ovale*, and those who develop malaria caused by either of these parasites, will require additional treatment with a drug such as primaquine, that is active against hypnozoites.

Persons taking Malarone for prophylaxis or treatment of malaria should take a repeat dose if they vomit within 1 hour of dosing. In the event of diarrhoea, normal dosing should be continued. Absorption of atovaquone may be reduced in patients with diarrhoea or vomiting, but diarrhoea or vomiting was not associated with reduced efficacy in clinical trials of Malarone for malaria prophylaxis. However, as with other antimalarial agents, patients with diarrhoea or vomiting should be advised to continue to comply with personal protection measures (repellants, bednets).

In patients with acute malaria who present with diarrhoea or vomiting, alternative therapy should be considered. If Malarone is used to treat malaria in these patients, parasitaemia should be closely monitored.

The co-administration of Malarone with other antimalarial drugs has not been evaluated.

Parasitaemia should be closely monitored in patients receiving concurrent metoclopramide or tetracycline (see **INTERACTIONS WITH OTHER MEDICINES**).

The concomitant administration of Malarone and rifampicin or rifabutin is not recommended (see **INTERACTIONS WITH OTHER MEDICINES)**.

Carcinogenicity, mutagenicity and impairment of fertility:
Oncogenicity studies of atovaquone alone in mice showed an increased incidence of hepatocellular adenomas and carcinomas at all dose levels tested, yielding exposures approximately 5 to 8 times the average steady-state plasma concentrations in humans during prophylaxis of malaria. The pattern of associated histological findings observed in the liver, is consistent with a species specific, non genotoxic, neoplastic response. Studies in rats at oral dose levels of up to 500 mg/kg/day were negative. Atovaquone is unlikely to present a carcinogenic risk to humans at therapeutic doses.

Oncogenicity studies on proguanil alone showed no evidence of carcinogenicity in rats and mice at doses resulting in exposures approximately equal to those obtained in humans during prophylaxis of malaria but considerably below exposures obtained during treatment of malaria. Carcinogenicity studies have not been conducted with atovaquone in combination with proguanil.

There was no evidence that either atovaquone or proguanil alone were mutagenic in bacterial and mammalian cell gene mutation assays *in vitro*, and in mouse bone marrow micronucleus assays for chromosome damage *in vivo*. Cycloguanil, an active metabolite of proguanil, was negative in a bacterial mutagenicity assay but positive in both a mammalian cell mutagenicity assay and a mouse micronucleus test. As the genotoxicity of cycloguanil is prevented or moderated by the co-administration of folinic acid, it appears to be related to the inhibition of mammalian dihydrofolate reductase, causing a reduction in the nucleotide pool and a consequent perturbation of DNA synthesis rather than a direct interaction with DNA. Neither proguanil nor cycloguanil is likely to present a genotoxic risk at clinical exposure levels. Mutagenicity studies have not been performed with atovaquone in combination with proguanil.

There are no data on the effect of atovaquone on human fertility. Data from animal studies show that atovaquone does not affect reproductive potential or performance at oral doses of up to 1000 mg/kg (approximately 6.5 times human exposure at the maximum recommended clinical treatment dose, based on AUC). A study in rats showed no impairment of male or female fertility at oral proguanil doses up to 16 mg/kg/day (approximately 0.03 times human exposure at the recommended clinical treatment dose, based on AUC). However, there is some evidence from published animal studies that proguanil and/or its main metabolite, cycloguanil, may cause impairment of fertility/early embryonic loss. No fertility studies have been performed in animals with atovaquone in combination with proguanil.

Findings in repeat dose studies with the atovaquone and proguanil hydrochloride combination were entirely proguanil related. As proguanil has been used extensively and safely in the treatment and prophylaxis of malaria at doses similar to those used in Malarone, these findings are considered of little relevance in the clinical situation.

Use in Pregnancy (Category B2):
The safety of the drug combination in human pregnancy has not been established. There is no information on effects of atovaquone administration during human pregnancy. Foetal death and malformation have rarely been reported in association with the use of proguanil. The relationship of these events to proguanil is not certain, and the overall number of reported events is low, given that the drug has been used in pregnant women for many years. Foetal loss is a known complication of *Plasmodium falciparum* malaria in pregnancy.

The proguanil component of Malarone acts by inhibiting parasitic dihydrofolate reductase. There are no clinical data indicating that folate supplementation diminishes drug efficacy. For women of childbearing age receiving folate supplements to prevent neural tube birth defects, such supplements may be continued while taking Malarone.

Embryofoetal development studies in animals with the combination of atovaquone and proguanil did not indicate any teratogenic potential in rats at doses up to 50:20 mg/kg/day (approximately 5 times the human exposure to atovaquone and 0.3 times human exposure to proguanil, based on treatment AUCs), nor in rabbits at doses up to 100:40 mg/kg/day (approximately 1 times the human exposure to atovaquone and 0.5 times the exposure to proguanil, based on treatment AUCs). In rabbits given atovaquone alone at 1200 mg/kg/day (approximately 1.4 times the estimated human exposure during treatment of malaria), an increased incidence of resorptions and decreased length and weight of foetuses was noted. These effects were observed only in the presence of maternal toxicity.

In a peri-postnatal study in rats dosed with proguanil alone up to 16 mg/kg/day (0.03 times the human exposure, based on treatment AUC), no treatment-related effects were seen in reproductive or other parameters in the F0, F1 and F2 generations.

However, as animal studies are not always predictive of human response, the use of atovaquone-proguanil in pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Use in Lactation:
It is not known whether atovaquone is excreted into human milk. In a rat study, the atovaquone concentrations in milk were 30% of the concurrent atovaquone concentrations in maternal plasma. Proguanil is excreted in human milk in small quantities. Breast feeding is not recommended during treatment with Malarone.

Renal Impairment:
Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30 mL/min) alternatives to Malarone for treatment of acute *P. falciparum* malaria should be recommended whenever possible (see **DOSAGE and ADMINISTRATION, CONTRAINDICATIONS** and **PHARMACOKINETICS**).

Hepatic Impairment:
Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. Malarone has not been specifically studied in patients with severe hepatic impairment.

Dosage in Children:
Dosage recommendations in children are based on body weight (see **DOSAGE AND ADMINISTRATION**).

Dosage in the Elderly:
Pharmacokinetic studies indicate that no dosage adjustments are needed in the elderly.

Effects on Ability to Drive and Operate Machinery:
There have been no studies to investigate the effect of atovaquone and proguanil hydrochloride on driving performance or the ability to operate machinery. Detrimental effect on such activities is not predicted from the pharmacology of the component drugs.

INTERACTIONS WITH OTHER MEDICINES:
Proguanil may potentiate the anticoagulant effect of warfarin and other coumarin based anticoagulants. The mechanism of this potential drug interaction has not been established. Caution is advised when initiating or withdrawing malaria prophylaxis or treatment with Malarone in patients on continuous treatment with coumarin based anticoagulants.

Concomitant treatment with tetracycline, metoclopramide, rifampicin and rifabutin have been associated with significant decreases in plasma concentration of atovaquone (see **PRECAUTIONS**). Concomitant administration of tetracycline and Malarone reduced the

plasma concentrations of atovaquone but had no effect on the efficacy of Malarone in curing *Plasmodium falciparum* malaria.

Concomitant administration of atovaquone and indinavir results in a 23% decrease in the C_{min} of indinavir in healthy individuals. Caution should be exercised when prescribing atovaquone with indinavir due to the decrease in trough levels of indinavir.

In clinical studies of atovaquone in the treatment of diseases other than malaria, small decreases in plasma concentrations were associated with concomitant use of paracetamol, benzodiazepines, aciclovir, opiates, cephalosporins, antidiarrhoeal agents and laxatives. The implications of these observations for use with Malarone are not known. In the same series of studies, the following medications were not associated with a change in steady state plasma concentrations of atovaquone: fluconazole, clotrimazole, ketoconazole, antacids, systemic corticosteroids, non-steroidal anti-inflammatory drugs, anti-emetic drugs (excluding metoclopramide) and H_2-antagonists.

There is no information available on whether interactions occur between atovaquone and terfenadine or cisapride.

Atovaquone is highly protein bound (>99%) but does not displace other highly protein bound drugs *in vitro*, indicating significant drug interactions arising from drug displacement are unlikely.

Coadministration of efavirenz with Malarone may result in a decrease in exposure to atovaquone and proguanil. When given with efavirenz or boosted protease-inhibitors, atovaquone concentrations have been observed to decrease as much as 75%. Since decreased concentrations of atovaquone and proguanil may result in a decrease of antimalarial efficacy, concomitant administration should be avoided whenever possible.

ADVERSE EFFECTS:

As Malarone contains atovaquone and proguanil hydrochloride, the type and severity of adverse reactions associated with each of the compounds may be expected. However, at the doses employed for both treatment and prophylaxis of malaria, adverse reactions are generally mild and of limited duration. There is no evidence of added toxicity following concurrent administration of the two compounds.

PROPHYLAXIS:

Individuals > 40 kg: The nature and frequency of adverse reactions reported in clinical trials of Malarone (atovaquone and proguanil hydrochloride) for the prophylaxis of malaria in individuals weighing > 40 kg were similar to those reported with placebo or the active comparator drug (mefloquine or chloroquine/proguanil). However, patients receiving Malarone had fewer neuropsychiatric and gastrointestinal adverse reactions than patients receiving mefloquine and chloroquine/proguanil respectively. Overall, Malarone has a better safety profile than mefloquine or chloroquine/proguanil (see Tables 2 and 3).

Table 2: Drug-Related Adverse Reactions, Occurring in ≥1% of Patients Taking Malarone Tablets (250/100) in Placebo Controlled Studies.

Adverse Event	Malarone (n=232)	Placebo (n=241)
Gastrointestinal		
Diarrhoea	2% (4)	4% (9)
Dyspepsia	2% (4)	4% (9)
Gastritis	3% (6)	2% (5)
Vomiting	1% (3)	<1% (1)
Abdominal Pain	7% (16)	9% (21)
Cutaneous		
Pruritus	1% (3)	<1% (2)
Nervous/psychiatric		
Headache	6% (13)	9% (22)

Table 3: Drug-Related Adverse Reactions*, Occurring in ≥1% of Patients Taking Malarone Tablets (250/100) in Active-Controlled Studies.

	MALB30010		MALB30011	
Adverse Event	**Malarone (n = 482)**	**MFQ (n =471)**	**Malarone (n=511)**	**C + P (n = 511)**
Gastrointestinal				
Diarrhoea	7% (36)	7% (35)	5% (24)	7% (37)
Nausea	3% (15)	9% (42)	2% (9)	7% (34)
Vomiting	1% (7)	2% (9)	0	2% (11)
Abdominal Pain	5% (26)	5% (23)	3% (15)	6% (30)
Oral Ulceration	6% (28)	4% (17)	4% (18)	5% (25)
Cutaneous				
Pruritus	1% (7)	2% (11)	1% (6)	<1% (5)
Hair Loss	1% (5)	0	<1% (4)	1% (6)
Nervous/psychiatric				
Headache	4% (19)	7% (34)	4% (21)	4% (19)
Dreams	7% (32)	14% (66)	4% (19)	3% (14)
Insomnia	3% (15)	14% (65)	2% (8)	2% (12)
Dizziness	2% (10)	9% (43)	3% (17)	4% (19)
Visual difficulties	2% (8)	3% (16)	2% (10)	2% (10)

MFQ = mefloquine, C = chloroquine, P = proguanil hydrochloride

* The duration of dosing for Malarone (1-2 days before until 7 days after travel) is shorter than for mefloquine (2-3 weeks before until 4 weeks after travel) or chloroquine (1 week before until 4 weeks after travel). Adverse reaction data is therefore presented for only the period the patient was receiving active treatment.

Individuals 11-40 kg:

The incidence of adverse reactions reported in clinical trials using Malarone Junior Tablets (62.5/25) for the prophylaxis of malaria in individuals weighing 11-40 kg were similar to those reported with placebo (MALB3003 & MAL30015). In studies MAL30010 and MAL30012, the incidence of drug-related adverse events was higher in the chloroquine/proguanil group (15% vs 11% for Malarone) during active treatment. Due to the low number of patients in

study MAL30010 (n=12), no drug-related adverse events were reported by the mefloquine recipients. Tables 4 & 5 list the common drug-related adverse reactions reported during chemoprophylaxis by treatment group.

Table 4: Drug-Related Adverse Reactions, Occurring in ≥1% of Patients Taking Malarone Junior Tablets (62.5/25) in Placebo Controlled Studies.

Adverse Event	Malarone n=264	Placebo n=270
Body as a Whole		
Abdominal pain	12% (32)	11% (30)
Headache	4% (10)	4% (11)
Gastrointestinal		
Vomiting	3% (7)	3% (8)

Table 5: Drug-Related Adverse Reactions*, Occurring in ≥1% of Patients Taking Malarone Junior Tablets (62.5/25) in Active-Controlled Studies.

Adverse Event	Malarone n=93	C + P n=81
Gastrointestinal		
Diarrhoea	4% (4)	4% (3)
Abdominal pain	0	9% (7)
Oral ulceration	2% (2)	2% (2)
Vomiting	1% (1)	6% (5)
Nausea	0	9% (7)
Decreased appetite	1% (1)	0
Nervous		
Dreams	3% (3)	0
Dizziness	1% (1)	1% (1)
Body as a Whole		
Lethargy	2% (2)	0
Fever	1% (1)	1% (1)
Skin and Appendages		
Pruritus	2% (2)	1% (1)
Special Senses		
Visual impairment	0	2% (2)
Respiratory		
Cough	1% (1)	0

C = chloroquine, P = proguanil hydrochloride

* Adverse reaction data is presented for only the period the patient was receiving active treatment.

TREATMENT:

The nature and frequency of adverse experiences reported in controlled clinical trials of atovaquone and proguanil hydrochloride for the treatment of malaria were generally similar in patients treated with the combination or with a comparator antimalarial drug. This suggests that the adverse experiences are largely due to the disease rather than to study drugs (see Table 6).

Table 6: Adverse Events Considered by Investigators to be Attributable to Study Medication, Occurring in ≥1% of Adults with Malaria in Completed Phase III Studies

Adverse Event	Malarone (n = 304)	PYR + S (n = 81)	MFQ (n = 91)	ADQ (n = 71)	C±PYR+S* (n = 55)
Gastrointestinal					
Abdominal Pain	15% (45)	21% (17)	0%	8% (6)	0%
Vomiting	12% (35)	15% (12)	0%	25% (18)	2% (1)
Nausea	11% (32)	14% (11)	2% (2)	21% (15)	2% (1)
Diarrhoea	8% (25)	11% (9)	0%	7% (5)	2% (1)
Anorexia	5% (15)	5% (4)	1% (1)	13% (9)	2% (1)
Hepatomegaly	2% (6)	6% (5)	0%	0%	0%
Constipation	1% (2)	0%	0%	0%	0%
Dyspepsia	1% (2)	0%	0%	0%	0%
Nervous/Psychiatric					
Headache	8% (25)	31% (25)	1% (1)	7% (5)	0%
Dizziness	3% (8)	11% (9)	0%	11% (8)	2% (1)
Insomnia	1% (3)	4% (3)	0%	25% (18)	0%
Body as a Whole					
Asthenia	7% (20)	16% (13)	0%	3% (2)	0%
Back **Pain**	1% (2)	4% (3)	0%	0%	0%
Abnormal liver function tests					
ALT	6% (18)	6% (5)	7% (6)	0%	0%
AST	5% (16)	5% (4)	7% (6)	0%	0%
Bilirubin	2% (7)	0%	1% (1)	0%	0%
Cardiovascular					
Hypotension, postural	2% (6)	17% (14)	0%	0%	0%
Palpitations	2% (5)	0%	0%	6% (4)	0%
Cutaneous					
Pruritus	2% (6)	2% (2)	0%	46% (33)	0%
Rash	1% (2)	0%	0%	0%	0%
Musculoskeletal					
Myalgia	3% (8)	6% (5)	0%	4% (3)	0%
Erythropoietic					
Splenomegaly	1% (4)	2% (2)	0%	0%	0%
Respiratory					
Coughing	1% (3)	0%	0%	2% (2)	0%

PYR = pyrimethamine, S = sulfadoxine, MFQ = mefloquine, ADQ = amodiaquine, C = chloroquine,
* Data for both comparator groups of chloroquine alone plus pyrimethamine and sulfadoxine.

A similar profile of clinical adverse events were reported in children with malaria treated with atovaquone and proguanil hydrochloride in phase III trials as occurred in the adult studies. Regardless of attributability, the following were also commonly reported (> 2%) in children: dehydration, tinnitus and anorexia.

Of the seven severe or treatment limiting adverse experiences reported in clinical trials with atovaquone and proguanil hydrochloride, three were considered to be treatment related; two were reports of nausea and/or vomiting and one report of an anaphylactic reaction. During clinical trials, two subjects receiving atovaquone monotherapy experienced psychiatric symptoms. One subject had a history of psychiatric illness and the other a history of drug and alcohol abuse. Two subjects receiving atovaquone/proguanil hydrochloride had seizures; in one of these cases the patient successfully continued treatment. Both subjects

had a prior history of seizures and the investigators did not consider the events attributable to the Malarone treatment.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000). Very common, common and uncommon events were determined from clinical trial data. Rare and very rare events were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those events where a frequency could not be estimated from the available data.

A summary of adverse events identified during world-wide post-approval use of Malarone or its components, atovaquone and proguanil hydrochloride is provided below.

Blood and Lymphatic system disorders

Common:	Anaemia[1], neutropenia[2]
Not known:	Pancytopenia in patients with severe renal impairment[4]

Immune system disorders

Not known:	Angioedema[4], anaphylaxis[3], vasculitis

Metabolism and nutritional disorders

Common:	Anorexia[1], Hyponatraemia[2]
Uncommon:	Elevated amylase levels[2] occurred in patients treated with atovaquone

Psychiatric disorders

Rare:	Hallucinations[1]

Nervous system disorders

Very common:	Headache[1]
Common:	Insomnia[1], dizziness[1]

Gastrointestinal disorders

Very common:	Abdominal pain[1], nausea[2], vomiting[1], diarrhoea[1]
Uncommon:	Stomatitis[1]
Not known:	Gastric intolerance[4], oral ulceration[4]

Hepatobiliary disorders

Common:	Elevated liver enzyme levels[2]
Not known:	Hepatitis[3], Cholestasis
	Clinical trial data for Malarone indicated that abnormalities in liver function tests were reversible and not associated with untoward clinical events.

Skin and subcutaneous tissue disorders

Common:	Rash[1]
Uncommon:	Hair loss[1], urticaria[1]
Not Known:	Stevens-Johnson syndrome[3], erythema multiforme[3]

General disorders and administration site conditions

Common: Fever[1]

Respiratory, thoracic and mediastinal disorders

Common: Cough[1]

1. Frequency calculated from atovaquone-proguanil clinical trials.

2. Frequency taken from atovaquone label. Patients participating in clinical trials with atovaquone have received higher doses and have often had complications of advance Human Immunodefficiency Virus (HIV) disease. Therefore, the casual relationship between the adverse experiences and atovaquone is difficult to evaluate. These events may have been seen at a lower frequency or not at all in clinical trials with atovaquone-proguanil.

3. Oberserved from post-marketing spontaneous reports and the frequency is therefore Not known.

4. Observed with proguanil and the frequency is therefore Not known.

DOSAGE AND ADMINISTRATION:

The daily dose should be taken with food or a milky drink at the same time each day.

In the event of vomiting, within 1 hour of dosing, a repeat dose should be taken.

Malarone (250/100) or Malarone Junior tablets (62.5/25) should preferably be swallowed whole. If difficulties are encountered when dosing young children, the tablet(s) may be crushed and added to a small amount of milk, all of which should be consumed immediately.

PROPHYLAXIS:

Prophylaxis should start 1 to 2 days before entering a malaria-endemic area, and be continued daily until seven days after leaving the area.

If patients are unable to tolerate food, Malarone Tablets should be administered, but systemic exposure of atovaquone will be reduced.

Dosage in Adults:

One Malarone Tablet (250/100) daily.

Dosage in Children:

Body weight (kg)	Single daily dosage
11-20	1 Malarone Junior Tablet (62.5/25)
21-30	2 Malarone Junior Tablets (62.5/25)
31-40	3 Malarone Junior Tablets (62.5/25)
>40	1 Malarone Tablet (250/100)

TREATMENT:

Dosage in Adults:

Four tablets as a single dose for three consecutive days.

Dosage in Children:

Body weight (kg)	Single dosage for 3 consecutive days
11-20	1 Malarone Tablet (250/100)
21-30	2 Malarone Tablets (250/100)
31-40	3 Malarone Tablets (250/100)
>40	4 Malarone Tablets (250/100)

Dosage in the Elderly (Prophylaxis and Treatment):
A pharmacokinetic study indicates that no dosage adjustments are needed in the elderly (see **PHARMACOKINETICS**).

Dosage in Hepatic Impairment (Prophylaxis and Treatment):
A pharmacokinetic study indicates that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment. (see **PHARMACOKINETICS**).

Dosage in Renal Impairment (Prophylaxis and Treatment):
Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30 mL/min) alternatives to Malarone should be recommended for the treatment of acute *P. falciparum* malaria whenever possible (see **PRECAUTIONS and PHARMACOKINETICS**). For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment see **CONTRAINDICATIONS**.

OVERDOSAGE:

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Contact the Poisons Information Centre (telephone 131126) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS:

Malarone Tablets (250/100): Round, biconvex, pink film-coated tablets, branded “GX CM3”.
Each tablet contains the active ingredients atovaquone 250 mg and proguanil hydrochloride 100 mg.

Malarone Junior Tablets (62.5/25): Round, biconvex, pink film-coated tablets, branded “GX CG7”. Each tablet contains the active ingredients atovaquone 62.5 mg and proguanil hydrochloride 25 mg.

Each tablet strength is provided in PVC aluminium foil blister packs or PVC-aluminium/paper child resistant foil blister packs* in the following pack sizes:
Malarone Tablets (250/100): 12 and 24 tablets
Malarone Junior Tablets (62.5/25): 12, 24 and 60 tablets

*complies with European Standard *EN 14375:2003 Child-resistant Non-reclosable Packaging for Pharmaceutical Products - Requirements And Testing.*

Not all pack sizes may be distributed in Australia.

Store tablets below 30°C.

NAME AND ADDRESS OF THE SPONSOR
GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE: S4

DATE OF FIRST INCLUSION IN THE ARTG: 04 May 1998

DATE OF MOST RECENT AMENDMENT: 8 August 2016

Malarone® is a registered trade mark of the GlaxoSmithKline group of companies.

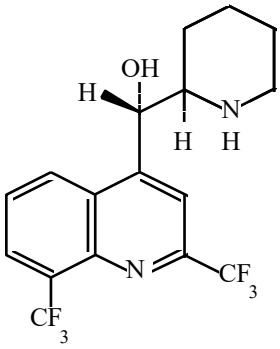
Version 8.0

NAME OF THE MEDICINE

Lariam®

mefloquine hydrochloride

Chemical name: *dl-erythro-alpha-2-piperidy-2,8-bis(trifluoromethyl)-4-quinoline methanol*



MW: 414.78
CAS registry number: 51773-92-3

DESCRIPTION

Mefloquine is an odourless, bitter-tasting, white crystalline powder. It is soluble in methanol and ethanol but practically insoluble in water. A 1% aqueous suspension has a pH of 5.6.

Lariam tablets are cylindrical biplanar, white to off-white, cross-scored with break bars on both faces and marked with "RO", "C", "HE" and an imprinted hexagon in the quadrants of one face. They contain 250 mg mefloquine in the form of mefloquine hydrochloride (274.09 mg). Lariam tablets also contain the following excipients: poloxamer 3800, microcrystalline cellulose, lactose, maize starch, crospovidone, ammonium calcium alginate, talc and magnesium stearate.

Lariam (mefloquine) is an antimalarial belonging to the quinoline-methanol group of medicines and is structurally related to quinine.

PHARMACOLOGY

Pharmacodynamics

The effectiveness in the treatment of malaria is due essentially to destruction of the asexual intraerythrocytic forms of the human malarial parasites: *Plasmodium falciparum, P. vivax, P. malariae and P. ovale*. However data concerning the treatment of *P.malariae* and *P.ovale* were limited.

It is also effective against *P. falciparum* infections resistant to other antimalarials such as chloroquine and other 4-amino-quinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations.

Laboratory animal studies have shown that resistance to mefloquine can be readily induced in the malarial parasite and that this resistance is stable during passage through the insect vector. Mefloquine resistance has also been seen in a few clinical isolates from patients receiving mefloquine.

Resistance of *P.falciparum* to mefloquine has been reported, mainly in parts of South-East Asia. Cross-resistance between mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed.

The basic mode of action of mefloquine has not been elucidated. However a number of studies of its actions in biochemical systems have been made.

Like quinine, mefloquine is able to form complexes with haemin. The ability to co-ordinate with haemin seems to correlate with the antimalarial activity of the compound. But, unlike chloroquine, quinacrine and quinine, mefloquine does not intercalate with DNA. Thus interaction with DNA does not seem to be involved in the antimalarial action of mefloquine.

Mefloquine does not exert antifolic activity and its antimalarial action is not antagonised by p-aminobenzoic acid.

Pharmacokinetics

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formulation compared with an oral solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability. In patients, the absorption half-life of mefloquine was 5 to 6 hours with plasma concentrations peaking 12 to 23 hours (mean about 16.6 hours). Maximum blood concentrations appear to be 2 to 3 times higher in Asian compared with non-Asian volunteers. Reasons for this ethnic difference are unclear. Also, plasma C_{max} were higher in patients with acute uncomplicated falciparum malaria.

In healthy volunteers a dose of 250mg once weekly produces maximum steady state plasma concentrations of 1000 to 2000 µg/L, which are reached after 7 to 10 weeks.

Distribution

In healthy adults, the apparent volume of distribution is approximately 20 L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitised erythrocytes. Experiments conducted in vitro with human blood using concentrations between 50 and 1000 mg/mL showed a relatively constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 minutes was found to be reversible. Mefloquine is approximately 98.2% protein bound.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see Use in Lactation).

Metabolism

Mefloquine is extensively metabolised in the liver by the cytochrome P450 system. *In vitro* and *in vivo* studies strongly suggested that CYP3A4 is the major isoform involved. Two metabolites of mefloquine have been identified in humans. The main metabolite 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *P.falciparum*.

In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma concentrations of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug.

In addition to the acid, other known metabolite is a mefloquine derivative with a hydroxy group in the piperidine moiety

Excretion

The average half-life of mefloquine in Caucasians is 21 days. Clinical studies carried out to date have shown that only a minute proportion of the active ingredient is excreted unchanged in the urine. Animal studies suggest that mefloquine is primarily excreted via the bile and faeces as unchanged drug and metabolites.

Pharmacokinetics in Special Populations

Renal Impairment

As only a small proportion of mefloquine is eliminated renally, no pharmacokinetic studies have been performed in patients with renal insufficiency. Mefloquine and its main metabolite are not appreciably removed by haemodialysis. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy subjects.

Hepatic Impairment

Mefloquine is extensively metabolised in the liver by the CYP P450 system with CYP3A4 likely to be the major isoform. There have been no formal clinical studies in patients with hepatic impairment, so that the magnitude of effect of hepatic impairment on mefloquine pharmacokinetics is not known. However, it is considered likely that patients with impaired liver function will be exposed to higher plasma mefloquine levels due to reduced clearance and will be at higher risk of adverse effects (see *CONTRAINDICATIONS*).

CLINICAL TRIALS

In a randomised, double-blind study, non-immune travellers received malaria chemoprophylaxis with Lariam (483 subjects) and atovaquoine-proguanil (493 subjects) who visited a malaria-

endemic area. Efficacy of chemoprophylaxis was evaluated as a secondary end point. The average duration of travel was ~2.5 weeks, and 79% of subjects travelled to Africa. 1013 subjects were initially randomised to receive Lariam (n=505) or atovaquone-proguanil (n=508). Thirty-seven subjects withdrew due to a variety of reasons. Of the 976 subjects who received ≥1 dose of study drug, 966 (99%) completed the trial and 963 completed the 60-day follow-up period and had efficacy information recorded. Although 10 subjects (5 in each study arm) were identified with circumsporozoite antibodies, none of them developed malaria (minimum efficacy for both Lariam and atovaquone-proguanil was 100%). Overall, there were no cases of confirmed malaria in this study (maximum efficacy for both Lariam and atovaquone-proguanil was 100%). Results indicated that Lariam and atovaquone-proguanil are similarly effective for malaria chemoprophylaxis in non-immune travellers (see Table 1).

Table 1 Estimates of minimum and maximum efficacy for malaria chemoprophylaxis

	Subjects who received	
Variable	Atovaquone-proguanil[c]	Lariam[c]
Subjects with 60-day efficacy data available, no.	486	477
Subjects who developed circumsporozoite antibodies, no.	5	5
Subjects with confirmed malaria, no.	0	0
Minimum efficacy, % (95% Cl)[a]	100 (48-100)	100 (48-100)
Maximum efficacy, % (95% Cl)[b]	100 (99-100)	100 (99-100)

[a] Minimum efficacy = 100 x [1 – (no. of subjects with confirmed malaria/no. with circumsporozoite antibodies)]

[b] Maximum efficacy = 100 x [1 – (no. of subjects with confirmed malaria/no. with 60-day efficacy data)]

[c]Atovaquone/proguanil administered daily (250/25 mg tabs.) in pat. > 40 kg BW, mefloquine weekly (250 mg tabs.) in pat. > 35 kg BW.

INDICATIONS

Malaria treatment

Lariam is indicated for the treatment of acute attacks of malaria due to *P.falciparum* infection resistant to conventional antimalarial drugs.

Following therapy of mixed *P.falciparum and P.vivax* malaria with Lariam, relapse chemoprophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate hepatic forms of *P.vivax*.

Malaria chemoprophylaxis

For travellers to countries with documented chloroquine and antifolate combination ([sulfadoxine/pyrimethamine] / [dapsone/pyrimethamine]) resistant *P.falciparum* malaria, who are considered to be at high risk for malaria in view of their residence or travel (of up to 3 months duration) through rural areas (between the dusk to dawn period).

For travellers hypersensitive to sulphonamides and sulphones, who are considered to be at high risk for malaria in view of their residence or travel (of up to 3 months duration) through rural areas, (between the dusk to dawn period) in countries with high level chloroquine-resistant *P.falciparum* malaria.

CONTRAINDICATIONS

Lariam is contraindicated in patients with known hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine) or any of the excipients in Lariam.

The use of Lariam is presently contraindicated in patients with renal insufficiency or severe impairment of liver function as no experience has been gained in such patients.

Patients with a past history of active depression, a recent history of depression, generalised anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders or convulsions should not be prescribed Lariam prophylactically.

PRECAUTIONS

Circumstances where special attention is required

Due to the risk of a potentially fatal prolongation of the QTc interval, halofantrine must not be given during Lariam therapy for chemoprophylaxis or treatment of malaria or within 15 weeks after the last dose of Lariam (see Pharmacokinetics, Elimination; Interactions with Other Medicines).

Due to increased plasma concentrations and elimination half-life of mefloquine following co-administration with ketoconazole, the risk of QTc prolongation may also be expected if ketoconazole is taken during Lariam therapy for chemoprophylaxis or treatment of malaria, or within 15 weeks after the last dose of Lariam (see *INTERACTIONS WITH OTHER MEDICINES*).

Concomitant administration of Lariam and quinine or quinidine may produce electrocardiographic abnormalities (see *Cardiac Effects and INTERACTIONS WITH OTHER MEDICINES*).

Concomitant administration of Lariam and quinine or chloroquine may increase the risk of convulsions (see *INTERACTIONS WITH OTHER MEDICINES*).

In patients with epilepsy, Lariam, especially when used in high doses may increase the risk of convulsions. Therefore in such patients Lariam should be used only for curative treatment

and only if there are compelling medical reasons (see *INTERACTIONS WITH OTHER MEDICINES*).

Hypersensitivity Reactions

Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted.

Cardiac Effects

As mefloquine is related structurally to quinine, its use in patients with cardiac disease should be avoided as data on the cardiac effects of mefloquine are at present inadequate to establish safety.

Although no cardiovascular action of Lariam, a myocardial suppressant has been observed during clinical trials, parenteral studies in animals show that it possesses 20% of the antifibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. The effect of Lariam on the compromised cardiovascular system has not been evaluated. However transitory and clinically silent ECG alterations have been reported during the use of Lariam. Alterations included sinus bradycardia, sinus arrhythmia, fist degree AV-block, prolongation of the QTc interval and abnormal T waves (see *INTERACTIONS WITH OTHER MEDICINES and ADVERSE EFFECTS*). The benefits of Lariam therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Ocular Effects

Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with Lariam.

Neuropsychiatric Effects

Lariam may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behaviour. On occasions, these symptoms have been reported to continue long after Lariam has been stopped. Lariam should not be prescribed in patients with a history of psychiatric symptoms (see *CONTRAINDICATIONS*) and should be used with caution in patients with a previous history of depression.

In chemoprophylaxis the safety profile of mefloquine is characterised by a predominance of neuropsychiatric adverse reactions. During prophylactic use, if signs of unexplained acute anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued. Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist after discontinuation of the drug. In a small number of patients it has been reported that some neuropsychiatric events (including depression, dizziness or vertigo and loss of balance) may continue for months or longer after discontinuation of the drug. Therapy should be initiated one week

before travel commences (see *DOSAGE AND ADMINISTRATION*), as acute psychiatric effects are more likely to manifest at the start of treatment.

Use in Patients with Hepatic Impairment

In patients with impaired liver function, the elimination of mefloquine may be prolonged; leading to higher plasma levels and a higher risk of adverse reactions (see *CONTRAINDICATIONS*).

Blood and Lymphatic System Disorders

Cases of agranulocytosis and aplastic anaemia have been reported during Lariam therapy.

Drug Resistance

Geographical drug resistance patterns of *P. falciparum* occur and preferred choice of malaria chemoprophylaxis might be different from one area to another. Resistance of *P.falciparum* to mefloquine has been reported, predominantly in areas of multi-drug resistance in South-East Asia. Cross-resistance between Lariam and halofantrine and cross-resistance between Lariam and quinine have been observed. For current advice on geographical resistance patterns competent national expert centres should be consulted.

The basic mode of action of mefloquine has not been elucidated.

Ability to Drive and Use Machines

Persons experiencing dizziness and loss of balance or other disorders of the central or peripheral nervous system should be cautious with regard to driving, piloting aircraft, operating machines, deep-sea diving, or other activities requiring alertness and fine motor co-ordination. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine.

Effects on Fertility

Epididymal lesions were evident in rats treated with 20 mg/kg/day (5 times the prophylactic dose on a mg/m^2 basis), while a lower number of viable spermatozoa and a lower fertility index were seen in male rats treated with 50 mg/kg/day (13 times the prophylactic dose).

Adverse effects on fertility were also evident in female rats treated with these doses. No adverse effects were observed in either male or female rats at 5 mg/kg/day, approximately equivalent to the prophylactic dose on a mg/m^2 basis.

Administration of 250 mg/week of mefloquine (base) in adult males for 22 weeks failed to reveal any deleterious effects on human spermatozoa.

Use in Pregnancy - Category B3

The use of Lariam in the treatment of malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus.

Chemoprophylaxis in high risk situations is also justified.

Women of childbearing potential who are travelling to malaria-endemic areas in which multi-drug resistant *P.falciparum* is found should use an effective contraceptive throughout the therapy and for at least 3 months after taking the last dose of Lariam.

Mefloquine crosses the placenta and is detectable in the foetal circulation.

Administered at 3 to 12 times the therapeutic dose in humans, Lariam was teratogenic in mice and rats and embryotoxic in rabbits; however, clinical experience with Lariam has not revealed an embryotoxic or teratogenic effect. Nevertheless, Lariam should be used during the first trimester only if the expected benefit justifies the potential risk to the foetus.

Women of childbearing potential should be advised to practice contraception during malaria chemoprophylaxis with Lariam and for up to 3 months thereafter. However, in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered an indication for pregnancy termination. For use of Lariam during pregnancy, current national and international guidelines should be consulted.

Use in Lactation

Mefloquine is excreted into breast milk in small amounts, the activity of which is unknown. Circumstantial evidence suggests that adverse effects do not occur in breast-fed infants whose mothers are taking Lariam. For use of Lariam in nursing mothers current national and international guidelines should be consulted.

Paediatric Use

Data are inadequate to establish the safety of Lariam in children below the age of 14 years.

Genotoxicity

The genotoxic potential of mefloquine was assessed in bacterial, yeast and mammalian mutagenicity tests, in a host-mediated assay in mice and a mouse micronucleus assay at appropriate concentrations or doses. In vitro tests were performed with and without metabolic activation. All assays returned negative results for mefloquine.

Carcinogenicity

The carcinogenic potential of mefloquine was investigated in 2 year feeding studies in mice and rats at doses up to 30 mg/kg/day, equivalent to 4 and 8 times the prophylactic dose on a mg/m^2 basis. There were no treatment-related increases in tumour incidence in either species.

INTERACTIONS WITH OTHER MEDICINES

Medicine interactions with Lariam have not been explored in detail.

Beta blockers, quinine, quinidine or chloroquine: Concomitant administration of Lariam and quinine, quinidine or medicines producing β-adrenergic blockade may produce electrocardiographic abnormalities or cardiac arrest.

Although no cardiovascular action of Lariam, a myocardial suppressant has been observed during clinical trials, parenteral studies in animals show that it possesses 20% of the antifibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. The effect of Lariam on the compromised cardiovascular system has not been evaluated. However transitory and clinically silent ECG alterations have been reported during the use of Lariam. Alterations included sinus bradycardia, sinus arrhythmia, fist degree AV-block, prolongation of the QTc interval and abnormal T waves. The benefits of Lariam therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Theoretically, co-administration of other medicines known to prolong cardiac conduction (e.g. anti-arrhythmic or β-adrenergic blocking agents, calcium channel blockers, antihistamines or H_1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval.

Concurrent administration of Lariam and the same related compounds (i.e. quinine, quinidine or chloroquine) could also increase the risk of convulsions.

Halofantrine: There is evidence that the use of halofantrine during Lariam therapy for chemoprophylaxis or treatment of malaria or within 15 weeks of the last dose of Lariam causes a significant lengthening of the QTc interval (see *PRECAUTIONS*).

Ketoconazole: Due to increased plasma concentrations and elimination half-life of Lariam following co-administration with ketoconazole, the risk of QTc prolongation may also be expected if ketoconazole is taken during Lariam therapy for chemoprophylaxis or treatment of malaria, or within 15 weeks after the last dose of Lariam.

Anticonvulsants: In patients taking an anticonvulsant (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of Lariam may reduce seizure control by lowering the plasma levels of the anticonvulsant. Dosage adjustments of anticonvulsant medication may be necessary in some cases.

Vaccines: When Lariam is taken at the same time or shortly before oral live typhoid vaccines, attenuation of the immunisation induced by such vaccines cannot be excluded. Vaccinations with attenuated live bacteria should be completed at least three days before the first dose of Lariam, keeping in mind that Lariam chemoprophylaxis should be started one week before arrival in a malarious area.

Effects on Laboratory tests: The most frequently observed laboratory alterations which could be possibly attributable to drug administration were decreased haematocrit, transient elevation of transaminases, leukopenia and thrombocytopenia. These alterations were observed in patients with acute malaria who received treatment doses of the drug and were attributed to the disease itself.

During prophylactic administration of Lariam to indigenous populations in malaria-endemic areas, the following occasional alterations in laboratory values were observed: transient elevation of transaminases, leukocytosis or thrombocytopenia.

Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist up to several weeks after discontinuation of the drug.

No other medicine interactions are known. Since interactions with oral anti-diabetics and oral anticoagulants have not been tested, the relevant parameters should be checked when Lariam is taken for malaria chemoprophylaxis.

Periodic evaluation of hepatic function should be performed during prolonged chemoprophylaxis.

Other Potential Interactions

Mefloquine does not inhibit the cytochrome P450 isoenzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 at prophylactic concentrations. Mefloquine does not induce CYP3A4. Although no information is available with regard to induction of other cytochrome P450 enzymes, mefloquine is not expected to alter the metabolism of concomitantly-administered medicines.

Inhibitors of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase in mefloquine plasma concentrations and potential risk of adverse reactions. Therefore, Lariam should be used with caution when administered concomitantly with CYP3A4 inhibitors. Similarly, inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine leading to a decrease in mefloquine plasma concentrations.

Inhibitors of CYP3A4

One pharmacokinetic study in healthy volunteers showed that the co-administration of ketoconazole, a strong inhibitor of CYP3A4, increased the plasma concentrations and elimination half-life of mefloquine.

Inducers of CYP3A4

The long term use of rifampicin, a potent inducer of CYP3A4, reduced the plasma concentrations and elimination half-life of mefloquine.

Substrates and inhibitors of P-glycoprotein

Mefloquine is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, interactions could potentially also occur with medicines that are substrates of this transporter. The clinical relevance of these interactions is not known to date. In a clinical interaction study in healthy volunteers, ritonavir, caused less than 7% changes with high precision (90% CIs: x12% to 11%) in overall plasma exposure ($AUC_{0,168h}$) and peak concentration (C_{max}) of mefloquine, its two enantiomers, and carboxylic acid metabolite, and in the metabolite/mefloquine and enantiomeric AUC ratios. Mefloquine significantly decreased steady state ritonavir plasma $AUC_{0,12h}$ by 31%, C_{max} by 36% and pre-dose levels by 43%, and did not affect ritonavir binding to plasma proteins.

ADVERSE EFFECTS

At the doses given for acute malaria, adverse reactions to Lariam may not be distinguishable from symptoms of the disease itself.

Among subjects who received Lariam for treatment, the most frequently observed adverse experiences included: dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhoea, skin rash, abdominal pain, fatigue, loss of appetite and tinnitus. Those side effects occurring less frequently included bradycardia, hair loss, emotional problems, pruritus, asthenia, transient emotional disturbances and telogen effluvium (loss of resting hair). Seizures have also been reported.

The rate of adverse events associated with Lariam is published to be similar to that with other antimalarial prophylactic medications. In chemoprophylaxis the safety profile of Lariam adverse events is characterised by a predominance of neuropsychiatric adverse reactions (see *PRECAUTIONS*).

Clinical Trials

A systematic review published in 2009 identified a double-blind, randomized study including 976 patients (483 patients on Lariam, 493 patients on atovaquone/proguanil), where treatment-related neuropsychiatric adverse events occurred in 139/483 (28.8%) patients receiving Lariam compared to 69/493 (14%) patients receiving atovaquone-proguanil (Tables 2 and 3). No drug-attributable serious adverse events occurred in either group.

Table 2 Adverse Events Attributed to the Study Drug[#]

	Lariam (n = 483)		**atovaquone-proguanil (n = 493)**	
Event	**Number**	**(%)**	**Number**	**(%)**
Any adverse event	204	(42.2)	149	(30.2)
Any neuropsychiatric event	139	(28.8)	69	(14)
Strange or vivid dreams	66	(13.7)	33	(6.7)
Insomnia	65	(13.5)	15	(3)
Dizziness or vertigo	43	(8.9)	11	(2.2)
Visual difficulties	16	(3.3)	8	(1.6)
Anxiety	18	(3.7)	3	(0.6)
Depression	17	(3.5)	3	(0.6)

	Lariam (n = 483)		atovaquone-proguanil (n = 493)	
Event	**Number**	**(%)**	**Number**	**(%)**
Any gastrointestinal event	94	(19. 5)	77	(15.6)
Diarrhoea	34	(7)	37	(7.5)
Nausea	40	(8.3)	15	(3)
Abdominal pain	23	(4.8)	26	(5.3)
Mouth ulcers	17	(3.5)	29	(5.9)
Vomiting	9	(1.9)	7	(1.4)
Headache	32	(6.6)	19	(3.9)
Itching	15	(3.1)	12	(2.4)

[#]Mean duration of treatment ± SD was 28 ± 8 days for atovaquone-proguanil and 53 ± 16 days for Lariam.

Post –Marketing

In the table below, an overview of adverse reactions is presented, based on post marketing data.

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention:
very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

Blood and lymphatic system disorders

Not known Agranulocytosis, aplastic anaemia, leukopenia, leukocytosis, thrombocytopenia

Metabolism and nutrition disorders

Not known Decreased appetite

Psychiatric disorders

Very common Abnormal dreams, insomnia

Common Anxiety, depression

Uncommon Agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania, paranoia, suicidal ideation

Nervous system disorders

Common	Dizziness, headache
Uncommon	Balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy

Eye disorders

Common	Visual impairment
Not known	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment

Ear and labyrinth disorders

Common	Vertigo
Uncommon	Vestibular disorders (long term) including tinnitus and hearing impaired

Cardiac disorders

Not known	Chest pain, Tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient conduction disorder, AV block

Vascular disorders

Not known	Cardiovascular disorders (hypotension, hypertension, flushing)

Respiratory, thoracic and mediastinal disorders

Not known	Dyspnoea, pneumonitis of possible allergic etiology

Gastrointestinal disorders

Common	Nausea, diarrhoea, abdominal pain, vomiting
Not known	Dyspepsia

Hepatobiliary disorders

Not known	Drug-related hepatic disorders from asymptomatic transient transaminase increase to hepatic failure

Skin and subcutaneous tissue disorders

Common	Pruritus
Not known	Rash, erythema, urticaria, alopecia, hyperhidrosis, erythema multiforme, Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders

Not known Muscular weakness, muscle spasms, myalgia, arthralgia

General disorders and administration site disorders

Not known Oedema, asthenia, malaise, fatigue, chills, pyrexia, hyperhidrosis

Due to the long half-life of Lariam, adverse reactions to Lariam may occur or persist up to several weeks after the last dose. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine. There have been rare reports of suicidal ideations. No relationship to drug administration has been established.

DOSAGE AND ADMINISTRATION

Malaria Treatment

Adults and children of more than 45 kg bodyweight:
The recommended total dosage of Lariam, 1250mg according to bodyweight, should be administered as follows:

A loading dose of 3 tablets (750 mg), followed 6 to 8 hours later by 2 tablets (500 mg).

For partially immune patients (i.e. for inhabitants of malaria endemic areas), a full standard dosage of Lariam should also be used.

A second full dose should be given to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30-60 minutes after a dose, an additional half dose should be given.

If a full treatment course has been administered without clinical cure, alternative treatments should be given. Similarly if previous chemoprophylaxis with Lariam has failed, Lariam should not be used for curative treatment and physicians should carefully evaluate which antimalarial to use for therapy. See PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES regarding the use of halofantrine.

Lariam can be given for severe acute malaria after an initial course of intravenous quinine lasting at least 2 – 3 days. Interactions leading to adverse events can largely be prevented by allowing an interval of at least 12 hours after the last dose of quinine.

Artemisinin combination therapy (ACT) is recommended as the standard of care for treatment of *P. falciparum* malaria, regardless of region of acquisition. Mefloquine is a recommended partner molecule for inclusion in ACT. As parasite sensitivity can vary geographically and over time, it is recommended that treatment be guided by national and international guidelines.

Malaria Chemoprophylaxis

Chemoprophylaxis of malaria with Lariam should be initiated 1 week before arrival in a malarious area.

The following dosage schedule is given as a guide:

Lariam can be used for up to 3 months in the chemoprophylaxis of malaria.

	Dosage	**Course of Chemoprophylaxis**
Adults and children of more than 45kg bodyweight	1 tablet	Stated dose to be given once weekly, always on the same day. First dose one week before departure. Further doses at weekly intervals during travel in malarious areas and for 2 weeks after leaving the area.

The tablets should be swallowed whole with plenty of liquid.

OVERDOSAGE

Symptoms

In cases of overdosage with Lariam, the symptoms mentioned under ADVERSE EFFECTS may be more pronounced.

Treatment

Patients should be managed by symptomatic and supportive care following Lariam overdose. There are no specific antidotes. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Packs of 8 tablets (cross-scored) each containing 250 mg mefloquine.
Store below 30 °C. Store in original container. Protect from moisture.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Ltd
ABN 70 000 132 865
Level 8, 30-34 Hickson Road

Sydney NSW 2000
AUSTRALIA

Customer enquiries: 1800 233 950

POISONS SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG):

27 January 1993

DATE OF MOST RECENT AMENDMENT:

10 January 2018

ANNEX C

SOCIAL MEDIA CAMPAIGN TO REPORT TAFENOQUINE ADVERSE EVENTS

Australian Mefloquine and Tafenoquine Veterans
19 February 2017 ·

TAFENOQUINE ADVERSE EVENT REPORTS TO THE TGA

For veterans who have experienced side effects from tafenoquine, please complete this report to the TGA. This will take no more than 10 minutes of your time. Don't hesitate to message us if you need us to talk you through the process.

Please note that "attempted suicide" and "completed suicide" are side effects which should be reported to the TGA.

This is VERY IMPORTANT because the ADF is still attempting to register tafenoquine for sale. If this happens, tafenoquine will cause extensive harm to people given the drug in future, on the false belief that it is a "safe" drug.

Please SHARE this with veterans of the following units/deployments:

- Peace Monitoring Group, Bougainville, December 1998 - September 1999.

- 3 RAR Group, East Timor, September 1999 - February 2000.

- 5/7 RAR Group, East Timor, October 1999 - May 2000.

- 1 RAR Group, East Timor, October 2000 - April 2001.

Thankyou!

TGA.GOV.AU

Report a side effect of a medicine

If you want to use this form please enable Javascript and reload this page. Alternatively you can complete the blue form and submit it to the TGA.


[redacted]
ADF pers given tafenoquine in 1999-2001 Timor & Bougainville drug trials, please send TGA adverse event reports.
m.facebook.com/story.php?stor...
8:28 PM - 21 Feb 2017
13 Retweets 8 Likes
1
13
8

ANNEX D

LETTER FROM THE US ARMY TO DR REMINGTON NEVIN

DEPARTMENT OF THE ARMY
HEADQUARTERS, US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
810 SCHREIDER STREET
FORT DETRICK, MARYLAND 21702-5000

REPLY TO
ATTENTION OF

DEC 3 0 2014

Freedom of Information/
Privacy Act Office (15-00315)

Dr. Remington Nevin
MuckRock News
DEPT MR 12940
PO Box 55819
Boston, MA 02205-5819

Dear Dr. Nevin,

This is in response to your Freedom of Information Act (FOIA) request dated and received in this office on December 4, 2014. You requested "All documents or emails produced or reviewed by the U.S. Army Medical Research and Materiel Command and subordinate activities, to include the U.S. Army Walter Reed Army Institute of Research, related to research on the neurotoxicity of the experimental antimalarial drug tafenoquine, from January 1, 2008 to the present day, specifically to include any funding documents, draft reports, pre-publication reviews, or emails addressed to or originating from staff of these organizations, related to Abstract 529.3, published in the Meeting Abstract Supplement of the Journal of the Federation of American Societies for Experimental Biology (FASEB), available at this URL: http://www.fasebj.org/cgi/content/meeting abstract/23/1 MeetingAbstracts/529.3.

Your request was processed in accordance with the Freedom of Information Act (FOIA), 5 United States Code (U.S.C.) § 552.

Within the U.S. Army Medical Research and Materiel Command research enterprise, there are no funding documents, draft reports, or pre-publication reviews related to Abstract 529.3, published in the Meeting Abstract Supplement of the Journal of the Federation of American Societies for Experimental Biology (FASEB) for the timeframe requested other than the abstract and poster referenced. Our inquiries indicate that this abstract was the result of the work of a summer student scientist and her work at the Walter Reed Army Institute of Research (WRAIR) and not from a formal research program or study.

Please see attached poster associated with Abstract 529.3 provided by Ms. Rebecca Agboruche with the receipt of this FOIA. Ms. Agboruche was a near-peer mentor in the Gains in the Education of Mathematics and Science (GEMS) program. Her stipend was paid by science education funds. She was offered and completed an in-laboratory

enrichment experience (a day or two a week) during that summer with Ms. Diana Caridha. Dr. Debra Yourick was her advisor for the STEM education program. The abstract and poster were never provided to WRAIR for standard clearance and our scientists had no prior experience with this data. The development team members studying tafenoquine are now aware of this information.

Fees associated with the processing of your request are waived in this instance.

Sincerely,

Sandra J. Rogers
Freedom of Information/Privacy Act Officer
U.S. Army Medical Research and
Materiel Command

ANNEX E

NUMBERS OF ADF PERSONNEL WHO HAVE TAKEN MEFLOQUINE (SINCE 2001) AND TAFENOQUINE

	Mefloquine	**Tafenoquine**
Personnel provided medication as part of study		
Tafenoquine eradication study (Bougainville and East Timor 1999-2000)		1017
Tafenoquine prophylaxis study (East Timor 2000-2001)	162	492
Mefloquine and Doxycycline prophylaxis study (East Timor 2001 - 2002)	1157	
Malaria Treatment Study (2001-2)		31
Personnel individually prescribed medication outside of studies		
2001	94	
2002	77	
2003	69	
2004	67	
2005	73	
2006	53	
2007	28	
2008	32	
2009	29	
2010	25	
2011	26	
2012	13	
2013	20	
2014	35	
2015	15	
2016	5	
2017	2	
2018	1[1]	
Totals	**1983**	**1540**

[1] As at 20 June 2018

ANNEX F

MEFLOQUINE STUDY – CONSENT FORMS AND INFORMATION SHEETS

The Mefloquine trials were conducted in two distinct ADF populations. This annex contains the consent forms and information sheet used in each group. D1 (version 1.6) relates to ADF members who volunteered as part of the 2nd Battalion Royal Australian Regiment Battalion Group in Timor Leste and D2 (MQ0) relates to those ADF members who volunteered as part of the 4th Battalion Royal Australian Regiment Battalion Group in Timor Leste . There are no material differences between the two form.

INFORMATION AND CONSENT FORM PROTOCOL

Regimental Number _____ Volunteers Initials: (

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

As you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to observe a less commonly used drug, Mefloquine, under field conditions.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent malaria infection from overseas deployments in the future.

WHAT IS THE MEDICINE?

Mefloquine one tablet weekly in the AO and for two weeks after return to Australia. You will initially be given at least six tablets prior to deployment. The usual medicine is Doxycycline one tablet daily through deployment and for two weeks after. You are initially given two tablets prior to deployment.

WHAT IS THE STUDY?

The study is looking at how satisfactory Mefloquine is under field conditions. You will be provided with one tablet weekly through the standard supply system in the field. Supply and use of each tablet weekly will be recorded. You will be asked immediately prior to deployment, several times throughout the deployment and on return to Australia, whether you had any problems you thought were due to the antimalarial tablet. A small group will be (randomly) selected to additionally give blood on two occasions during deployment.

LENGTH OF THE STUDY

The study will begin 4 weeks prior to your redeployment and will be continued until 12 months after your deployment is completed. Your only involvement after redeployment will be if you develop malaria.

STUDY TESTS

All volunteers will be asked to complete a questionnaire immediately prior to deployment, during 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).

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have had any anxiety attacks or serious depression in the past you also may not be able to use Mefloquine. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

CONFIDENTIALITY

In all reports only a number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

Mefloquine is authorised to use as an antimalarial by civilian authorities in Australia in addition to being directed for use as an alternative to Doxycycline by the Director General, Defence Health Services in HPD215. This trial has also been approved by the Australian Defence Medical Ethics Committee.

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the RMO or AMI (0407 150384).

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the RMO or study investigators. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3925

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal antimalarial course of Doxycycline daily and an eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____ **Date:** _____

INVESTIGATOR'S SIGNATURE _____ **Date:** _____

CONSENT FORM PROTOCOL No.MQ0

Regimental Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

As you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to observe a less commonly used drug, Mefloquine, under field conditions.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent malaria infection from overseas deployments in the future.

WHAT IS THE MEDICINE?

Mefloquine one tablet weekly in the AO and for two weeks after return to Australia. You will initially be given at least six tablets prior to deployment.

The usual medicine is Doxycycline one tablet (100mg) daily through the deployment and for two weeks after. You are initially given two tablets prior to deployment.

WHAT IS THE STUDY?

The study is looking at how satisfactory Mefloquine is under field conditions. You will be provided with one tablet weekly through the standard supply system in the field. Supply and use of each tablet weekly will be recorded. You will be asked immediately prior to deployment, several times throughout the deployment and on return to Australia, whether you had any problems you thought were due to the antimalarial tablet. A small group will be (randomly) selected to additionally give blood on two occasions during deployment.

LENGTH OF THE STUDY

The study will begin 4 weeks prior to your redeployment and will be continued until 12 months after your deployment is completed. Your only involvement after redeployment will be if you develop malaria.

STUDY TESTS

All volunteers will be asked to complete a questionnaire immediately prior to deployment, during 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.

The most frequently observed reactions to Mefloquine include the following:

Common (>1%)

- sleepiness, insomnia, abnormal dreams, dizziness, loss of balance, headache, nausea and vomiting, diarrhoea, abdominal pain,

Uncommon (<1%)

- 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, lowering of the clotting cells in the blood, or white cells (used for fighting infection),

Rare (<0.1%)

- brain damage, psychotic events, severe hypersensitivity reactions in the skin and heart block

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have had any anxiety attacks or serious depression in the past you also may not be able to use Mefloquine. If you have

experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

CONFIDENTIALITY

In all reports only a number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

Mefloquine is authorised to use as an antimalarial by civilian authorities in Australia in addition to being directed for use as an alternative to Doxycycline by the Director General, Defence Health Services in HPD215. This trial has also been approved by the Australian Defence Medical Ethics Committee.

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the RMO or AMI (0407 150384).

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the RMO or study investigators. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP4-7-65
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3818

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal antimalarial course of Doxycycline daily and an eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____
Date: _____

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____
Date: _____

PREVENTION STUDY - CONSENT FORM AND INFORMATION SHEET

APPENDIX B

INFORMATION SHEET

A randomised, double-blind comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Principal Investigators:
LtCol Peter Nasveld, MBBS, BScMED, FACRRM
LtCol Mike Edstein, PhD

Protocol No.
SB 252263/033 (ADMEC 216/00)

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE OF THE STUDY

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to look at the safety and effectiveness of a new drug, ***tafenoquine***, for the prevention of malaria. We also wish to compare tafenoquine with another drug, ***mefloquine***, which has been widely used over the past decade and is one of the alternative drugs currently used by the ADF to prevent malaria.

WHAT IS THE MEDICINE?

If you agree to take part in the study, you will be assigned at random to one of two treatment groups. The study will be "*double-blinded*" which means that neither you nor your doctor will be aware which medication you are taking.

You will receive either one tafenoquine (200mg) capsule each day for three consecutive days during pre-deployment training followed by one tafenoquine capsule weekly throughout the deployment or one mefloquine (250mg) capsule each day for three consecutive days during pre-deployment training followed by one mefloquine capsule weekly throughout the deployment. You will have a 75% chance of being on tafenoquine and a 25% chance of being on mefloquine. You will take all medication with food to reduce side effects. The doses will be issued to you weekly so we can accurately record when you have taken your medication.

When you return to Australia, you will undergo treatment to get rid of any malaria parasites that may have collected in your liver. Those who received mefloquine will be given the standard drug used for this purpose called primaquine. You will take one capsule (15mg) twice a day for 14 days. If you received tafenoquine, this eradication course is not necessary, therefore you will take one capsule of placebo twice a day for

14 days. As before, you will not know which treatment you are taking, but you will have a 75% chance of receiving placebo and a 25% chance of receiving primaquine.

While tafenoquine has been given to several thousand individuals safely (including more than 1,000 ADF personnel during trials in Bougainville and East Timor), it has not yet been registered with the regulatory authorities in Australia or the USA. Consequently it is still defined as an "experimental" compound.

WHAT IS THE STUDY?

The study involves up to 700 volunteers receiving tafenoquine or mefloquine weekly throughout the deployment. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain details on how you should be investigated, how to contact the investigators, and how you should be treated if malaria is diagnosed.

LENGTH OF THE STUDY

The study will begin during pre-deployment training in Townsville, continue during the deployment, with follow-up until 6 months after your deployment is completed. Your only involvement after redeployment will be normal follow-up (after 6 and 12 weeks) by your RAP according to LHQ directives, plus telephone interviews at 18 and 24 weeks after returning to Australia. Should you get malaria after this, your Doctor or RAP will undertake normal reporting to AMI. There are no additional blood tests during the follow-up period over those normally required for personnel re-deploying from overseas service.

STUDY TESTS

As the investigators are looking at drug levels in your blood, checking your blood for malaria and measuring biochemical (liver and kidney function) and haematological (blood cell) levels in your blood to monitor safety, you will be requested to provide samples of blood from your arm. These tests involve the drawing of 9mls (two teaspoons) of blood on up to 9 occasions. Three (3) of these samples would be required anyway as part of your deployment requirements as directed by LHQ. Over the course of the study, a total of 81mls of blood will be collected.

A selected Company sized group will also have additional tests (including chest X-ray and ECG) done to look at other effects that either of the study drugs may have, as well as having eye and lung function tests done before and after the deployment. This will require an additional 20 mls of blood to be taken.

Female volunteers will have pregnancy testing performed on their blood samples on all occasions that blood is taken. No additional blood will be taken for this purpose.

RISKS / DISCOMFORTS

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

Tafenoquine has a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In eight previous clinical trials involving human subjects, including studies in ADF personnel on Bougainville, tafenoquine was noted to produce nausea, vomiting and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Similar side effects are seen with mefloquine. In addition, mefloquine has also rarely (about 1:10,000) been associated with depression and anxiety. Both tafenoquine and mefloquine are considered to be safe, however, neither are recommended for use in pregnant females. Primaquine has similar side-effects to tafenoquine including the risk of producing the bleeding disorder related to a lack of G6PD, as described above.

Although you will be taking study medication designed to prevent malaria, there is a very small chance that you may contract malaria while on the study. However, if you do contract malaria you will be treated by your company medic or study investigator and followed up until you are better.

BENEFITS

The benefit of taking part in the study is that you will be more closely monitored for the development of malaria during and after your deployment. You will be taking a medication once weekly rather than once daily with the ADF standard drug, doxycycline. In addition, the study results may provide a better understanding on how to prevent malaria infection on future overseas deployments.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, please discuss this with the study Medical Officer.

Pregnancy - If you think (females only) that you may be pregnant or intend to become pregnant within one month of returning to Australia, please discuss this with the study Medical Officer. It is recommended not to become pregnant within 3 months of ceasing the medication.

Contraception – While taking this medication, it is recommended that females use an accepted form of contraception*, which may include abstaining, barrier methods or pharmaceutical methods (“the pill”). Tafenoquine and mefloquine are not considered to interact with Oral Contraceptive Pills. If you are concerned about such interactions or have any questions about contraception while on the medication, please discuss this

with the study Medical Officer. Continue precautions for 3 months after stopping treatment.
*It should be remembered that no barrier or pharmaceutical method of contraception is 100% effective.

CONFIDENTIALITY

In all reports, publications or presentations about this research, information about you and your participation in this study will be kept in the strictest confidence and will not be released in any form that personally identifies you (a study number only will be used). The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

From time to time a monitor representing the sponsors of the study (SmithKline Beecham / US Army Medical Research and Materiel Command), or a regulatory authority such as the Therapeutic Goods Administration in Australia or the US Food and Drug Administration, may require access to your medical records to ensure that the study is being carried out to the international standards under Good Clinical Practice (GCP). This access will be supervised by one of the study team and all monitors are bound by a confidentiality agreement.

It is the policy of the USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into the Command's Volunteer Registry Database. This is a confidential database and the data entered include name, address, social security number (or equivalent) and details of the clinical trial. This information is needed to answer questions concerning subjects participating in research sponsored by USAMRMC, and to ensure that subjects can be contacted if there is new information on the study drug. The information will be stored for 75 years.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. Compensation other than medical care will be provided according to the compensation provided as a member of the Australian Army. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study. Should you consider injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility. The study investigators may be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600
Tel: (02) 6266 3925

INVESTIGATOR RESPONSIBILITIES

The investigators are responsible for ensuring that the study is conducted according to accepted Good Clinical Practice (GCP) standards, and for ensuring that the well being of study participants is always considered over all other considerations. Additionally, they are required to advise you in a timely manner should any other information become available that may be relevant to your willingness to participate in the study.

YOUR RESPONSIBILITIES

Should you agree to enter the study, you should be prepared to undertake all doses of drug required during the deployment, as well as all tests and follow-up required. Should you experience any medical problems, including suspected side effects to the study drugs, you should report these promptly to your Company medic, RAP or study investigator. If you want any further information on the study, please contact the study investigator named on the attached consent form.

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. Should you choose to be omitted from the study, or to withdraw from the study at any stage, there will be no detriment to your medical care or your career. If you choose to leave the study you should advise the study investigators. The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so. This will be done if he/she feels that it is not in your best interest to continue either because of side effects of the drugs, or other injuries or illnesses you may experience during the deployment.

Should you not wish to participate in the study, you will require:

a) the normal prevention course for malaria of **doxycycline daily** during the deployment,

b) a malaria eradication course on returning to Australia including:
   i) two weeks of **doxycycline daily** and
   ii) two weeks of **primaquine three times a day**, and

c) all the required **blood samples** taken for deployment and post deployment screening.

SB 252263/033

Volunteer ID: _____

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me in this information sheet (dated……). All questions raised by me have been answered to my satisfaction. I have been given a copy of this Information Sheet and Consent Form. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____

Date: _____

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____

Date: _____

WITNESS SIGNATURE _____

Printed Name: _____

Date: _____

ADDRESS OF SUBJECT: Lavarack Barracks, Townsville, Queensland, Australia.

ANNEX H

ERADICATION STUDY– CONSENT FORMS AND INFORMATION SHEETS

The Eradication trials were conducted in three distinct ADF populations. This annex contains the consent forms and information sheet used in each group. G1 (ARM 1 Protocol A), G2 (ARM 1 Protocol B) and G3 (ARM 1 Protocol C) relates to those ADF members who volunteered as part of rotations of the Peace Monitoring Group in Bougainville. There are no substantive differences except in the description of 'What is the medicine?' This reflect a change in the name of the investigational drug from Etaquine to Tafenoquine and the use of doxycycline by participants.

G4 (ARM 2 Protocol D) relates to those ADF members who volunteered as part of the 3rd Battalion Royal Australian Regiment Battalion Group in Timor Leste and G5 (ARM 3 Protocol E) relates to those ADF members who volunteered as part of the 5th/7th Battalion Royal Australian Regiment Battalion Group in Timor Leste. There are no substantive differences except in the description of 'What is the medicine?' This reflects differences in the dose of Tafenoquine used.

Arm 1 – Protocol A

CONSENT FORM / INFORMATION SHEET – ETA001

Volunteer Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. Additionally, on completion of your deployment you will be given different drugs to eliminate the stage of vivax malaria, which can lie dormant in your liver (hypnozoites). The purpose of this study is to look at how efficient two of these eradication drugs are in eliminating the hypnozoites (liver) stage. One of these drugs, primaquine, is the current in service eradication course, while the other, etaquine, is a new drug reported to be more effective and taken over a shorter period of time.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent Vivax malaria infection following overseas deployments in the future.

WHAT IS THE MEDICINE?

Two drug schedules will be used in the study. They are:

a. Primaquine - one 7.5 mg tablet taken 3 times daily for 14 days; and
a. Etaquine - one 500 mg tablet taken once a day for 3 days.

Etaquine is an experimental compound developed by the US Army. It is currently undergoing final clinical trials in Thailand and Kenya. The AMI study is designed to test the compound in the Southwest Pacific. The Therapeutic Goods Administration and the Australian Defence Medical Ethics Committee have reviewed the study and given approval for it to go ahead. The drug does not have TGA registration for use in Australia at this stage. Registration can not be finalised until all clinical trial data is analysed.

WHAT IS THE STUDY?

The study involves half of the redeploying group receiving the standard eradication drug, primaquine, while the other half of the group takes the newer drug, etaquine. Should you develop a fever within 12 months of returning home, you will be asked to attend your local health facility and show them your study ID card. This ID card will contain details on how you should be investigated, how to contact the investigators, and how you should be treated if malaria is diagnosed.

Initials_____

LENGTH OF THE STUDY

The study will begin 4 days prior to your deployment and will be continued until 12 months after your deployment is completed. However, your only involvement after redeployment will be to send back to AMI your single *Side Effects Questionnaire* and *Eradication Course Record*, unless of course you develop fever.

STUDY TESTS

As the investigators are looking at baseline drug levels in your blood, and measuring your biochemistry and haematology levels to monitor safety, you will be requested to donate a sample of blood from your arm. The first samples will be taken along with the sample taken for HIV and hepatitis screening which is a requirement of your deployment. A second 7ml sample will be taken on day 3-4 to measure drug levels. The additional amount of blood collected amounts to no more than about 20 mls, or the equivalent of 4 teaspoons.

Additionally, you will be asked to complete a questionnaire and keep a record of your medication during the study.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm. There may be some discomfort and a possibility of infection may exist. All action to minimise these risks will be taken, and your blood will only be taken by appropriately trained personnel.

Both study drugs have a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In seven clinical trials involving human subjects, Etaquine was noted to produce some nausea and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Primaquine produces similar side effects that are usually more marked. Both drugs are considered to be safe. No other significant reactions have been reported for either of the test compounds.

Neither drug is recommended for use in pregnant females. **Female members who are pregnant are not to take part in the study.** ***If you think you may be, or would intend becoming pregnant within 4 weeks of taking the last dose of either drug you should advise the study doctors.***

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (rash or marked itching) or anaphylaxis (significant allergic responses with collapse) you may not be able to take part in the study. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

Initials_____

CONFIDENTIALITY

In all reports you will only be identified by a number. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP4-6-45
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3807

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment to your career or medical care, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so.

Initials_____

WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEERS SIGNATURE _____

Printed Name: _____
Date:

STUDY DOCTORS SIGNATURE _____ _____

Printed Name: _____
Date: _____

ARM 1 – PROTOCOL B

ANNEX A to
Protocol ETA001

CONSENT FORM / INFORMATION SHEET

Volunteer Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. Additionally, on completion of your deployment you will be given different drugs to eliminate the stage of vivax malaria that can lie dormant in your liver (hypnozoites). The purpose of this study is to look at how efficient two of these eradication drugs are in eliminating the hypnozoites (liver) stage. One of these drugs, Primaquine, is the current in service eradication course, while the other, Tafenaquine, is a new drug reported to be more effective and taken over a shorter period of time.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent vivax malaria infection following overseas deployments in the future.

WHAT IS THE MEDICINE?

Two drug schedules will be used in the study. They are:

a. Primaquine - one 7.5 mg tablet taken 3 times daily for 14 days; and
b. Tafenaquine - one 500 mg tablet taken once a day for 3 days.
c. Doxycycline 100mg daily is continued by all personnel for 2 weeks after leaving the area as per current ADF policy

WHAT IS THE STUDY?

The study involves half of the redeploying group receiving the standard eradication drug, Primaquine, while the other half of the group takes the newer drug, Tafenaquine. The allocation to either drug is determined at random. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain details on how you should be investigated, how to contact the investigators, and how you should be treated if malaria is diagnosed.

Initials: _____

LENGTH OF THE STUDY

The study will begin 4 days prior to your deployment and will be continued until 12 months after your deployment is completed. However, your only involvement after redeployment will be to send back to AMI your *Personal Medication Diary*, unless of course you develop fever.

STUDY TESTS

As the investigators are looking at baseline drug levels in your blood, and measuring your biochemistry and haematology levels to monitor safety, you 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.

Additionally, you will be asked to keep a record of your medication and complete the diary section recording any adverse experiences you may notice while on the medication. This diary is then to be returned to AMI two weeks after you return to Australia on redeployment.

RISKS / DISCOMFORTS

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

Both study drugs have a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In seven clinical trials involving human subjects, Tafenaquine was noted to produce some nausea and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Primaquine produces similar side effects that are usually more marked. Both drugs are considered to be safe. Neither drug is recommended for use in pregnant females.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

Initials:_____

CONFIDENTIALITY

In all reports a number only will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP4-6-45
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3807

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so.

Initials:_____

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____
Date: _

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____
Date: _____

ARM 1 — PROTOCOL E.

ANNEX A to
Protocol ETA001

CONSENT FORM / INFORMATION SHEET

Volunteer Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. Additionally, on completion of your deployment you will be given different drugs to eliminate the stage of vivax malaria that can lie dormant in your liver (hypnozoites). The purpose of this study is to look at how efficient two of these eradication drugs are in eliminating the hypnozoites (liver) stage. One of these drugs, Primaquine, is the current in service eradication course, while the other, Tafenaquine, is a new drug reported to be more effective and taken over a shorter period of time.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent vivax malaria infection following overseas deployments in the future.

WHAT IS THE MEDICINE?

Two drug schedules will be used in the study. They are:

a. Primaquine - one 7.5 mg tablet taken 3 times daily for 14 days, with Doxycycline 100mg once daily for 14 days; and
b. Tafenaquine - one 500 mg tablet taken once a day for 3 days.

WHAT IS THE STUDY?

The study involves half of the redeploying group receiving the standard eradication drug, Primaquine, while the other half of the group takes the newer drug, Tafenaquine. The allocation to either drug is determined at random. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain details on how you should be investigated, how to contact the investigators, and how you should be treated if malaria is diagnosed.

LENGTH OF THE STUDY

The study will begin 4 days prior to your redeployment and will be continued until 12 months after your deployment is completed. However, your only involvement after redeployment will be to send back to AMI your *Personal Medication Diary*, unless of course you develop fever.

STUDY TESTS

As the investigators are looking at baseline drug levels in your blood, and measuring your biochemistry and haematology levels to monitor safety, you 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.

Additionally, you will be asked to keep a record of your medication and complete the diary section recording any adverse experiences you may notice while on the medication. This diary is then to be returned to AMI two weeks after you return to Australia on redeployment.

RISKS / DISCOMFORTS

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

Both study drugs have a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In seven clinical trials involving human subjects, Tafenaquine was noted to produce some nausea and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Primaquine produces similar side effects. Both drugs are considered to be safe. Neither drug is recommended for use in pregnant females.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

Initials:_____

CONFIDENTIALITY

In all reports a number only will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP4-6-45
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3807

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so.

Initials: _____

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____
Date: / /

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____
Date: _____

ARM 2 - PROTOCOL D

ANNEX A to
Protocol ETA001

CONSENT FORM / INFORMATION SHEET

Volunteer Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

Because you are deploying to an area where malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. Additionally, on completion of your deployment you will be given different drugs to eliminate the stage of vivax malaria that can lie dormant in your liver (hypnozoites). The purpose of this study is to look at how efficient two of these eradication drugs are in eliminating the hypnozoites (liver) stage. One of these drugs, primaquine, is the current in service eradication course, while the other, tafenoquine, is a new drug reported to be more effective and taken over a shorter period of time.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent vivax malaria infection following overseas deployments in the future.

WHAT IS THE MEDICINE?

Three drug schedules will be used in the study. They are:

a. Tafenoquine - two 200 mg base capsules taken daily for 3 days;
b. Tafenoquine – two 200 mg base capsules taken daily as a split dose for 3 days; and
c. Primaquine - one 7.5 mg base tablet taken 3 times daily for 14 days

Those soldiers on primaquine will also have to take doxycycline (100mg) daily for 2 weeks after leaving the area as per current ADF policy.

WHAT IS THE STUDY?

The study involves one-third of the redeploying group receiving the standard eradication drug, primaquine, while the other two-thirds of the group takes the newer drug, tafenoquine. The allocation to either drug is determined at random. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain information that you have been on an eradication trial for malaria and how to contact the investigators for follow-up if you are subsequently diagnosed with malaria.

LENGTH OF THE STUDY

The study will begin 4 days prior to your deployment and will be continued until 12 months after your deployment is completed.

STUDY TESTS

As the investigators are looking at baseline drug levels in your blood, and measuring your biochemistry and haematology levels to monitor safety, you 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.

Both study drugs have a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In seven clinical trials involving human subjects, tafenoquine was noted to produce vomiting, nausea and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Primaquine produces similar side effects that are usually less marked. Both drugs are considered to be safe. Neither drug is recommended for use in pregnant females.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

CONFIDENTIALITY

In all reports a number only will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP4-6-45
Department of Defence
Canberra, ACT, 2600

Phone: (02) 6266 3807

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal eradication course of primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____
Date: _____

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____
Date: _____

ARM 3 – PROTOCOL E.

REGT No _____
RANK _____
NAME _____

ANNEX A to
Protocol TQ001

CONSENT FORM/INFORMATION SHEET

Volunteer Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. Additionally, on completion of your deployment you will be given different drugs to eliminate the stage of vivax malaria, which can lie dormant in your liver (hypnozoites). The purpose of this study is to look at how efficient two of these eradication drugs are in eliminating the hypnozoites (liver) stage. One of these drugs, Primaquine, is the current in service eradication course, while the other, Tafenoquine, is a new drug reported to be more effective and taken over a shorter period of time.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent Vivax malaria infection following overseas deployments in the future.

WHAT IS THE MEDICINE?

Two drug schedules will be used in the study. They are:

a. Primaquine - one 7.5 mg tablet taken 3 times daily plus Doxycycline 100 mg daily for 14 days after leaving the area
b. Tafenoquine - one 250 mg capsule taken once a day for 3 days.

WHAT IS THE STUDY?

The study involves one third of the redeploying group receiving the standard eradication drug, primaquine, while the other two thirds of the group takes the newer drug, Tafenoquine. The allocation to either drug is determined at random. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain information that you have been on an eradication trial for malaria and how to contact the investigators for follow-up if you are subsequently diagnosed with malaria.

LENGTH OF THE STUDY

The study will begin 4 days prior to your redeployment and will be continued until 12 months after your deployment is completed..

STUDY TESTS

As the investigators are looking at baseline drug levels in your blood, and measuring your biochemistry and haematology levels to monitor safety, you 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.

Both study drugs have a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD.You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In seven clinical trials involving human subjects, Tafenoquine was noted to produce vomiting, nausea and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Primaquine produces similar side effects that are usually less marked. Both drugs are considered to be safe. Neither drug is recommended for use in pregnant females.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

CONFIDENTIALITY

In all reports you will only be identified by a number. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the phone number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3818

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I may keep a copy of this consent form if I wish. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____
Date:

STUDY DOCTOR'S SIGNATURE _____

Printed Name: _____
Date: _____

ANNEX I

DRAFT COPY OF LETTER SENT TO PARTICIPANTS WHO HAD TAKEN TAFENOQUINE – VORTEX KERATOPATHY

DEPARTMENT OF DEFENCE
AUSTRALIAN ARMY MALARIA INSTITUTE

Gallipoli Barracks, Enoggera, Queensland 4052
Phone:+ 61 (0)7 3332 4801 Fax: +61 (0)7 3332 4800

548-7-41

Insert Address Block

Dear Study Participant

DOSING WITH THE STUDY DRUG TAFENOQUINE

In *(insert year)* you were given the drug TAFENOQUINE for *(insert duration x days/weeks/months)*, under my care, as part of a malaria study to assess the safety and effectiveness of this drug that is under development by the drug company GlaxoSmithKline and the US Army. This study was run by the clinic at (*insert location*).

Nearly 3000 people, including yourself, have been given TAFENOQUINE in studies. These people have been recruited from Australia, Asia, Africa, Europe and the United States. No serious problems, or long term effects, have been reported with TAFENOQUINE since dosing began in humans over 5 years ago.

In a recently completed study in soldiers given TAFENOQUINE for 6 months, a group of the soldiers had additional examinations of their eyes – both before the study began, and at the end of the study after taking the drug for 6 months. In this group many of the soldiers who received TAFENOQUINE developed tiny deposits on the front of their eyes (the cornea). It is important for you to know that none of these soldiers had any symptoms – their vision was not affected in any way. Exactly the same changes are seen with other drugs used all over the world for a variety of diseases and conditions. This includes the drug chloroquine that has been used for many years in treating and preventing malaria. With all these drugs it is also important for you to know that these deposits disappear completely, given time. We know from the examinations in the soldiers that, for TAFENOQUINE, deposits disappear after about 6 months. You may have received TAFENOQUINE for a far shorter time period than these soldiers. We do not believe these deposits have any long-term effects on your eye or your vision.

Very recently a group of expert eye doctors from all over the world met in America to review the findings in the soldiers and provide advice. They agreed that these deposits were of little concern, would completely disappear with time, they do not affect vision, and are not a reason to stop taking drug. This group of doctors also reviewed other examinations on these soldiers – such as how well they could read letters on a chart, colour vision, and looking at the back of

the eye. They confirmed that none of the soldiers had suffered any loss of vision as a result of taking TAFENOQUINE.

We hope you find this information reassuring, in that there is currently no evidence that vision has been affected in any subject given TAFENOQUINE. If you finished your study more than 1 year ago, these totally harmless deposits are extremely unlikely to be present.

However, if you are still concerned, you may want to contact your local doctor or clinic for further advice. Please, make an appointment by contacting your local Regimental Aid Post or Medical Centre for initial assessment. If your doctor thinks that further specialist assessment is required, he/she will then contact us at the Malaria Institute to arrange suitable followup.

You should take a copy of this letter with you to your appointment so that your doctor can advise us of any findings or followup required. Additionally, we would appreciate it if you could sign and date the copy of the letter included and return it to us in the pre-paid envelop provided so that we can be sure that this information has reached you. Alternatively, you may wish to acknowledge receipt or seek clarification by emailing the Principal Investigator at the email address listed below.

Yours sincerely

PETER NASVELD
Lieutenant Colonel
Principal Investigator

Double click here to add promulgation date

I, _____, acknowledge receipt of the above information.

(please print name clearly)

Signature of Study Volunteer:_____

Vol ID number*(if known)*:_____

Date:_____

ANNEX J

OVERVIEW OF TESTING FOR NEW MEDICATIONS - CLINICAL STUDIES

Clinical trials are how new medications are evaluated to ensure they are effective and safe. These trials must be done before these treatments can be formally approved by regulators and become accessible to the general population.

Prior to any medication being used in humans it goes through a series of standardised tests in at least two different animal species. These tests are designed to identify short and longer term toxicity, demonstrate that the drug has the desired effect and to help establish the dosage to be used in subsequent human trials.

In Australia clinical trials of unapproved (unregistered) therapeutic goods (e.g. vaccines, medications) may be conducted under one of two schemes:

- The Clinical Trial Exemption (CTX) scheme – Under this scheme the researcher makes an application to conduct the clinical trial to the Therapeutic Goods Administration (TGA), which reviews the available relevant scientific data. For the trial to proceed the TGA must have notified the researcher that there is no objection to the conduct of the trial. The trial must also have been approved by a human research ethics committee and the organisation in which the trial is to be conducted.
- The Clinical Trial Notification (CTN) scheme – Under this scheme the researcher applies directly to a human research ethics committee, which reviews the trial protocol and provides ethical approval if it is satisfied that the proposed trial is scientifically and ethically sound. The ethics committee also assumes responsibility for monitoring the trial. The trial cannot start until the TGA has been notified.

Clinical trials are routinely described by "phase". Phase I – III trials are conducted sequentially prior to a medication being registered by the TGA. Phase IV (post marketing) trials are conducted with medications that are already registered and being used in the community.

Most clinical trials conducted by the Army Malaria Institute have been Phase IV trials of TGA registered medications, although the trials involving the anti-malarial medication tafenoquine were Phase III trials.

Any clinical trials involving ADF members in the field or on operations are done after the Phase I and II trials have been conducted in a more controlled civilian environment.

The following describes clinical trials by phase:

- Phase I clinical trials are done to test a new medication for the first time in a small group of people (e.g. 20-80) to evaluate safety (e.g. to determine a safe dosage range and identify side effects).
- Phase II clinical trials are done to study a medication in a larger group of people (several hundred) to determine efficacy (that is, whether it works as intended) and to further evaluate its safety.
- Phase III studies are done to study the efficacy of a medication in large groups of trial participants (from several hundred to several thousand) by comparing the intervention to other standard or experimental medications (or to non-interventional standard care).

Phase III studies are also used to monitor adverse effects and to collect information that will allow the medication to be used safely.

- Phase IV studies are done after a medication has been approved and registered by the TGA and is in routine use in the community. These studies are designed to monitor the effectiveness of the approved medication in the general population and to collect information about any adverse effects associated with widespread use over longer periods of time. They may also be used to investigate the potential use of the medication in a different condition, or in combination with other therapies.

More information about the regulation of clinical trials is available from the Department of Health – Therapeutic Goods Administration website on https://www.tga.gov.au/clinical-trials ; and https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials .

ANNEX K

LITERATURE REVIEW FOR JOINT HEALTH COMMAND
NEUROPSYCHIATRIC EFFECTS OF MEFLOQUINE - MARCH 2016
GPCAPT ALEXANDER C MCFARLANE AO

Literature Review for Joint Health Command

Neuropsychiatric effects of Mefloquine

March 2016

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Literature Review for Joint Health Command

Neuropsychiatric Effects of Mefloquine

Introduction

Mefloquine has been extensively used for the prophylaxis against malaria. It has been prescribed since its development to millions of people, both for the prophylaxis and treatment of malaria. Whilst there is some uncertainty about the precise mechanism of action, these include inhibition of cellular crystalline hemozoin formation and alternations in heme iron transport (1). One particular advantage of the drug is that it can be used in lower doses for prophylaxis on a weekly basis due to its long half-life (13 to 30 days) (2). One of the challenges of antimalarial prophylaxis is that these drugs are prescribed essentially to healthy populations who are not ill prior to departure to an area where malaria infestation is possible. Such agents used in prophylaxis should be well tolerated with an associated very low risk-benefit profile (3).

Some 10 years after mefloquine's introduction, the first reports of neurotoxicity emerged. Subsequently, there has been a growing interest in the possible neurotoxicity of mefloquine that has attracted media attention. These potential adverse effects tend to evoke particular concern when described in military cohorts because of the necessity of ingestion in the course of conducting military service (3). A range of adverse effects have been associated with mefloquine use, including sleep disturbance, dizziness, anxiety, depression, nausea and frank psychosis, to name a few (4). A particular concern arises from case reports linking mefloquine to suicide and aggression, including homicide. The prevalence of these adverse effects has varied widely in different reports.

The challenge exists as to how to interpret these divergent findings, particularly when the drug is being used for malaria prophylaxis. This review examines the different types of reports and research papers as their distinct methodologies leads to different emphases and conclusions. It will not systematically review the literature.

The challenge of interpretation arises because a number of the side effects attributed to mefloquine are prevalent symptoms in general populations in the absence of prescribed medications. These include symptoms such as nausea, fatigue, and anxiety. Also, travel is associated with a range of health risks that can lead to psychiatric symptoms, including jet lag, illicit drug ingestion, as well as accidents and intercurrent infectious diseases (5). Hence, the challenge of establishing causality to particular adverse effects in a given individual is significant.

Part of the reason for mefloquine's adverse press coverage is that it was developed in a private/public venture between a pharmaceutical company and the US Department of Defence (6). Phase 3 testing apparently was not required prior to its approval for usage. At the time of its early introduction, there were few troops taking mefloquine exposed to combat. This has led to significant concerns about inadequate

surveillance. It is against this background that the mechanisms of psychotropic effects and the adverse reactions of mefloquine are reviewed.

Possible Modes of Neurotoxicity

The observations about the possibility of the neurotoxicity of mefloquine have led to an extensive investigation of its actions in the central nervous system (1,4,7). These studies have identified a range of possible actions that could account for these side effects. These include acetyl-cholinesterase and butyl-cholinesterase inhibition, enhancement of striatal amino butyric acid (GABA) and connexin blockage. Other research has focused on the impact of mefloquine on cellular homeostatic mechanisms such as potassium ATP channel inhibition and calcium iron homeostasis. Specific effects on particular transmitter receptors such as adenosine 2A receptor blockade have been considered.

Other investigations have had a particular interest in the role of mefloquine in causing nightmares, hallucinations, and exacerbation of symptoms of PTSD (1). These investigations have compared the radioligand binding of mefloquine with several hallucinogen and psychotropic stimulants. They have come to the conclusion that mefloquine unlike chloroquine does share some in vitro receptor activity with some hallucinogens.

A more recent concern has arisen that some of the deleterious effects associated with mefloquine have the potential to continue after the drug has been stopped. This has led to the proposition that there are long-term neurotoxic effects (7), which in turn prompted a recent warning from the United States food and drug administrations (8). One suggestion has been that mefloquine may cause oxidase stress leading to changed neuronal structure and that this neurotoxicity may be mediated by interactions with non-receptor tyrosine kinase (1).

In summary, the range of potential direct psychotropic effects of mefloquine indicates that its CNS effects could underpin mechanisms that may directly account for the range of neuropsychiatric symptoms that have been associated with mefloquine prescription.

Further Possible Origins of Adverse Effects

The scientific literature highlights that other experiences may occur in the course of ingestion of mefloquine that may impact or modify its effects and lead to possible adverse psychological consequences. These experiences include the stresses of travel and the ingestions of illegal substances (5). However, the literature does not consider a more important question, particularly in military populations, as to whether mefloquine or antimalarials more generally, may impact on soldiers' reactions and adaptations to the stresses of combat.

This question arises because there are other important examples in the scientific literature of how intercurrent medication use, prescribed for other reasons, impacts on the development of symptoms of PTSD and treatment response (9). For example, the serendipitous observation, ACE inhibitors used for treating hypertension have been noted to lessen PTSD symptoms (10). Similarly cyclosporine, an anti-tuberculus

antibiotic has been used to assist in cognitive behaviour therapy in posttraumatic stress disorder because of its impact on the MNDA receptors which influences fear extinction (11). Other examples, that have been trialled in preventative interventions in PTSD, include the use of cortisol given at the time of stress exposure to lessen the prevalence of PTSD (12). This intervention arose out of the observation that patients treated in intensive care units had lower rates of PTSD if given this drug. Intervention trials have supported the potential benefit of the ingestion of cortisol. Similarly, morphine has been found to have a potentially preventive effect on the onset of PSTD (13).

Given that mefloquine has a range of psychotropic effects, it is reasonable to hypothesise that its ingestion may modify an individual's stress responsivity. In particular, its action in the inhibition of acetylcholinesterase can possibly mimic drugs such as rivastigmine (14) and donezepil (15) that are used to improve memory function in dementia. Given that the consolidation of memory and the fragmentation of memory are thought to be an important component of the traumatic stress response, the possibility that mefloquine may impact on the stress response is not without a sound scientific base. Also, the roles of acetylcholinesterase inhibiting medications has been raised in other settings, when they were postulated as agents possibly underpinning the pathophysiology of Gulf War Syndrome (15).

The direction of the effect of mefloquine is unclear. For example, there are case reports (15) suggesting that donezepil can trigger posttraumatic stress disorder whereas rivastigmine has been shown in case reports to be a valuable add on in the treatment of the condition. While these effects of acetylcholinesterase inhibition are in individuals long after their stress exposure, this impact of memory circuitry is relevant to the onset of PTSD (16,17). Hence, this action of mefloquine could readily impact on stress reactivity and modify its symptomatic manifestations. Furthermore, these cholinergic inhibition effects appear to interact with other neurotransmitter systems such as GABA. The possibility exists for the complex modification of stress reactivity.

A number of papers have highlighted the potential mechanisms of action and the possibility that mefloquine can have psychotropic effects (1,4,7). These studies have investigated the possible mechanisms, particularly that might underpin the symptoms of psychosis. It has also been hypothesised that mefloquine may lead to a PTSD-like syndrome. In regards to the psychotic like episodes that have been observed, a potential mechanism is the similarity of mefloquine receptor interactions with certain hallucinogens. This similarity of receptor activity has been postulated to explain the occurrence of psychotic symptoms that arise in a small percentage of patients.

The Potential Overlap of PTSD and Mefloquine Psychotropic Effects

The overlap of PTSD and the manifestations of the adverse effects of mefloquine warrants further consideration. The more common adverse reactions to mefloquine include common psychiatric symptoms that are shared with a number of syndromes including PTSD such as anxiety, sleep disturbance, irritability and anger, withdrawal, and nightmares (17). Hence, many of these symptoms lack specificity and may mimic a PTSD-like presentation. This overlap has the potential to cause diagnostic confusion and concern in the veteran community. A second possibility is that if the

individual has had a significant traumatic exposure, subsyndromal symptoms experienced in the aftermath could be significantly exacerbated by the ingestion of mefloquine. Hence, mefloquine if given to an individual, who had subsyndromal symptoms of PTSD or another psychiatric condition, has the potential to exacerbate the presentation.

This clinical picture highlights the diagnostic challenge where many of the symptoms of PTSD are shared with other disorders and where these symptoms have low specificity. A diagnosis based on the phenomenology of the clinical presentation may fail to address the true complexity of the multifactorial underlying aetiology of the condition. When discussing the aetiology of posttraumatic stress disorder, it is also critical to emphasise the role of a range of neurobiological systems including catecholamines, corticosteroid production, endorphins, dopamine and inflammatory mediators (16). Hence there is a range of biological systems, which are progressively deregulated with the emergence of the symptoms of PTSD. If mefloquine impacts on any of these biological cascades, it could play a role in the manifestation of PTSD. This does not mean that the condition is substantially different but rather it highlights the multifactorial aetiology of this condition.

An example of this confusion of reasoning is the overlap of aetiology is highlighted in the role that mild traumatic brain injury can play in the onset of posttraumatic stress disorder (18). The mistake in the scientific literature is to assume the independence of the aetiological mechanisms in the onset of these conditions. In fact, there are many shared aspects of their neurobiology and neurophysiology. The same argument may apply to PTSD and the adverse effects of mefloquine.

The Nature of the Evidence about Mefloquine Toxicity

An important confound to consider in discussing the literature about the adverse effects of mefloquine is the genetic variations in its metabolic pathways (7). These polymorphisms have implications for the adverse reactions to other commonly used psychotropic drugs, such as antidepressants. Hence genetic and other biological differences such as female gender, which increases the probability of adverse reactions in mefloquine, are the likely underpinnings of the variability of reactions. This fact emphasises that there may be subgroups of individuals who carry a particularly high risk of adverse consequences of mefloquine usage. This variability of individual response highlights the complexity of discussing the issues of Mefloquine toxicity at a population-based level due to the low incidence of these atypical reactions. Whilst the drug may at a population level appear to have a high level of tolerability and a low risk profile, certain individuals may be at a risk of both acute and long-term toxicity.

This background underpins the challenge of representing the complexity of the literature in a balanced manner. Therefore in appraising the adverse consequences and side effects of mefloquine use, it is important to review the methodology of the various types of reports. The methodology underpinning these reports is an important determinant of how the conclusions reached should be considered in relation to a population-based response as against the management of individual cases.

a. Case Reports

There are a significant number of case reports (19-23) that have highlighted the particular syndromes, symptoms, or diagnoses that have been attributed to mefloquine usage. These include side effects that emerge in the short term prescription of the drug such as acute psychosis anxiety, paranoia and suicidal ideation, and potentially life threatening reactions, such as grand mal seizures.

Such reports highlight reactions at the severe end of the spectrum. The challenge with interpreting case reports, however, is they do not establishment definitive causal associations. The literature in general has focused on reactions that are observed during the ingestion of drug or immediately following its cessation. Given that the drug has a half-life of 13 to 30 days (2), there is a long tail of effect.

b. Health Surveys of Travellers

This approach has been developed as a form of post marketing surveillance. In general, the numbers of participants in these studies have been relatively small, although several studies have had over 1,000 participants (8). These observational studies depend upon the continued participation following the completion of travel. Several of these studies have used controlled populations (24). This study found that malarial prophylaxis led to symptoms reported in 59% versus 41% of controls. Although neuropsychiatric symptoms were common amongst mefloquine users, the statistical differences were not significant. There was an association between anxiety about prophylaxis and the later report of symptoms.

These studies have identified relationships such as the greater prevalence of adverse neuropsychiatric effects in females (24). Such reports led to further surveillance where as part of the surveillance, sustained attention testing and reaction times were measured. These indicated that women aged less than 20 had a demonstrable change, indicating impaired information processing (25). A range of these studies have allowed the comparison of the tolerability of the drug between different malarial prophylactic agents (26). This survey found greater compliance with mefloquine compared with other agents but a higher relative risk of reporting depression, strange thoughts, and altered spatial perception in mefloquine users. These symptoms were perceived as more severe when they occurred amongst the mefloquine group. However, these types of surveys highlight the problem of recreational drug usage, particularly amongst younger travellers that could also influence the patterns of symptomatic distress due to interactions with the malarial prophylaxis regime (27). The differences between mefloquine and other malarial prophylactic agents appear to be small at a population level (28).

A review of these studies led the Centre for Disease Control and Prevention to offer a travel advisory (8). In particular, it recommended that travellers should not take mefloquine if they had an active history of depression or recent depression, a history of psychosis, and other psychiatric disorders as well as seizures. A year earlier (2003), the Food and Drug Administration had produced a medication guide that included warnings about possible suicidal ideation.

c. Health Database Surveillance

A further strategy in considering the safety of use of various anti malarial agents has been the examination of long-term registers or health surveillance datasets. Various strategies have been used (8). For example, a Danish cohort examined a national register of side effects to medications. It then approached the individuals who had reported acute psychiatric effects of mefloquine and found that over half of the population of 73 participants continued to have ongoing symptoms of anxiety, phobic anxiety or depression. These long term effects were continuing to impact on functioning to a significant degree (29). These long-term symptoms raise concerns about neurotoxicity but do not prove causation.

Other datasets that have been examined include those from randomised controlled trials and systematic reviews (30). This allowed the direct comparison of mefloquine with other anti malarial drugs. The authors argued that the strength of such an approach is that it minimised the risk associated with anecdotal reporting that can be coincidental rather than indicative of actual harm. In particular, this study looked at the thresholds of risk and is one of the few publications that highlighted the risk of stress exposure as being a potential confound in ascertaining the exact rates of neuropsychiatric events. Whilst concluding that "*signals for serious adverse events pertinent to neuropsychiatric events were not detected from mefloquine*", the ongoing potential risks were highlighted.

Another database that specifically examined military populations investigated US service personnel and examined any hospitalisation in a substantial cohort of 8,858 individuals who had received mefloquine and compared them with over 350,000 other individuals who either had other antimalarials or no medication. The conclusion was reached that no association between mefloquine prescription and severe adverse health effects was documented as indicated by hospitalisation using a wide range of outcomes (31). However, the limitation of such a study is that this strategy of looking at hospitalisations only detects serious and high acuity complications of medication usage. This is likely to include episodes of psychosis. Hence, whilst offering information about serious complications, it does not address the issue of the more prevalent and low risk side effects.

Another strategy which has been used is the mining of general practice research databases (5). This strategy allows a nested case control design looking for first episode anxiety, stress related disorders including psychosis, depression, epilepsy, and other potential consequences and comparing a range of different malarial prophylaxis regimes. Those utilising these regimes could then be compared to unexposed travellers. This UK based study indicated that there were similar risks of neuropsychiatric disorders in the different drug regimes but these were not different from the controls who were not ingesting medication. This led to a conclusion of "*relatively little evidence for an increased risk of neuropsychiatric disorders in travellers with current or past exposure to mefloquine or other antimalarials*" (5).

The limitation of a study such as this is that the register depends upon the general practitioner identifying and diagnosing the side effect. It is known that there is significant under detection of psychiatric symptoms in general practice settings. However, such reviews focus on symptoms of concern in the target population and remove the issues of bias.

A previous study had been done in the UK general practice research database (32), which concluded that there was a low absolute risk of psychosis or panic attacks with all of the antimalarials. There was no evidence about mefloquine leading to greater rates of depression.

d. Military Cohorts

A range of studies report usage in military cohorts. One study (33) compared the use of doxycycline and mefloquine in British military units sent to train in Kenya from 2012 to 2013. This particular study examined the impact of malarial prophylaxis on the capacity to perform one or more tasks required by the participant's job. Doxycycline users had more adverse effects impacting on their ability to function (22.2% verses 12.6%). However, the doxycycline symptoms were gastro intestinal and dermatological in contrast to the mefloquine side effects which were neuropsychiatric. This recommended that organisations managing a workforce may favour the use of mefloquine to doxycycline. However, it did not discuss the potential consequences of the different impairments on role performance.

A tolerability study in the American military (34) highlighted that one of the challenges in comparing mefloquine and doxycycline is that the rates of compliance with daily dosage with doxycycline was substantially less than mefloquine (60% verses 80%). Rates of discontinuation were higher in the doxycycline group (10% versus 4% for mefloquine users). This highlights one of the challenges in comparing surveillance reports between different antimalarial drugs because of the probable higher rates of compliance in mefloquine groups.

A further challenge in dealing with military cohorts is the rates of adverse effects in stressful environments. For example, a UK study (35) found higher rates of adverse events amongst employed military personnel than civilians in a questionnaire based cohort study of 150 deployed personnel. The complexity of interpreting this data is highlighted by different rates of tolerability being reported on different deployments. For example, more side effects were reported with mefloquine in a Swedish deployment to Liberia in contrast to atovaquone/proganil prophylaxis. A military study reported in Australian soldiers deployed to East Timor (36) highlighted that mefloquine was generally well tolerated but 6.5% of individuals receiving the drug had to cease the medication due to side effects such as sleep disturbance, headache, tiredness and nausea. 94% indicated that they would use the drug again. 89% were using doxycycline.

Military populations in summary provide valuable insights but an oversight of the literature would suggest that there are significant inter-population differences.

e. Systematic Reviews

A further method of attempting to ascertain the tolerability and side effect profiles of particular anti malarial drugs has been the use of systematic reviews, for example using the Cochrane methodology (30). This review included data from 10 trials encompassing 2,750 individuals. Five of these studies were in military personnel. When compared with other forms of chemoprophylaxis, no differences in tolerability were found but withdrawal rates were consistently higher in placebo controlled trials.

This review concluded that "*there is evidence from non-randomised studies that mefloquine has potentially harmful effects in tourists and business travellers and its use needs to be carefully balanced against this*". This review updated several earlier reviews conducted by these authors.

Such systematic reviews provide valuable insights. However, the differences in the conclusions from other reported studies highlight the complexity of making conclusive recommendations.

f. General Reviews

Given the breadth of literature about the mechanism, clinical usage, and surveillance outcomes, there have been a number of published reviews that aim to aggregate the available information and make recommendations. These highlight the complexity of an evidence-based decision where the adverse effects need to be balanced against the risks and potential fatal consequences of malaria. In general, these conclude that mefloquine, whilst having an important role as a first line anti malarial should be prescribed in the context of assessing the potential risk to the individual and to inform users of the potential side effects (37). These reviews raise important concerns about the neuropsychological impacts of mefloquine and the possibility that this may impair performance on those operating machinery and soldiers in combat. However, one review highlighted the challenge in prescribing as the authors also concluded that there were no performance deficits in individuals who tolerate the drug (38).

More specific reviews have addressed issues such as the neurotoxicity of mefloquine (4). The challenge of interpreting such reviews is the difference in emphasis with the concluding statements stating "*the accumulated preclinical and clinical evidence supports mefloquine being psycho active and neurotoxic, and provides a number of explanatory mechanisms for this: interaction with neurotransmitters and receptors, inhibition of the SERCA and interference with neuronal calcium homeostasis*". They therefore highlight prudence in its prescription particularly in the prophylactic setting. There is another body of literature reviews that more specifically focus on cellular mechanisms of actions and possible hypotheses to explain the acute neuropsychiatric sequelae of the drug (7).

Other reviews make more specific recommendations about mefloquine's use in military settings. These included that its use in military settings "*maybe problematic"* (3). This review in particular highlighted military risks and highlighted that suicide and suicidal ideation was a particular concern in military settings. The use amongst aviators was also of particular concern. It is noteworthy that this review did not address the issue of the potential interaction between the neuropsychiatric effects of Mefloquine and deployment.

g. Published Clinical Trials

The various systematic reviews and more general reviews reference multiple published clinical trials and unpublished databases, examining mefloquine's use. These will not be discussed or examined.

Summary of Reports

The use of mefloquine in the prophylaxis of malaria is an area that continues to evoke controversy, in part driven by concerns of its use in military populations. The fact that it has an inhibitory effect on the cholinesterase enzymes draws on concerns that prophylactic agents against nerve gases used in the First Gulf War were hypothesised causes of Gulf War Syndrome. Providing a balanced scientific response to these concerns is therefore challenging (15). This question is further confounded by some divergence of the conclusions arising from the range different methodologies that have been used to review mefloquine's side effect profile.

The substantial challenge that receives little attention in the literature is to distinguish the neuropsychiatric complications actually due to mefloquine that occur in a subgroup of people patients, in contrast to those people who used mefloquine and have developed the same symptoms but due to different causes. The complexity of the problem is highlighted by the fact that the background rates of these phenomena/symptoms is relatively common in the general population in the absence of meflouqine exposure. Some studies, such as data extracted from the UK General Practice Register even suggest that there are no substantial effects of mefloquine prescription (5). However these conclusions are very different from the emphasis in specific case reports highlighting the risks of complications (eg 19). Such reports are subject to the bias arising from the fact of a substantial temporal association between the drugs ingestion and the onset of symptoms. The plausibility of these reports comes from the evidence of mefloquine's impact on central nervous system neurotransmission. The longer term neuropsychiatric consequences are also difficult to judge. Whilst a follow up of individuals who have had adverse neuropsychiatric consequences documents a significant rate of ongoing psychopathology, this does not necessarily demonstrate causality because of the potential for the occurrence of the adverse reactions being coincidental. The more powerful argument is the development of animal models and neuropathological studies of mechanism that highlight the potential for mefloquine to be a neurotoxin (7). These latter studies particularly highlight the need for long-term surveillance.

The existence of some studies which contrast mefloquine with other prophylactic strategies highlight similar levels of tolerability and impact on functional capacity. However, the effects of mefloquine disrupting function tend to be more prevalent in the neuropsychiatric domain than other side effects that lead to lack of tolerability of doxycycline (33). This emphasises the importance of the careful dissection of the conclusions of scholarly and well-written reviews.

A further complication with the literature is that it appears that mefloquine has better compliance rates because of its weekly ingestion compared with daily regimes such as doxycycline. As a consequence of the higher compliance rates, the mefloquine group have a greater probability of side-effects. This effect is not being highlighted generally in the literature may lead to a greater prevalence of adverse consequences simply because of greater rates of compliance.

The literature highlights that there are particular populations at risk, including females and individuals of low BMI (25). The literature also discusses the role of other intercurrent factors that may impact on the occurrence of neuropsychiatric symptoms

which are infrequently systematically examined. These include the impact of jet lag, intercurrent illness, alcohol, and illicit drug consumption (5). These on their own can contribute to adverse neuropsychiatric effects.

A striking absence in the literature is a consideration of the role of stress exposure, particularly in the military context and how this potentially could modify the adverse side effect profile of mefloquine. As highlighted, there are substantial theoretical and evidentiary reasons as to the possibility that mefloquine may impact on the long term consequences of exposure to traumatic stressors. This is an area where there is an urgent need for further investigation.

Diagnosis of Mental States induced by Mefloquine

A review of the literature does not provide any oversight or discussion of the diagnostic practice in the categorisation of the neuropsychiatric side effects of mefloquine. This lack of literature is because the diagnostic rules are broadly accepted in psychiatry that avoids the inclusion of the cause in the name of the disorder unless the evidence of causation is unequivocal. This convention is understood within diagnostic practice and is reflected in the Diagnostic and Statistical Manuals of Mental Disorders, of the American Psychiatric Association, since the 3rd edition (39).

The disorders in the DSM categories are essentially descriptors of a range of distinct mental states. Since DSM-III was first published in 1980 (40), the issue of aetiology has largely been removed from the name of conditions diagnosed. With the acute and chronic organic brain syndromes, the names were changed to delirium and dementia in DSM III. In DSM-5, dementia was again reformulated to major neurocognitive disorder with sub-types being defined if there were known causal factors (40). However, in general, even if there is a substantial organic contributor to a condition, such as schizophrenia or depression, this causal agent would not been reflected in the diagnosis. For example, interferon is known to be a cause of major depressive disorder (41,42). Other examples included where major depressive disorder can arise as a consequence of hypothyroidism (43), white matter hyper-intensities (44) and vitamin B12 deficiency (45). Schizophrenia can be brought on as a consequence of chronic amphetamine use (46,47) or regular cannabis ingestion (48,49). However these aetiologies do not give rise to a distinct category of diagnosis. Equally, if an organic factor contributes to the aetiology or symptom severity of PTSD (50), this is not reflected in the diagnosis.

The application of these diagnostic rules in the setting of neuropsychiatric side effects of mefloquine means that the disorder that characterises the patient's mental state would be diagnosed, whether this is depression, anxiety, delirium, schizophrenia or PTSD. If the diagnosis of PTSD were used, this is because the individual had experienced an event as set out in the stressor criterion for PTSD, as well as satisfying the other diagnostic criteria using intrusive distressing recollections, avoidance behaviours, negative cognitions related to the trauma and hyperarousal.

This practice reflects the fact that most psychiatric disorders have a complex matrix of biological, psychological and social factors that contribute to the aetiology and manifestation of the disorder (51). In certain circumstances, the genetic

vulnerabilities may not only reflect a familial predisposition to a psychiatric diagnosis but also may determine a particular pattern of metabolism of a drug, leading to the onset of a range of symptoms, eg with cannabis usage and schizophrenia (52). This general application of this convention in practice is not to negate or minimise the potential significance or relevance of a drug such as mefloquine in contributing to neuropsychiatric symptoms.

Treatment of Neuro-Psychiatric Effects of Mefloquine

When it comes to the treatment of mefloquine induced neuropsychiatric side effects, this standard practice reflects the broad approach to treatment in psychiatry. Again there is no specific literature addressing this topic. Essentially, treatments of psychiatric conditions are symptomatic. In other words, if an individual presents with a psychotic syndrome, whether this be amphetamine induced, or related to a high familial genic loading, the treatment will involve the prescription of antipsychotics and psychosocial interventions. In the case of a condition where there is a significant contributing organic factor, this will be addressed. For example, in an individual who is abusing amphetamines or cannabis, the importance of abstinence will be addressed in the course of treatment. In the case of a major depressive disorder that was induced by an organic factors such as hypothyroidism, the underlying condition will be treated, ie the prescription of thyroxine in conjunction with the evidence based treatment of a major depressive disorder.

In the case of mefloquine induced mental state, the drug would be ceased and the underlying condition would be treated as set out in the evidence-based literature whether this be delirium, a major depressive disorder or an anxiety disorder. This approach would also be applied to PTSD. If an individual has developed the typical phenomenology of PTSD while on mefloquine, for example in combat environment, the available literature would suggest that the disorder requires management using the current known treatments, including medication and exposure-based psychotherapies. Use of these approaches does not negate the fact that mefloquine may or may not have contributed to the onset of the condition.

An issue that has not been addressed in the literature is that one of the challenges with mefloquine toxicity is its very long half-life (2). Hence, it may take months for the drug to be fully excreted from the body even if this was ceased immediately. The necessary step of ceasing the drug does not mean that there will not be continuing and lingering pharmacological effects for a period until complete elimination is achieved. If there was proven long-term neurotoxity the same principles of symptomatic treatment would apply to managing the resultant abnormal mental state.

Conclusion

This non-systematic review of the scientific literature about the short and long term consequences of mefloquine highlights a series of issues that limit the capacity to make conclusive statements. It is important to differentiate published literature about adverse consequences in individual cases which highlight potentially serious adverse effects from case control studies that have looked at large cohorts of both military and non-military populations who have been prescribed mefloquine where the health

outcomes are compared with other types of malarial prophylaxis, as well as control populations.

In general, there does appear to be an over representation of neuropsychiatric consequences ranging at the lower end of severity of sleep disturbance, depression and anxiety to more severe reactions such as psychosis (53).

However, in using practice registries and hospital admissions, there do not appear to be clinically significant adverse outcomes even in the neuropsychiatric domain reported with a higher incidence in mefloquine users. The limitation of these cohort studies is that they do not address the issue of there being particular subgroups of individuals where the emergence of adverse effects are directly as a consequence of the drug as against an intercurrent episode of the same symptoms for unrelated reasons. Hence, the lack of differences in studies does not resolve the fact that there may be a small cohort of individuals who do have substantial adverse consequences to the use of mefloquine.

The argument for the existence of such a subgroup is based on studies demonstrating CNS neurotransmitter effects of mefloquine. The potential for significant differences in expression of these neurotransmitter effects can also be influenced by genetic differences in drug metabolism.

A substantial deficiency in the literature is that it does not address the important potential of traumatic stress exposure to modify the effects of mefloquine. Whilst body and weight (BMI) in female gender have been identified, it is equally plausible that exposure to traumatic stress at the time of ingestion may influence the resultant neuropsychiatric consequences of usage. This includes the onset of psychiatric disorders, for example on military deployment where mefloquine ingestion may modify the risk and course of the onset of a disorder.

The literature does not provide any specific directions for the treatment of the psychiatric side effects of mefloquine prophylaxis or treatment other than cessation of the drug. Rather the underlying symptomatic disorder should be treated as is the general practice in psychiatry.

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DEFGRAM 42/2016 - MEFLOQUINE USE IN THE ADF

Department of Defence

DEFGRAM 42/2016

Issue Date: **08 February 2016**
Expiry Date: **13 May 2016**

MEFLOQUINE USE IN THE ADF

1. Recent media reporting regarding the use of mefloquine in the ADF may have caused concern for some members of the ADF. To address these concerns and correct the misinformation included in some reports Defence released a statement on 30 November 2015 to clarify the situation for past and present ADF members. http://news.defence.gov.au/2015/11/30/statement-on-the-use-of-mefloquine-in-the-adf/

2. To further inform serving and ex-serving members, Joint Health Command has developed a new resource about malaria and the ADF which is now available as part of the online Health Portal. This resource has information about malaria, medications used to prevent malaria, the Army Malaria Institute (AMI) and the studies conducted in Timor-Leste in 2000-2002, during which some participants took mefloquine. It also provides contacts and links to other departments and agencies, such as the Department of Veterans' Affairs. This resource can be accessed at http://www.defence.gov.au/Health/HealthPortal/Malaria/default.asp.

3. Individuals who are concerned about potential effects of mefloquine on their health are advised to make an appointment to discuss this with their usual medical practitioner. Garrison Health medical practitioners are equipped to address any concerns.

4. General inquiries about the AMI studies and requests for copies of individual trial records can be directed to ADF.malaria@defence.gov.au.

Tracy Smart
Air Vice-Marshal
Commander Joint Health Command
Joint Health Command

Contact Officer: **Dr Victoria Ross**
Acting Director Military Medicine

MEFLOQUINE MANAGEMENT GUIDELINES 09 JUNE 2016

Clinical Guidelines for providing appropriate care to ADF members concerned about having been prescribed Mefloquine

Version 2, 09 Jun 2016

PURPOSE

These clinical guidelines are primarily designed to assist clinicians manage patients who are concerned about having been prescribed mefloquine and specifically those that are suffering from neuropsychiatric symptoms which they attribute to historical use of mefloquine (often from the 2000-2002 period). They may also be useful in managing any patients with neuropsychiatric symptoms attributed to other antimalarials and other medications more generally, or symptoms of unknown cause.

BACKGROUND

There has been much publicity in the civilian media and concerns raised by some serving and ex-serving ADF members relating to the use of mefloquine for chemoprophylaxis by the Australian Defence Force. The United Kingdom is experiencing similar concerns and the United States has experienced similar concerns in the past.

On 30 November 2015, Defence released a statement on the use of mefloquine in the ADF that advised if "any ADF member, past or present is concerned that they might be suffering side-effects from the use of mefloquine Defence encourages them to raise their concerns with a medical practitioner so they may receive a proper diagnosis and treatment."

http://news.defence.gov.au/2015/11/30/statement-on-the-use-of-mefloquine-in-the-adf/

It is anticipated that Defence medical officers will encounter ADF members who are concerned that they may be suffering side-effects from historical use of mefloquine.

Mefloquine side-effects

Mefloquine has been registered for malaria chemoprophylaxis in Australia since 1993, and has been prescribed to over 35 million people worldwide. The side-effect profile is well known with most of the recent changes in product information relating to the duration that neurological side-effects may last. It is now acknowledged that in some cases these side-effects may be permanent.

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=PI&q=Lariam&r=/

The neuropsychiatric side-effects of mefloquine have received the most attention and are best considered as psychiatric – disturbed sleep, anxiety, paranoia, depression, hallucinations and psychosis; and neurological – vertigo, loss of balance, tinnitus, sensorineural hearing loss and neuropathy.

Side-effects from mefloquine usually occur soon after commencing the medication. Side-effects usually resolve within days to weeks after ceasing the medication. Due to mefloquine's long half life it is possible for symptom onset to be weeks after cessation. In rare cases, side-effects may persist for months or longer and more rarely some neurological symptoms become permanent.

Mefloquine and Post-traumatic Stress Disorder (PTSD) or minor traumatic brain injury (mTBI)

There is no evidence that mefloquine causes or triggers PTSD or mTBI. In the acute situation, there is potential for acute mefloquine-related psychiatric symptoms to confound a PTSD or mTBI diagnosis. There is no evidence to suggest that a PTSD diagnosis made months or years after ceasing mefloquine can be attributed to past mefloquine use.

Mefloquine toxicity – CNS toxicity syndrome – mefloquine toxidrome

Dr Remington Nevin, an ex-US Army medical officer has published a number of opinion articles proposing the adoption of diagnoses to describe long term or permanent neurological symptoms related to mefloquine use. None of the terms have been officially accepted and there are no accepted diagnostic criteria, diagnostic tests nor any treatment. Clinicians should understand that members may present seeking one of these diagnoses.

It is important to acknowledge that mefloquine has been associated with long term or permanent neurological side-effects which can be diagnosed.

Tafenoquine

Tafenoquine is a relatively new anti-malarial medication which is chemically closely related to primaquine. As a quinine derivative, it falls into the same broad class of antimalarials as mefloquine however it acts quite differently in the body and its known side-effect profile more closely reflects those of primaquine. It is not yet

registered for use in Australia and is still undergoing Phase 3 clinical trials. It was trialled by the ADF in the late 1990s and early 2000s as an option for prophylaxis, eradication and treatment of malaria.

There is no evidence that tafenoquine causes serious neuropsychiatric effects, either acute or chronic. Long term use is associated with an eye condition, vortex keratopathy (small deposits in the cornea), also seen with long term use of chloroquine. The condition does not affect vision and has no symptoms. It is benign and resolves completely after tafenoquine is stopped.

CLINICAL APPROACH

Persons presenting with neurological or psychiatric symptoms with a history of previous mefloquine use should be thoroughly assessed. It is important to accept that the member has concerns that their symptoms may be related to historical mefloquine use and the concerns should not be summarily dismissed.

Members presenting who are concerned because they have taken mefloquine in the past but have no symptoms (the worried well), need to have their concerns noted and addressed.

What can the general practitioner do?

1. Document any symptoms as part of a comprehensive history. Note the date of symptom onset in relation to mefloquine use and the nature of symptoms after ceasing mefloquine.
2. Examine the patient and document any abnormal neurological or other signs. All patients should receive an audiogram and a Sharpened Romberg test.
3. Assess the patient with readily available psychological screens, if relevant. For example, K-10, DASS-21, DAR or CAPS-5.
4. Arrange further diagnostic investigations or specialist referral as appropriate.
5. Members presenting with neurological symptoms will often require referral to one or more of the following to confirm a diagnosis, quantify symptoms and recommend treatment:
    a. Neurologist; and /or
    b. Neuropsychologist (including a request for a battery of tests to baseline neuropsychological function)
6. Members presenting with psychiatric symptoms should be referred to a psychiatrist, where available, preferably a psychiatrist with experience in military populations.

7. Assess and document risk.

8. **Explore useful treatments.** Treatment options will depend on the symptoms being experienced and whether a condition can be diagnosed.

   a. Where a clinical diagnosis (including a provisional diagnosis) is made, evidence based treatment for the condition should be provided.

   b. No specific treatment has been proposed for mefloquine related neuropsychiatric problems apart from ceasing the medication.

   c. Generally, pharmacotherapy or psychotherapy should be withheld until a disorder is diagnosed, however treatment of specific symptoms causing significant distress should be considered even without a provisional or definitive diagnosis (e.g. Prochlorperazine for dizziness).

   d. Document the claims in the medical record. Include details of deployment location, operation and dates; the antimalarial taken or believed to have been taken and if relating to the 1998-2003 period whether they participated in an Army Malaria Institute trial.

9. Advise the member that there is additional information on anti-malarial use in the ADF available on the Joint Health Command external web site: http://www.defence.gov.au/Health/HealthPortal/Malaria/default.asp

In addition, clinicians may find this article from the September 2015 Australian Family Physician useful: *Managing medically unexplained illness in general practice* http://www.racgp.org.au/afp/2015/september/managing-medically-unexplained-illness-in-general-practice/

Risk Assessment and Mental Health Management

Defence members who present with mental health symptoms, psychological distress or increased risk should be assessed and managed in accordance with HD 294 *Risk Assessment and Management of Defence members at Risk of Suicide, Self-Harm or Harm-to-Others.* Defence members who require mental health assessment and treatment are to be managed in accordance with HD 289 *Coordinated Care and Management of Defence members receiving Mental Health Services in Garrison.* The immediate assessment and management of risk, when identified, is the priority.

MEC and MECRB management

MEC considerations will depend on the health status, functional capacity and health support needs of the individual. If a member is not deployable, and the period of non-deployability extends beyond 12 months from onset of illness, MECRB consideration is required.

If the member has raised the possibility of mefloquine being associated with their symptoms, this needs to be documented in the MEC Review.

In summary:

1. Be respectful and acknowledge the concerns
2. Treat when appropriate
3. Offer referral to appropriate specialists for testing/documentation of function and exclusion of other causes
4. Document the member's health record
5. Assess and manage risk

ANNEX N

LETTER FROM RADM ROBYN WALKER TO REPATRIATION MEDICAL AUTHORITY APRIL 2015

JOINT HEALTH COMMAND

CP2-7-121, PO Box 7911, Campbell Park Offices, Campbell ACT 2610

CJHLTH/OUT/2015/R1930364

Mr Paul Murdoch
Repatriation Medical Authority
GPO Box 1014
BRISBANE QLD 4001

Dear Mr Murdoch,

Major Stuart McCarthy made representations through his local member in relation to concerns about the use of mefloquine by Defence. As part of the ministerial response, I undertook to write to the Repatriation Medical Authority (RMA) and request that you review the scientific evidence of long term or permanent side effects caused by mefloquine with a view to updating the Statements of Principle (SOP) as appropriate.

I acknowledge that a number of SOPs already list mefloquine as a causal or aggravating factor. A review of the Therapeutic Goods Administration (TGA) approved mefloquine product information indicates post marketing data has identified mefloquine has been associated with a number of adverse events that may be covered by other RMA SOPs.

Major McCarthy's paper highlights mefloquine's potential association with minor traumatic brain injury (concussion) and posttraumatic stress disorder (PTSD). Whilst I can not identify any scientific evidence to support a causal relationship it may be appropriate to examine these SOPs as well.

The enclosed Request for Investigation/Review details the RMA SOPs that may warrant review and the supporting documentation.

Yours sincerely

R.M. WALKER, AM
Rear Admiral, RAN
Commander Joint Health

April 2015

Australian Government

Repatriation Medical Authority

Request for an Investigation/Review

R2930374

It is recommended that you read the Repatriation Medical Authority's Information sheet for Applicants requesting an Investigation/Review.

This form is to be completed by a person or organisation requesting the Repatriation Medical Authority (the Authority) to:

[Please indicate - X]

■ carry out an investigation in respect of a particular kind of injury, disease or death with a view to make a Statement of Principles; or

☐ review a decision not to make a Statement of Principles; or

☐ review some or all of the contents of a current Statement of Principles.

Name of person making request	Rear Admiral Robyn Walker AM, Surgeon General Australian Defence Force
Name of organisation making request	Australian Defence Force
Address for correspondence	CP2-7-121, PO Box 7911, Campbell Park Offices, Campbell ACT 2610
Telephone Contact	

I make this request as:

[Please indicate - X]

☐ a person eligible to make a claim for pension under Part II or Part IV of the *Veterans' Entitlements Act 1986* (the VEA);

☐ a person eligible to make a claim for compensation under section 319 of the *Military Rehabilitation and Compensation Act 2004* (the MRCA);

■ on behalf of an organisation representing veterans, Australian mariners, members of the forces, members of Peacekeeping Forces, members within the meaning of the MRCA, or their dependants;

☐ the Repatriation Commission or the Military Rehabilitation and Compensation Commission.

I request that the Authority:

1. carry out an investigation into a particular kind of injury, disease or death with a view to make a Statement of Principles concerning **mefloquine as a factor for the development of neurological or psychiatric conditions.**

or

2. review some or all of the contents of a Statement of Principles concerning

.....

.....

or

3. review the decision of the Authority **NOT** to make a Statement of Principles concerning

.....

.....

Date of Authority decision. ...../...../.....

Instrument No/s. .....

[**NB**. If you require only 'some' of the contents of a Statement of Principles to be reviewed you should identify this content in the space provided]

In the space provided below, please supply any information which you consider is related to your request. Additional pages may be attached if the space below is insufficient. Should you be requesting the Authority to review only 'some' of the contents of a Statement of Principles, please state what it is you request be reviewed.

Please also see the covering letter.

This application is only seeking to have the contents of relevant Statements of Principles (SOP) reviewed in terms of the use of mefloquine as a causal or aggravating factor.

Mefloquine has received considerable media attention in recent years, particularly in relation to its neuropsychiatic side-effects. It is acknowledged that mefloquine is recognised as a factor for the following SOPs Myasthenia gravis (15/2007 & 16/2007), Trigeminal neuropathy (29/2009 & 30/2009), Heart block (3/2006 & 4/2006), Depressive disorder (27/2008 & 28/2008), and Bipolar disorder (27/2009 & 28/2009).

A review of the mefloquine product information listed with the Therapeutic Drug Administration (TGA) dated 12 Nov 2014 (enclosure 1) indicates that post maketing data has identified that mefloquine has been associated with a number of adverse events that may be covered by other RMA SOPs; Anxiety disorder (102/2014 & 103/2014), Panic disorder (68/2009 & 69/2009), Epileptic seizure (77/2013 & 78/2013), Peripheral neuropathy (64/2014 & 75/2014), Meniere's disease (59/2006 & 57/2006), Tinnitus (33/2012 & 34/2012), Sensorineural hearing loss (5/2011 & 6/2011), Acquired cataract (39/2008 & 40/2008) and Toxic maculopathy (39/2009 & 40/2009).

A paper drafted by Major Stuart McCarthy (enclosure 2) draws a number of other associations that do not appear to supported by the product information however consideration of mefloquine as a factor for SOP Concussion (64/2012 & 65/2012) and Posttraumatic stress disorder (82/2014 & 83/2014) may be appropriate.

A brief literature review utilising Pubmed (enclosure 3) contains relevent scientific publications.

Enclosures:

1. TGA approved product information for mefloquine updated 12 Nov 2014
2. Mefloquine neurotoxicity Commonwealth duty of care and veterans mental health: A case for proactive outreach. Major Stuart McCarthy Jan 15
3. Pubmed abstracts for mefloquine associated side effects extracted 28 Apr 15

Disclosure of Information

Under section 196K of the VEA, certain decisions made by the Authority are reviewable by the Specialist Medical Review Council (SMRC). If a valid application for review by the SMRC is made, the VEA requires the Authority to disclose to the SMRC all information relevant to its determination or decision. This includes applications for investigation or review, and submissions received relevant to the matter being review by the SMRC.

Signature of applicant	.....
Organisational position (if relevant)	Surgeon General Australian Defence Force
Date	May 2015

This form is to be sent to: **Repatriation Medical Authority**
8th Floor, 259 Queen Street, Brisbane Qld 4001

[GPO Box 1014, Brisbane Qld 4001]

ANNEX O

LETTER FROM AVM SMART TO RMA APRIL 2016

VICE CHIEF OF THE DEFENCE FORCE

Joint Health Command

☆ ☆

CJLTH/OUT/2016/R25523246

Mr Paul Murdoch
Repatriation Medical Authority
GPO Box 1014
BRISBANE QLD 4001

Dear Mr Murdoch

You may be aware of recent media attention relating to anti-malarial drug trials conducted by the Army Malaria Institute (AMI) involving ADF members deployed to Timor Leste in 2000-2002. My predecessor, Rear Admiral Walker wrote to you on 30 April 2015 requesting a review of RMA Statements of Principle relating mefloquine as a causal factor and I have been appreciative of the reviews conducted to date.

Whilst the focus of attention had been on the ADF's use of mefloquine, more recently concerns have been raised about the use of an experimental drug currently known as tafenoquine although previously called etaquine or WR238605. Chemically, tafenoquine is an 8-aminoquinoline and an analogue of another anti-malarial drug – primaquine. Tafenoquine is still going through the initial drug registration process and therefore there is limited publically available information on the drug's side-effect and no post-marketing information.

The enclosed Request for Investigation/Review details the RMA SOPs that may warrant review and supporting documentation.

Yours sincerely

Tracy Smart AM
Air Vice-Marshal
Commander Joint Health
Surgeon General Australian Defence Force

PO Box 7911
Department of Defence
Canberra BC ACT 2610

12 April 2016

Enclosure:
1. Request for Investigation/Review

Australian Government
Repatriation Medical Authority

Request for an Investigation/Review

It is recommended that you read the Repatriation Medical Authority's Information sheet for Applicants requesting an Investigation/Review.

This form is to be completed by a person or organisation requesting the Repatriation Medical Authority (the Authority) to:

[Please indicate - X]

■ carry out an investigation in respect of a particular kind of injury, disease or death with a view to make a Statement of Principles; or

☐ review a decision not to make a Statement of Principles; or

☐ review some or all of the contents of a current Statement of Principles.

Name of person making request	Air Vice Marshal Tracy Smart, Surgeon General Australian Defence Force
Name of organisation making request	Australian Defence Force
Address for correspondence	CP2-7-121, PO Box 7911, Campbell Park Offices, Campbell ACT 2610
Telephone Contact	

I make this request as:

[Please indicate - X]

☐ a person eligible to make a claim for pension under Part II or Part IV of the *Veterans' Entitlements Act 1986* (the VEA)*;*

☐ a person eligible to make a claim for compensation under section 319 of the *Military Rehabilitation and Compensation Act 2004* (the MRCA)*;*

■ on behalf of an organisation representing veterans, Australian mariners, members of the forces, members of Peacekeeping Forces, members within the meaning of the MRCA, or their dependants;

☐ the Repatriation Commission or the Military Rehabilitation and Compensation Commission.

I request that the Authority:

1. carry out an investigation into a particular kind of injury, disease or death with a view to make a Statement of Principles concerning **tafenoquine as a factor for the development of neurological or psychiatric conditions.**

or

2. review some or all of the contents of a Statement of Principles concerning

…..……

……..……

or

3. review the decision of the Authority **NOT** to make a Statement of Principles concerning

……

……..…..……

Date of Authority decision. ……/……/……

Instrument No/s. …….

[**NB**. If you require only 'some' of the contents of a Statement of Principles to be reviewed you should identify this content in the space provided]

In the space provided below, please supply any information which you consider is related to your request. Additional pages may be attached if the space below is insufficient. Should you be requesting the Authority to review only 'some' of the contents of a Statement of Principles, please state what it is you request be reviewed.

Please also see the covering letter.

This application is only seeking to have the contents of relevant Statements of Principles reviewed in terms of the use of tafenoquine as a causal or aggravating factor.

Tafenoquine is an experimental anti-malarial drug from the 8-aminoquinolines group and an analogue of another anti-malarial drug, primaquine that has been extensively used by Defence.

As tafenoquine has not been registered by any drug regulatory agency there is no post marketing information. The most significant side-effects identified during clinical trials appear to vortex be keratopathy and methaemoglobinaemia. The potential for haemolytic anaemia in G6PD enzyme deficient individuals is also identified.

It would appear that tafenoquine, as an 'anti-malarial' would be accepted as a causal factor in epileptic seizure and as a drug that causes oxidation of haemoglobin as causal factor for methaemoglobinaemia. It is not clear whether it would be accepted for tinnitus and sensorineral hearing loss as a "quinine derivative".

It may meet the reasonable hypothesis standard that tafenoquine would share similar side-effects as primaquine and chloroquine given their drug class relationship and the observed side-effects of tafenoquine. It is therefore requested that consideration be given to adding tafenoquine to SoP's that currently include either primaquine or chloroquine as a causative or aggravating factor.

Enclosures:

1. TGA approved product information for Primacin (primaquine)
2. TGA approved product information for Plaquenil (chloroquine)
3. Summary of published literature on tafenoquine

Disclosure of Information

Under section 196K of the VEA, certain decisions made by the Authority are reviewable by the Specialist Medical Review Council (SMRC). If a valid application for review by the SMRC is made, the VEA requires the Authority to disclose to the SMRC all information relevant to its determination or decision. This includes applications for investigation or review, and submissions received relevant to the matter being review by the SMRC.

Signature of applicant	.....……....
Organisational position (if relevant)	Surgeon General Australian Defence Force
Date	April 2015

This form is to be sent to: **Repatriation Medical Authority**
8th Floor, 259 Queen Street, Brisbane Qld 4001

[GPO Box 1014, Brisbane Qld 4001]

CORRESPONDENCE FROM RMA 24 JUN 16

Australian Government
Repatriation Medical Authority

ABN 23 964 290 824
GPO Box 1014
Brisbane Qld 4001
Phone (07) 3815 9404
Fax (07) 3815 9412
www.rma.gov.au

24 June 2016

Air Vice Marshal Tracey Smart AM
Commander Joint Health
Surgeon General Australian Defence Force
PO Box 7911
Department of Defence
CANBERRA BC ACT 2610

Dear Air Vice Marshal Smart

RE: YOUE REQUEST FOR REVIEW OF THE CONTENTS OF VARIOUS STATEMENTS OF PRINCIPLES WITH REGARD TO TAFENOQUINE

I refer to your request to the Repatriation Medical Authority (the Authority) dated 12 April 2016 made under section 196E of the *Veterans' Entitlements Act 1986* (the Act) seeking the inclusion of tafenoquine in these Statements of Principles (SOPs) which currently include either primaquine or chloroquine as causal or aggravating factors.

Decision not to carry out a review under 196CA of the Act

Your request was considered in relation to the following Statements of Principles:

- aplastic anaemia, Instrument Nos. 50 & 51 of 2012, as amended
- bipolar disorder, Instrument Nos. 27 & 28 of 2009
- cardiomyopathy, Instrument Nos. 85 & 86 of 2015
- heart block, Instrument Nos. 1 & 2 of 2014
- myasthenia gravis, Instrument Nos. 75 & 76 of 2015
- Parkinson's disease & secondary parkinsonism, Instrument Nos. 55 & 56 of 2016
- peripheral neuropathy, Instrument Nos. 74 & 75 of 2014
- porphyria cutanea tarda, Instrument Nos. 43 & 44 of 2012
- toxic maculopathy, Instrument Nos. 39 & 40 of 2009

The request was considered by the Authority at its meeting of 7 June 2016.

In accordance with section 196CA of the Act, the Authority has decided not to carry out investigations to review the contents of the SOPs listed above. The reason for this decision is that the Authority considers that the request does not identify sufficient relevant information to support the grounds on which the review is sought. A formal statement of reasons is attached.

Current Statements of Principles with factors relating to the use of tafenoquine

As you have suggested in your correspondence, there are a number of SOPs containing variously worded factors which cover the use of tafenoquine. The Authority decided that no further action was required in relation to these SOPs:

- tinnitus, Instrument Nos. 33 & 34 of 2012
- sensorineural hearing loss, Instrument Nos. 5 & 6 of 2011
- epileptic seizure, Instrument Nos. 77 & 78 of 2013
- psoriasis, Instrument Nos. 31 & 32 of 2012
- methaemoglobinaema, Instrument Nos. 47 & 48 of 2010
- asthma, Instrument Nos. 60 & 61 of 2012

Finalised review of suicide and attempted suicide

As you may be aware, the Authority had previously notified a review of the SOPs concerning suicide and attempted suicide in the Government Notices Gazette and that review has now been finalised. After reviewing the available evidence, the Authority determined new Statements of Principles, Instrument Nos. 65 & 66 of 2016, concerning suicide and attempted suicide. These Instruments were signed by the Chairperson on 24 June 2016 with a date of commencement of 25 July 2016.

These new instruments result from an examination of the sound medical-scientific evidence now available to the Authority. The information you provided with your submission concerning tafenoquine was considered as part of the investigation, however the available sound medical-scientific evidence did not support the inclusion of a factor relating to tafenoquine either directly or by analogy to primaquine. The evidence did support the inclusion of a factor relating to mefloquine and chloroquine at the reasonable hypothesis standard of proof, and the inclusion of a factor concerning mefloquine at the balance of probabilities standard of proof.

Under section 196Y of the Act you have the right to request the Specialist Medical Review Council (SMRC) to review the contents of a Statement of Principles if you are not satisfied with the outcome of the investigation. Should you wish to exercise this right, which must be exercised within three months of the making of the Statement of Principles, you should contact the SMRC Secretariat on (07) 3223 8840 for further information and advice on the review process.

Alternatively you may wish to contact the SMRC via their website at www.smrc.gov.au or write to them at the following address:

The Registrar
Specialist Medical Review Council
PO Box 895
WODEN ACT 2606

Other reviews of psychiatric conditions where tafenoquine will be considered

Reviews of the contents of the Statements of Principles concerning anxiety disorder (focussed review), panic disorder (focussed review), and schizophrenia have previously been notified in the Government Notices Gazette and have yet to be finalised. The information you have provided with your submission will be considered during the investigation process for these three conditions. These reviews are expected to be completed by late 2016.

For your information, I have prepared the attached table as an overview of the SOPs that contain factors relating the quinine derivative class of drugs to which tafenoquine belongs. I hope it is of assistance to you.

You are entitled to have access to the information considered by the Authority during investigationa, including a list of references. Please let me know if you would like this further information for any of the investigations completed to date.

If you have any questions please do not hesitate to contact me

Yours sincerely

Sandra Pollitt
Deputy Registrar
Repatriation Medical Authority

Encl.

TABLE 1. STATEMENTS OF PRINCIPLES WITH FACTORS CONCERNING QUININE DERIVATIVE ANTIMALARIAL DRUGS (AS OF 24 JUNE 2016)

Condition	Instrument Nos.	Terminology used in factor or associated definition
aplastic anaemia	50 & 51 of 2012, as amended	chloroquine
asthma	60 & 61 of 2012	an immunologic or non-immunologic stimulus
bipolar disorder	27 & 28 of 2009	chloroquine
cardiomyopathy	85 & 86 of 2015	chloroquine, hydroxychloroquine
epileptic seizure	77 & 78 of 2013	antimalarials (including chloroquine, primaquine)
heart block	1 & 2 of 2014	chloroquine, including chloroquine sulphate, chloroquine phosphate and hydroxychloroquine
methaemoglobinaema	47 & 48 of 2010	drugs which cause oxidation of haemoglobin
myasthenia gravis	75 & 76 of 2015	chloroquine
Parkinson's disease & secondary parkinsonism	55 & 56 of 2016	chloroquine
peripheral neuropathy	74 & 75 of 2014	chloroquine, hydroxychloroquine, mefloquine
porphyria cutanea tarda	43 & 44 of 2012	chloroquine, hydroxychloroquine,
psoriasis	31 & 32 of 2012	synthetic antimalarial drugs (e.g., quinacrine, hydroxychloroquine, chloroquine, primaquine, mefloquine)
sensorineural hearing loss	5 & 6 of 2011	quinine and quinine derivatives
suicide and attempted suicide [1]	65 & 66 of 2016	chloroquine, mefloquine
tinnitus	33 & 34 of 2012	quinine and quinine derivatives
toxic maculopathy	39 & 40 of 2009	chloroquine, hydroxychloroquine or mepacrine

[1] SOPs signed on 24 June 2016, with expected date of commencement of 25 July 2016

Australian Government
Repatriation Medical Authority

Statement of Reasons

APLASTIC ANAEMIA, BIPOLAR DISORDER, CARDIOMYOPATHY, HEART BLOCK, MYASTHENIA GRAVIS, PARKINSON'S DISEASE & SECONDARY PARKINSONISM, PERIPHERAL NEUROPATHY, PORPHYRIA CUTANEA TARDA, TOXIC MACULOPATHY

FACTS

The Repatriation Medical Authority (the Authority) received a letter from Air Vice Marshal Smart, Surgeon General Australian Defence Force, dated 12 April 2016, requesting the Authority to investigate an association between tafenoquine and any conditions that have Statements of Principles (SOPs) that currently include either primaquine or chloroquine as causal or aggravating factors, with a view to inclusion based on a drug class effect.

The request was made under s196E of the VEA on behalf of an organisation representing members of the forces, the Australian Defence Force.

The request was considered in relation to the following SOPs determined under s196B(2) & (3) of the *Veterans' Entitlements Act 1986* (the VEA):

- aplastic anaemia, Instrument Nos. 50 & 51 of 2012, as amended
- bipolar disorder, Instrument Nos. 27 & 28 of 2009
- cardiomyopathy, Instrument Nos. 85 & 86 of 2015
- heart block, Instrument Nos. 1 & 2 of 2014
- myasthenia gravis, Instrument Nos. 75 & 76 of 2015
- Parkinson's disease & secondary parkinsonism, Instrument Nos. 55 & 56 of 2016
- peripheral neuropathy, Instrument Nos. 74 & 75 of 2014
- porphyria cutanea tarda, Instrument Nos. 43 & 44 of 2012
- toxic maculopathy, Instrument Nos. 39 & 40 of 2009

Tafenoquine is already covered by factors in the SOPs for six conditions, with the factors expressed as 'quinine derivatives', 'antimalarials', 'synthetic antimalarial drugs', 'drugs which cause oxidation of haemoglobin' and 'an immunologic or non-immunologic stimulus'. These SOPs, determined under s196B(2) & (3) of the VEA, are as follows:

- tinnitus, Instrument Nos. 33 & 34 of 2012
- sensorineural hearing loss, Instrument Nos. 5 & 6 of 2011
- epileptic seizure, Instrument Nos. 77 & 78 of 2013
- psoriasis, Instrument Nos. 31 & 32 of 2012

- methaemoglobinaema, Instrument Nos. 47 & 48 of 2010
- asthma, Instrument Nos. 60 & 61 of 2012

Tafenoquine is therefore already included in the SOPs with regard to factors relating to a drug class effect, as opposed to a specific drug effect.

BACKGROUND

At the time that the Statements of Principles listed above were determined, the Authority had before it information including:

- a briefing paper concerning aplastic anaemia prepared in August 2012 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning bipolar disorder prepared in April 2009 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning cardiomyopathy prepared in June 2015 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning heart block prepared in December 2013 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning myasthenia gravis prepared in June 2015 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning peripheral neuropathy prepared in August 2014 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning porphyria cutanea tarda prepared in June 2012 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning Parkinson's disease & secondary parkinsonism prepared in April 2016 by a Repatriation Medical Authority medical researcher; or
- a briefing paper concerning toxic maculopathy prepared in June 2009 by a Repatriation Medical Authority medical researcher; and
- an extensive number of articles published in the peer-reviewed literature concerning these conditions.

NEW INFORMATION CONSIDERED BY THE AUTHORITY

Air Vice Marshal Smart's request was received by the Authority on 18 April 2016.

In support of the request, the applicant provided the following:

- TGA approved product information for Primacin (primaquine)
- TGA approved product information for Plaquenil (chloroquine)
- Published peer-reviewed journal articles concerning tafenoquine:
  - Rajapakse S, Rodrigo C, Fernando SD. (2015) Tafenoquine for preventing relapse in people with Plasmodium vivax malaria. Cochrane Database Syst Rev. Apr Vol 29; 4: CD010458
  - Cannon J, Fitzgerald B, Seed M, et al (2015). Occupational asthma from tafenoquine in the pharmaceutical industry: implications for QSAR. Occup Med, Vol 65(3): 256-8.
  - Green JA, Patel AK, Patel BR, et al (2014).Tafenoquine at therapeutic concentrations does not prolong fridericia-corrected QT interval in healthy subjects. J Clin Pharmacol, Vol 54(9): 995-1005.

- Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, et al (2014). Tafenoquine plus chloroquine for the treatment and relapse prevention of plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. Lancet, Vol 22; 383(9922): 049-58.
- Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team. (2010) Randomized, double-blind study of the safety, tolerability, and efficacy of tofenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. 2010 Feb; Vol 54(2): 792-8.
- Leary KJ, Riel MA, Roy MJ, et al (2009). A randomized, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. Am J Trop Med Hyg, Vol 81(2): 356-362.
- Elmes NJ, Nasveld PE, Kitchener SJ, et al (2008). The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of plasmodium vivax malaria in the southwest pacific. Trans R Soc Trop Med, Vol 102(11): 1095- 101.
- Kitchener S, Nasveld P, Edstein MD (2007). Short report: tafenoquine for the treatment of recurrent plasmodium vivax malaria. Am J Trop Med Hyg, Vol 76(3): 494-6.
- Walsh DS, Eamsila C, Sasiprapha T, et al (2004). Efficacy of monthly tafenoquine for prophylaxis of plasmodium vivax and multidrug-resistant p. falciparum malaria. J Infect Dis, Vol 190(8): 1456-63.
- Nasveld P, Kitchener S, Edstein M, et al (2002). Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. Trans R Soc Trop Med Hyg, Vol 96(6): 683-4.
- Hale BR, Owusu-Agyei S, Fryauff DJ, et al (2003). A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against plasmodium falciparum. Clin Infect Dis, Vol 36(5): 541-9.
- Lell B, Faucher J-F, Missinou MA, et al (2000). Malaria chemoprophylaxis with tafenoquine: a randomised study. Lancet, Vol 355(9220): 2041-5.
- Walsh DS, Looareesuwan S, Wilairantana P, et al (1999). Randomized dose-ranging study of the safety and efficacy or WR238605 (tafenoquine) in the prevention of relapse of plasmodium vivax malaria in Thailand. J Infect Dis, Vol 180(4): 1282-7.
- Brueckner RP, Lasseter KC, Lin ET and Schuster BG (1998). First-time-in -humans safety and pharmacokinetics of WR238605, a new antimalarial. Am. J. Trop. Med. Hyg. Vol 58 (5): 645-649.

REASONS

The Authority was cognisant of the provisions of the VEA, and had particular regard to subsection 5AB(2) sound medical-scientific evidence, s.5D injury/disease, and Part XI.

Sound medical-scientific evidence (SMSE) is defined as follows:

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

(a) the information:

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

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

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

The Authority noted s.196B(7), s.196CA and s.196E, which relevantly provide:

196B(7)

If the Authority:

(a) is asked under section 196E to review:

(i) some or all of the contents of a Statement of Principles;

the Authority must, subject to subsection 196C(4) and section 196CA in a case where paragraph (a) applies, carry out an investigation to find out if there is new information available about:

(d) how the injury may be suffered, the disease may be contracted or the death may occur; or

(e) the extent to which the disease, injury or death may be war-caused or defence-caused.

196CA

(1) The Authority may decide not to carry out an investigation in respect of a request for a review made under paragraph 196E(1)(e) or (f) if:

(a) the request does not state the grounds on which the review is sought; or

(b) the Authority considers that the request does not identify sufficient relevant information:

(i) to support the grounds on which the review is sought; or

(ii) to otherwise justify the review; or

(c) the request is vexatious or frivolous.

196E

(1) Any of the following:

(b) a person eligible to make a claim for a pension under Part II or IV;

(ba) a person eligible to make a claim for compensation under section 319 of the MRCA;

(c) an organisation representing veterans ....

may ask the Repatriation Medical Authority:

(f) to review the contents of a Statement of Principles in force under this Part.

Together with its own expert knowledge, the Authority took into consideration:

- the information provided by Air Vice Marshal Smart;
- the information held by the Authority and obtained during its previous considerations leading to the determination of each of the Statements of Principles listed in review; and
- a discussion paper prepared by a Medical Researcher.

Sound Medical-Scientific Evidence

The information supplied largely consisted of clinical trials which support the safety and efficacy of tafenoquine. Only one subject taking tafenoquine reported a severe adverse event (diarrhoea and abdominal pain in one of the Australian Defence Force trials). Other adverse events were mild and self-limiting, with gastrointestinal effects being the most common. There was also one case

report of a person developing asthma after prolonged occupational exposure to tafenoquine by inhalation. This situation is covered by the SOPs concerning asthma by a factor expressed as 'an immunologic or non-immunologic stimulus'.

There were no reports of peripheral neuropathy, myasthenia gravis or porphyria cutanea tarda occurring during the clinical trials (that is, at the time of taking the drug, as specified in the SOP factors). Likewise, there were no reports of aplastic anaemia, secondary parkinsonism or bipolar disorder occurring within the six month follow up periods of any of the clinical trials (that is within six months, three months or one month, as specified in the factors in those SOPs). Given that tafenoquine has only been available for clinical trials and that there have been no reports of these conditions, there would be no veterans who would be claiming tafenoquine as a cause of these conditions.

Clinical trials do not report on adverse effects beyond the duration of the trial, so longer term effects of tafenoquine are unknown. Tafenoquine has been trialled in the shorter term for prophylaxis (up to six months) or *Plasmodium vivax* eradication (up to eight weeks). Some of the evidence for chloroquine is based on long term consumption, as chloroquine and hydroxychloroquine are sometimes used for chronic management of autoimmune diseases. This is reflected in the wording of the factors (e.g., daily consumption of chloroquine for at least one year in the SOPs for cardiomyopathy, heart block and toxic maculopathy).

Conclusions

Air Vice Marshal Smart requests that tafenoquine be included as a factor in the SOPs that include either primaquine or chloroquine. The SOPs for 9 conditions which include factors concerning primaquine or chloroquine, and which do not cover tafenoquine by way of an alternatively expressed factor, are as follows:

- aplastic anaemia, Instrument Nos. 50 & 51 of 2012, as amended
- bipolar disorder, Instrument Nos. 27 & 28 of 2009
- cardiomyopathy, Instrument Nos. 85 & 86 of 2015
- heart block, Instrument Nos. 1 & 2 of 2014
- myasthenia gravis, Instrument Nos. 75 & 76 of 2015
- Parkinson's disease & secondary parkinsonism, Instrument Nos. 55 & 56 of 2016
- peripheral neuropathy, Instrument Nos. 74 & 75 of 2014
- porphyria cutanea tarda, Instrument Nos. 43 & 44 of 2012
- toxic maculopathy, Instrument Nos. 39 & 40 of 2009.

It is unknown whether tafenoquine would cause any of the conditions with specific primaquine or chloroquine factors, but the existing literature suggests that they do not occur in the short term (during treatment or up to six months after taking the drug). There is no SMSE indicating that tafenoquine would cause these conditions after longer periods of treatment. Factors for a drug class effect have already been included in relevant SOPs where the evidence has supported this.

In summary the Authority considered that the request does not identify sufficient, relevant information to support the grounds on which the reviews are sought or to otherwise justify the reviews.

DECISION

The Authority decided at its meeting on 7 June 2016 not to carry out investigations in respect of the request from Air Vice Marshal Smart to review the contents of the following Statements of Principles:

- aplastic anaemia, Instrument Nos. 50 & 51 of 2012, as amended
- bipolar disorder, Instrument Nos. 27 & 28 of 2009
- cardiomyopathy, Instrument Nos. 85 & 86 of 2015
- heart block, Instrument Nos. 1 & 2 of 2014
- myasthenia gravis, Instrument Nos. 75 & 76 of 2015
- Parkinson's disease & secondary parkinsonism, Instrument Nos. 55 & 56 of 2016
- peripheral neuropathy, Instrument Nos. 74 & 75 of 2014
- porphyria cutanea tarda, Instrument Nos. 43 & 44 of 2012
- toxic maculopathy, Instrument Nos. 39 & 40 of 2009

The Authority considered that the request does not identify sufficient relevant information to support the grounds on which the reviews are sought.

Pressor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

24 June 2016

LETTER TO COMCARE REGARDING MEFLOQUINE INQUIRY - 13 APRIL 2016

VICE CHIEF OF THE DEFENCE FORCE

Joint Health Command

☆ ☆

CJHLTH/OUT/2016/R24896475

Mr Justin Napier
General Manager Regulatory Operation Group
COMCARE
GPO Box 9905
CANBERRA ACT 2601

DEFENCE'S USE OF THE ANTI-MALARIA DRUG MEFLOQUINE

Dear Mr Napier

Thank you for your letter of 20 January regarding Defence's use of the anti-malaria drug mefloquine.

I regret the delay in replying, however I thought it appropriate to ensure that my response was made with knowledge of any recommendations relating to the ADF use of mefloquine from the Senate's Foreign Affairs, Defence and Trade Reference Committee 'Inquiry into the mental health of Australian Defence Force members and veterans' (Senate Inquiry) released on 17 March 2016.

As discussed during our meeting of 09 February 2016 Defence has undertaken a considerable amount of work relating to mefloquine use in the ADF since our previous response on 02 April 2015 and these initiatives are detailed below.

Defence is aware of the associations made in the literature between mefloquine and suicide that Dr Chan identified. Defence has conducted a cross reference between the Defence Suicide Register, which lists all serving members since 2000 who committed suicide or are suspected of committing suicide, with the database of those who were administered mefloquine since 2000. There were no matches between the two databases. It is my view that there is no requirement to further investigate this area at this stage.

Defence also recognised the concerns raised in the media relating to potential serious long term effects of mefloquine in ADF members. A review of the medical employment classification of ADF members prescribed mefloquine as part of the Army Malaria Institute trials in 2000-2002 and those prescribed other anti-malaria medications was conducted. It was found that there was no significant difference in the rates of being medically unfit for service or developing PTSD between these two groups.

To address the concerns of serving members, ex-serving members and their families Defence has conducted a public information program targeting serving ADF members but with significant outreach to ex-serving members and their families.

The program is based around comprehensive web pages, accessible from the internet at http://www.defence.gov.au/Health/HealthPortal/Malaria/default.asp through the ADF Health Portal. The "Malaria, mefloquine and the ADF" web pages provide information about malaria and the prevention of malaria in the ADF. They include possible short term and long term side effects of anti-malarial medications with a focus on mefloquine. The website also provides transparent information in relation to past anti-malarial drug trials and Defence's response to recent concerns about mefloquine use in the ADF.

Defence has also developed an email address that members and ex-serving members or their families can utilise to get further information. As at 07 April 2016, 157 requests for information had been received including 20 members seeking information unrelated to past anti-malarial drug trials.

The website and inquiry email address have been widely promoted to serving ADF members through a DEFGRAM, a 'spotlight' on the Defence Protected Network, articles in Service newspapers and communications to all Defence medical practitioners working in Garrison health facilities.

The public information program has advised any serving or ex-serving ADF members concerned about past anti-malarial medication to contact the doctor for a full assessment and appropriate treatment.

Defence has also developed clinical guidelines (enclosed) to assist Defence doctors in assessing serving members with concerns relating to past mefloquine use. The guidelines include the conduct of a neurological examination and psychological screens. Where clinically indicated the guidelines provide for further specialist neurologist examination and investigations. These guidelines have been shared with the Department of Veterans' Affairs (DVA).

Whilst the Defence website and inquiry email address is available to and being utilised by ex-serving members, Defence is also working with DVA and ex-Service organisations to enhance awareness of the resource amongst past ADF members.

Complementing these initiatives, Defence has commissioned an independent review by Professor Sandy McFarlane, of published literature on mefloquine. I have engaged with concerned community groups, presenting at a public forum in Townsville on 13 March 2016 and the Ex-Service Organisation Round Table on 12 April 2016.

The Senate Inquiry made two recommendations relating the use of mefloquine in the ADF, one of which suggested an outreach programme be established for all members who have previously been prescribed the drug, and the other that an Inspector General of the Australian Defence Force (IGADF) investigation on mefloquine be released publicly.

With respect to the first recommendation I believe that the initiatives undertaken by Defence to date that are detailed above satisfy the intent of an outreach program.

Regarding the second matter, an IGADF investigation is being undertaken into a complaint about the 2000-2002 Army Malaria Institute trials involving mefloquine. Release of IGADF Inquiry reports are subject to the Defence (Inquiry) Regulations 1985 and decisions on release of these reports are made on a case by case basis, with due regard to privacy and legal issues. The IGADF's Office has advised that the Inquiry is ongoing, and that requests for release of the report are premature.

I trust that this information satisfies your concerns regarding Defence's use of mefloquine.

Yours sincerely

Tracy Smart
Air Vice-Marshal
Commander Joint Health
Surgeon General, Australian Defence Force

Tel: (02) 6266 3919

13 April 2016

Enclosures:

1. Clinical Guidelines for providing appropriate care to ADF members concerned about having been prescribed Mefloquine dated 05 Feb 2016
2. Neuropsychiatric effects of Mefloquine

ANNEX R

SUMMARY OF THE EVOLUTION OF DEFENCE MALARIA POLICIES

Date	**03 Sep 1990**	**13 Apr 1992**	**20 Oct 1994**	**23 May 1996**	**15 Dec 2000**	**29 Nov 2006**	**29 Jan 2013**
ADF Policy	**Technical Policy Directive 215**	**Health Policy Directive 215**	**Health Policy Directive 215**	**Health Policy Directive 215**	**Health Policy Directive 215**	**Health Directive 215**	**Health Directive 215**
Changes to previous policy	First tri-service policy.	Short and long term stays defined as less or more than 8 weeks. Introduces permethrin treatment of uniforms and mosquito nets. Tables introduced listing malarious countries and drug resistance.	Introduces routine screening of new entrants for G6PD, and pre-deployment for those who have not previously had primaquine. Introduces loading dose of mefloquine (day 7, 4 and 1 before entering malarious area). Chloroquine removed from eradication course. Maloprim no longer used routinely for prophylaxis. flow charts introduced for working out malaria prophylaxis schedules.	The only change is re G6PD deficiency. This now stipulates that the UMR is to reflect the date and result of the test rather than the previous 'health records marked accordingly'	Duration of prophylaxis regimens. Doxy 100mg and Mefloquine now recommended for stays of 6 months or more. Loading dose regimen adjusted to three consecutive days. No longer refers to areas with drug sensitive or resistant malaria. Introduces Malarone as an option once TGA approved (occurred 01 Nov 2001) or if both Doxy and MQ contraindicated. Eradication course adjusted (15mg base twice a day for EM, Indonesia, PNG, SI, Vanuatu; 15mg base once daily for everywhere else). No longer distinguishes between drug sensitive and drug resistant malarious areas. More clarification about G6PD testing. More detailed information about side effects and drug interactions/precautions. Choice dependent on potential or known side effects and likelihood of compliance by the individual.	Introduces rapid diagnostic testing and more clinical info about malaria/diagnosis. More explanation of MQ loading dose and side effects, advice if these occur, precautions and contraindications. More information about all drug effects and contraindications. Pre-deployment briefings about the importance of prophylaxis, members to be informed of any potential side effects, should be advised to contact MO if develop any unusual symptoms while taking prophylaxis, record the briefing in UMR. Health reviews during deployment should be conducted by MO or NO at least every 3 months (more frequently if possible) for duration of course of prophylaxis and documented in UMR (both for promotion of compliance and checking tolerance of regimen).	Defence members are to be briefed that extended usage of antimalarial drugs is not officially endorsed by the drug manufacturers or the Therapeutics Goods Administration. However, there is clinical evidence and experience from other Western militaries, including the United States and United Kingdom Defence Forces, supporting the continuous use of antimalarials for up to two years while on deployment. Explicitly states: Within the Australian Defence Force doxycycline is the first-line drug for malaria prophylaxis. Proguanil/Atovaquone combination (Malarone™), an approved drug combination for malaria prophylaxis, is the preferred second-line drug for individuals who are intolerant of doxycycline. Mefloquine (Lariam®) has also been used for Defence members who are unable to take doxycycline.
Long Term Use	**Area with chloroquine sensitive malaria.** Long term stay. Chloroquine 300mg base weekly (start one week prior to arrival and continue for 4 weeks after leaving). Substitute Proguanil (200mg daily) if chloroquine medically contraindicated. Commence seven days before entering and continue for 28 days after leaving.	**Area with chloroquine sensitive malaria.** Stay >8 weeks. Chloroquine 300mg base weekly or proguanil 200mg daily if chloroquine medically contraindicated. Commence seven days before entering and continue for 28 days after leaving.	**Areas with drug sensitive malaria.** Chloroquine 300mg base weekly or proguanil 200mg daily if chloroquine medically contraindicated. Commence seven days before entering and continue for 28 days after leaving.		Stay >6 months. Doxycycline 50mg daily plus chloroquine (310mg base) weekly, and carry Malarone for standby treatment. OR mefloquine 250mg weekly beginning with loading dose of 250gm on day 7, 6 and 5 before deployment and continue for 2 weeks following redeployment, and carry Malarone for standby treatment if medical care not immediately available.	Stay >6 months. Doxycycline 100mg/day. If longer than 6 months should have periodic health reviews at least every 3 months, documented in UMR. Alternatively: first six months doxycycline 100mg/day, next 3 months Malarone, next 3 months doxycycline 100mg/day. For deployments over 12 months, thee month alternating cycles of Malarone and doxycycline, after the initial six months on doxycycline. If mefloquine or chloroquine the primary prophylactic gent - continue treatment up to 2 years if no adverse effects. If want to use Malarone for more than 6 months, consult AMI (limited experience with long term use of Malarone, new drug).	Doxycycline 100mg daily OR Malarone one tablet daily OR mefloquine 250 mg weekly (after loading dose on day 7, 6, 5 before deployment). Those on MQ to contact MO if experience anxiety/depression/restlessness/ confusion - discontinue MQ and use doxycycline or Malarone. Alternative regimen provided for deployments longer than six months, as previous version.

R-2

Date	03 Sep 1990	13 Apr 1992	20 Oct 1994	23 May 1996	15 Dec 2000	29 Nov 2006	29 Jan 2013
Long Term Use	**Area with chloroquine resistant malaria**. Long term. Chloroquine 300 mg base plus Maloprim (one tablet) on same day each week.	**Area with chloroquine resistant malaria.** Stay <8 weeks. Chloroquine 300mg base weekly and Maloprim (1 tab) taken on same day each week	**Areas with drug resistant malaria.** Stay of more than 4 weeks. Doxycycline 50mg daily plus chloroquine 300mg base weekly. Doxycycline 100mg daily for up to six months can be considered if very high risk of exposure to malaria. OR if doxycycline contraindicated or not tolerated, mefloquine 250mg weekly (first three doses taken 7, 4 and 1 day before entering a malarious area, then continued weekly until 14 days after leaving malarious area. Currently not approved for use beyond 3 months.) If need prophylaxis for more than 3 months may use chloroquine 300mg base weekly with standby mefloquine (start chloroquine seven days before entering and continue for 28 days after leaving malarious area).				Alternative regimen provided for stays over 6 months. First six months, doxycycline 100mg daily. Next three months, Malarone 1 tablet daily. Next three months, doxycycline 100mg daily. For deployments over 12 months, three month alternating cycles of Malarone and doxycycline, after first six months on doxycycline. Consult with AMI. Mefloquine or chloroquine can be continued for up to 2 years if there are no adverse effects found at each routine three monthly health check.
	Areas with both chloroquine and anti-folate resistant malaria. **Seek SGADF advice.** Long term, options include: mefloquine 250 mg weekly up to three months (start one week before arrival and continue for 2 weeks after leaving) OR doxycycline 50mg daily plus chloroquine 300 mg base weekly OR chloroquine 300mg base weekly with mefloquine on standby if develop symptoms/signs of malaria.	**Areas with both chloroquine and anti-folate resistant malaria.** Long term (>8 weeks). Doxycycline 50mg daily plus chloroquine 300mg base weekly OR mefloquine 250 mg weekly OR chloroquine 300mg base weekly with mefloquine available for treatment if symptoms/signs of malaria.					
Short Term Use	Short term (<6 weeks). Doxycycline 100 mg daily (start one day prior to arriving and continue for 3 days after leaving). If doxycycline medically contraindicated, mefloquine 250 mg weekly, or chloroquine/Maloprim as per long term stay.	<8 weeks. Doxycycline 100mg daily (start one day before entering malarious area, continue for 3 days after leaving) OR mefloquine 250mg weekly if doxycycline medically contraindicated. Start mefloquine seven days before entering malarious area and continue for 14 days after leaving, but do not use for more than 3 months or in Thailand/Cambodia because of mefloquine resistant malaria there. OR Chloroquine and Maloprim (one tab of each taken on same day weekly) starting seven days before and continued for 28 days after leaving malarious area.	Stay of 4 weeks or less. Doxycycline 100mg daily.		Stay <6 months. Doxycycline first line 100mg daily, start 2 days before entering malarious area and continue for 14 days after. OR mefloquine 250mg weekly, loading dose of 250mg on each of 7, 6 and 5 days before deployment, continue for 2 weeks post deployment (mefloquine not approved in aircrew in flying ops). OR Malarone if both doxy and mefloquine contraindicated (not to be used for prophylaxis until TGA approval given unless no alternative)	Stay <6 months. Doxycycline 100mg daily starting 2 days before deployment until 14 days after. OR Malarone 1 tab daily staring 2 days before deployment and for one week after (as is relatively new medication, monitor these members closely). OR mefloquine 250mg - loading dose on day 7,6,and 5 before deployment then weekly up to 2 weeks after leaving malarious area. Periodic (at least 6 monthly) LFT during prolonged prophylaxis with any antimalarial.	

Date	03 Sep 1990	13 Apr 1992	20 Oct 1994	23 May 1996	15 Dec 2000	29 Nov 2006	29 Jan 2013
Short Term Use		**Areas with multi-drug resistant malaria**. <8 weeks. Doxycycline 100mg daily (start day before entering malarious area and continue for 3 days after leaving). If doxycycline medically contraindicated, mefloquine 250mg weekly OR chloroquine/Maloprim (one tablet of each on same day each week starting 7 days before and continued for 28 days after leaving malarious area)					
Precautions	Prolonged Maloprim prophylaxis - sporadic case reports of agranulocytosis. Full blood count should be done 2 months and 6 months after commencing Maloprim then annually. Any episode of fever and sore throat in first three months of use need haematological investigation.	No change. Prolonged Maloprim prophylaxis - sporadic case reports of agranulocytosis. Full blood count should be done 2 months and 6 months after commencing Maloprim then annually. Any episode of fever and sore throat in first three months of use need haematological investigation.	Maloprim no longer used routinely because of the risk of uncommon but serious haematological side effects. Safety of long term doxycycline (1-3 years) not established but has been taken for long periods for acne treatment. Gastrointestinal side effects and photosensitivity noted, Doryx brand (enteric coated sustained release) preferred. Drug Interactions - issue of methoxyflurane nephrotoxicity while taking long term doxycycline is explained. Baseline liver and renal function tests advised for those who will be taking long term (>12 months) doxycycline and repeated annually. Long term chloroquine prophylaxis has not been associated with retinopathy.		Doxycycline generally first line - compliance may be a problem, side effects often self-limiting and cease within first week of prophylaxis. These include nausea, abdominal cramps, oesophagitis, photosensitivity and superinfection. Drug interactions listed (as per last version). Mefloquine S/E include balance and gastrointestinal disturbance, sleep disturbance and mood disorders. These generally manifest during loading dose. Malarone - few reported side effects, not approved for aircrew involved in flying ops. Primaquine not to be used in people with G6PD deficiency.	All antimalarials should be taken with a substantial meal. Personnel should contact MO if any unusual symptoms from any antimalarial. Those on mefloquine must be advised to immediately contact MO if experience anxiety, depression, restlessness or confusion: stop and replace with doxycycline or Malarone if these occur. Periodic (at least 6 monthly) liver function tests during prolonged prophylaxis with any antimalarial. Consider risks/likelihood of exposure and seasonality - can halt prophylaxis during low risk periods as per HSP. Primaquine not to be used in people with G6PD deficiency.	As previous version but with much more detail. Re mefloquine: noted to have been taken by over 20 million people worldwide. If a person has tolerated mefloquine chemoprophylaxis previously, it is nearly unknown that they would subsequently have severe adverse events when mefloquine is again used for chemoprophylaxis at appropriate dosages. The most frequently reported adverse events are nausea, vomiting, loose stools, abdominal pain, dizziness, loss of balance, headache, and sleep disorders including very vivid dreams. These are usually mild and will often manifest themselves during the initial three-day loading dose. These symptoms often decrease or disappear with continued use. The main problem with mefloquine is that severe neuropsychological effects have been observed in a very small proportion of people taking the drug.

R-4

Date	03 Sep 1990	13 Apr 1992	20 Oct 1994	23 May 1996	15 Dec 2000	29 Nov 2006	29 Jan 2013
Contraindications	Mefloquine not recommended for aircrew and divers (dizziness or vertigo may disturb coordination and spatial perception). Unfit for flying/diving while taking primaquine eradication because gastro side effects may impair performance.	Mefloquine not recommended for aircrew and divers (dizziness or vertigo may disturb coordination and spatial perception). Unfit for flying/diving while taking primaquine eradication because gastro side effects may impair performance.	Mefloquine not recommended for aircrew and divers (dizziness or vertigo may disturb coordination and spatial perception). Unfit for flying/diving while taking primaquine eradication because gastro side effects may impair performance.		Mefloquine and Malarone not to be used in aircrew involved in flying ops.	Mefloquine not approved for those with previous history of neuropsychiatric illness/epileptic seizures. Not to be used by divers or aviation related occupations. Use with caution in those found to be more susceptible to neuropsychological adverse events. Not to be used in Thailand, Cambodia, Burma or other areas with mefloquine resistance.	Mild symptoms. Complaints of dizziness, sleeplessness, strange or vivid dreams, or anxiety may be reported by about one-third of patients using the drug. Women travelers with a low body mass index report more neuropsychological effects in controlled as well as questionnaire-based studies. For this reason, women should be made aware that they are at greater risk than men of developing neuropsychological problems with mefloquine use. Severe symptoms: Gross evidence of neurotoxicity is rare in travelers on mefloquine prophylaxis. More severe events, such as seizures and psychoses, are more common in individuals with a previous history of psychiatric disease. This implies that every effort should be made to identify individuals with a strong risk of relapse following mefloquine use and prescribe alternative malaria prophylaxis for them. Mefloquine should not be given to individuals with active depression, a recent history of depression, generalised anxiety disorder, schizophrenia or other major psychiatric disorders, or with a history of convulsions. If acute anxiety, depression, restlessness or confusion occur during prophylaxis, these could be prodromal for a more serious event. In these cases mefloquine should be discontinued immediately and an alternative drug should be substituted. Because of the long half-life of the drug, adverse reactions to mefloquine may persist for several weeks after the last dose. Mefloquine not to be used by divers, aircrew or JBAC.
Eradication	Chloroquine (600mg base stat then 300mg 6 hours later then 300 mg daily for two more days) plus primaquine 7.5mg twice daily for 14 days. If returning from PNG, Solomon Islands or Vanuatu, primaquine dose is 7.5mg thee times daily for 14 days.	No change. Chloroquine (600mg base stat then 300mg 6 hours later then 300 mg daily for two more days) plus primaquine 7.5mg twice daily for 14 days. If returning from PNG, Solomon Islands or Vanuatu, primaquine dose is 7.5mg three times daily for 14 days.	Primaquine 7.5mg twice a day for 14 days (or one 15mg daily after food). For PNG, Solomon Islands and Vanuatu, dose is 7.5mg three times daily for 14 days.		East Timor, Indonesia, PNG, SI or Vanuatu - 15mg base twice daily for 2 weeks. All other places, 15 mg once daily for two weeks.	15mg base twice daily 14 days. Alternative regimens given for those that don't tolerate primaquine well.	15mg base twice daily 14 days. Alternative regimens given for those that don't tolerate primaquine well.

Date	03 Sep 1990	13 Apr 1992	20 Oct 1994	23 May 1996	15 Dec 2000	29 Nov 2006	29 Jan 2013
G6PD Screening	**G6PD screening** not required routinely, only for those with increased risk/likelihood of deficiency. Recommended adult doses of primaquine unlikely to cause serious haemolytic crisis	No change from previous. **G6PD screening** not required routinely, only for those with increased risk/likelihood of deficiency. Recommended adult doses of primaquine unlikely to cause serious haemolytic crisis	Commencing 01 Jan 94, all ADF entrants to be tested. All other personnel to be tested prior to deployment unless have previously successfully completed a primaquine eradication course. Because of genetic mixing, no longer possible to exclude any racial group from being at risk.				
Civilian Guidelines	**NHMRC Guidelines 1989.** Recommend chloroquine for areas with chloroquine sensitive malaria, chloroquine/Maloprim if there is chloroquine resistant malaria. Mefloquine or doxycycline for areas with chloroquine and antifolate resistant malaria. Recommended dosing schedule of mefloquine for long stays one tablet weekly for first to fourth dose then fortnightly.		**NHMRC guidelines 1993.** Recommends mefloquine for short stays (<8 weeks) in chloroquine resistant areas and for standby treatment for long stays in chloroquine/multi drug resistant areas. Mefloquine approved for chemoprophylaxis for up to 3 months. Doxycycline for prophylaxis approved up to 8 weeks, for longer periods reduce doxy dose to 50mg and add weekly chloroquine.		Recommendations generally consistent with CDC Yellow Book. http://hetv.org/resources/cdc/yellowbk99.pdf Advises MQ can be used for long term prophylaxis.	WHO international travel and health 2003 supports long term prophylaxis with any of these agents. Data indicate no increased risk of serious side effects with long term use of mefloquine if the drug is tolerated in the short term. Recommends starting mefloquine 2-3 weeks before entering malarious area. Malarone cannot yet be recommended for long term prophylaxis because of the lack of data. British National Formulary and other studies suggest adequate safety of doxycycline 100mg daily for up to 2 years.	WHO international travel and health 2007 - no change in Mefloquine recommendations from 2003 edition.
	Notes that WHO wants to delay development of drug resistance to mefloquine as it is the only readily available and effective antimalarial for multidrug resistant falciparum malaria. Its use as prophylactic therefore should be restricted to short and long term visitors to high risk areas where both chloroquine and antifolate resistance is present.		The driver for loading dose mefloquine was the US military experience during high exposure events such as African deployments in the early 1990s (published in literature). In Somalia the US marines started on doxycycline and some were then ordered to switch to mefloquine which they did in place without loading doses. Stopped doxy, started mefloquine at same time. There was a small outbreak of falciparum malaria while on mefloquine, largely because they lacked any protective concentrations for about 2 weeks after the switch from one to another. The conclusion was that loading doses were indicated when intense exposure was expected (e.g. Africa, PNG) and the time to deployment short (less than 1-2 months).				

ANNEX S

DEFENCE HEALTH POLICY DIRECTIVE - MALARIA 2000

DEFENCE HEALTH POLICY DIRECTIVE NO 215

AMENDMENT NO 7

Recipients of Defence Health Policy Directive No 215 are requested to amend the Directive as detailed below.

Sequence	Remove	Insert	Remarks
1	HPD 215 AL6	HPD 215 AL7	Complete Revision

W.P. RAMSEY
Brigadier
Director-General Defence Health Service

15 December 2000

DEFENCE HEALTH POLICY DIRECTIVE NO 215

Note: Defence Health Policy Directives are of a permanent nature and remain in force until cancelled. They are reviewed every three years and repromulgated only where a significant change of content is necessary. Publications can be accessed on the Defence Intranet at http://defweb.cbr.defence.gov.au/home/documents/adfdocs/healthindex.htm

15 DECEMBER 2000

MALARIA

References:
A. Australian Defence Force Publication 705—*Pesticides Manual*, chapter 2
B. Health Policy Directive (HPD) 224—*Notification of Infectious Diseases*

INTRODUCTION

1. Malaria is a serious disease affecting approximately 270 million people worldwide and causing up to 2.5 million deaths a year. The disease is now mainly confined to tropical regions. Previously malaria was endemic in some areas of Europe, North Asia, North America and Australia. The disease was eradicated from Australia in the 1950s, though the potential for reintroduction exists in malaria receptive areas north of 19°S latitude (between Townsville, Qld and Derby, WA).

2. Malaria continues to be reported in Australia with the Australian Malaria Register documenting 730 cases in 1997. Most of these cases have been from returning travellers or visitors to Australia. In recent years, malaria has continued to affect Australian Defence Force (ADF) personnel operationally deployed to locations such as Irian Jaya, Papua New Guinea and East Timor.

AIM

3. This HPD details the measures to be taken in the ADF to prevent personnel contracting malaria and the clinical and administrative management of the disease when it occurs. This policy is not intended to provide guidance on the treatment of complicated malaria, when specialist physician advice should be sought.

POLICY

Prevention

4. Malaria prevention should involve the following general measures:

a. **Risk Assessment.** Health intelligence relevant to the anticipated area of operations should be evaluated carefully as part of pre-deployment preparations. Malaria transmission risks vary according to the geographic location (including urban/rural), season, climatic conditions, and time of day. For example, in East Timor, Batugade and Oecussi are high-risk areas whereas the centre of Dili is a low risk area for malaria.

b. **Environmental controls.** Where possible the ADF will undertake environmental control of vectors. This may include controlling breeding sites, using knock down agents, providing barriers to mosquitoes and other measures to reduce exposure. These measures are the responsibility of both individuals and units. ADF Preventive Medicine personnel provide expertise in field environmental measures.

c. **Personal protection.** (*See* reference A, chapter 2). Mosquitoes are also vectors of other diseases including Ross River Fever, Dengue, Japanese Encephalitis, Yellow Fever, and Filariasis. Effective self-protective measures to reduce man-insect contact should be routinely employed because no effective chemoprophylaxis or treatment is available for many of these diseases. Such self-protective measures include:

(1) **Appropriate clothing.** Appropriate clothing includes long trousers and long sleeved shirts, socks and boots or shoes (not sandals), at and after sunset, (Note: Most Anopheles mosquitoes bite predominantly after dark. Permethrin impregnation of clothing should be used where possible;

(2) **Insect repellents.** Effective repellents are to be used on all exposed skin surfaces;

(3) **Mosquito netting.** (or suitable functional screening of sleeping accommodation). Permethrin impregnation of netting should be used wherever possible; and

(4) **Pesticide sprays.** Suitable knock down sprays, or fogging for quarters or accommodation areas is to be utilised.

5. **Chemoprophylaxis.** Malarial chemoprophylaxis is detailed in annex A. Chemoprophylaxis is only one part of the overall protection against malaria. It is not more important than personal protective measures as no single drug or drug combination is completely effective against malaria. The Defence Health Service Branch (DHSB) will notify changes to these regimens. Different regimens are not to be used without prior approval from the DHSB. Compliance with these regimens is mandatory for all ADF personnel deploying on duty to a malarious area.

6. In the case of accompanying dependants, chemoprophylaxis should be in accordance with National Health and Medical Research Council guidelines.

Diagnosis of malaria

7. Malaria is one of the most common endemic diseases of tropical and subtropical areas. It is characterised by fever primarily in the acute and sub-acute stages. More chronic infections may present with anaemia and splenomegaly. However, as one or more organ systems may be involved, malaria can have other clinical presentations, and an incorrect diagnosis may be made. Consequently, malaria must always be considered in the diagnosis of any illness occurring in a person in a malarious area or who has visited a malarious area within the past year.

8. Diagnosis can be confirmed by examining suitably prepared thick and thin blood films. Experience is required in reading these films, as the number of parasites may be low and morphology variable. Skilled staff using light microscopy may make rapid estimates of the level of parasitaemia, the level of anaemia and the presence of other blood parasites. The quality of the blood slides is very important in reaching a correct diagnosis. In some instances, poor technique or inexperienced personnel reading the slides may compromise the quality of reporting. Allowances should be made for this and, if necessary, repeat slides should be examined over 2–3 days.

9. Diagnosis can also be confirmed by non-microscopic tests that have recently become available. One of the simplest field tests is the AMRAD/ICT immuno-chromatographic test. The ICT Pf test is sensitive and specific for falciparum parasite densities as low as 10 to 50 parasites per µl of blood. The ICT Pf/Pv test is a newer, combined test which detects both falciparum and vivax malaria. The limitation of the ICT Pf/Pv test is its low positive predictive value, with about 400 parasites per µl of blood being required to reliably produce a positive result for the vivax component. Clinicians should be aware that a negative Pv card test does not exclude the diagnosis of malaria.

10. The pink line on the test card, showing the captured malaria antigen, remains visible after the test and is to be kept as a diagnostic record. Both the ICT Pf test and the ICT Pf/Pv test are suitable for field deployment and are particularly useful when accurate microscopic diagnosis is not available, such as in an RAP unsupported by a laboratory.

Role of the Army Malaria Institute

11. Army Malaria Institute (AMI) is responsible for ensuring that the best possible protection is available to ADF personnel against malaria and other mosquito-borne diseases. To achieve this it is actively involved in various aspects of research—from drug evaluation to field-testing of equipment and repellents. In addition, AMI provides the following malarial services to the ADF:

a. Diagnostic assistance;

b. Clinical management advice;

c. Operational preparation advice;

d. Maintenance of the Central Malaria Register;

e. Plasma concentrations of all anti-malarial drugs;

f. Drug sensitivity testing of malarial parasites;

g. Evaluation of anti-malarial drugs; and

h. Training of Preventive Medicine and Pathology personnel in malariology techniques.

12. In all cases where malaria has been diagnosed, Defence Health Service (DHS) units are to provide AMI with the following samples:

a. Thick and thin blood films to confirm malaria and species diagnosis;

b. Any AMRAD/ICT test cards; and

c. Plasma samples as required in annex B.

13. The purpose of these tests is to assist clinicians with the clinical management of their patients should the initial malaria or species diagnosis have been in error. (In some locations, laboratories at tertiary level hospitals cannot be relied upon to confirm malaria and/or species diagnosis.) In addition, microscopic and drug analysis can monitor the effectiveness of the patient's prophylaxis or treatment and provide an early warning that alternative medication should be used.

Notification of Malaria Cases

14. Malaria is a notifiable disease in all States and Territories of Australia. In malaria receptive areas, ie. north of latitude 19°S, notification should be made immediately by telephone to Public Health Authorities for appropriate public health precautions to be initiated. All DHS units (DHS personnel, pathology laboratories and hospitals) are to comply with State and Commonwealth reporting requirements in accordance with reference B.

15. In addition, all cases of malaria in ADF personnel, or in their dependants, (whilst on posting to malarious areas) are to be reported to AMI on Form PM 040—*Central Malaria Register* (*see* appendix 1 to annex B). Annex B details all notification action required for cases of malaria.

16. Monthly statistics on all ADF malaria cases are to be forwarded to the DHSB (for the Directorate of Preventive Health) by AMI.

Treatment of malaria

17. The treatment of malaria varies according to the type of malaria responsible for the infection. With the continual spread of resistance to anti-malarial agents, there is no universal regimen for the treatment of malaria. Regimens approved for use in the ADF are in annex C.

Eradication Course and Glucose-6-Phosphate Dehydrogenase Deficiency

18. On departure from a malarious area, ADF personnel are required to undertake eradication of possible residual parasites. Eradication courses are detailed in annex A. Primaquine can cause haemolytic episodes in individuals with a Glucose-6-Phosphate Dehydrogenase (G6PD) enzyme deficiency. G6PD deficiency occurs in some ethnic groups more commonly than others. Such groups include black Africans, Papua New Guineans, and individuals of Mediterranean and Asian origin.

19. However, it is not possible to exclude any racial group from being at risk of this trait. All entrants to the ADF (after 01 January 1994) are tested for G6PD deficiency. Their Unit Medical Record (UMR) is to reflect, on the front cover, the date and result of the test. All other ADF personnel posted or deployed to a malarious area are to be tested prior to deployment, with the date and result recorded on the UMR front cover.

20. Once a test has been performed and the result recorded, no further testing for G6PD deficiency is required for subsequent deployments or postings. There is no Service requirement for accompanying dependants to be tested, however testing is a wise precaution before taking Primaquine.

Members at Special Risk during deployment to Malarious areas

21. **Pregnancy.** Pregnant Servicewomen are not to be posted to malarious areas. The risk to both the prospective mother and the foetus is significantly increased when pregnancy is complicated by malaria. The parasites have the ability to concentrate in placental tissue resulting in reduced blood flow through the placenta and low birth weights of surviving offspring.

22. Servicewomen who become pregnant during deployments or postings to malarious areas are to be evacuated out of the area at the earliest opportunity. Pending evacuation, maximum effort needs to be taken to protect the individual from exposure to malaria vectors. Chloroquine 600mg per week given on the same day of the week is to be initiated pending evacuation. Doxycycline is contraindicated in pregnancy.

23. **Splenectomy.** Splenectomy is not an absolute contraindication for deployment to a malarious area. However, members who have undergone a splenectomy should be warned that they might be at greater risk from malaria. Although there remain many unanswered questions with regard to the protective function of the spleen in human malaria, case reports often indicate a more abrupt onset of symptoms, more severe infections, and a slower response to treatment in splenectomised patients.

24. Members who have had a splenectomy and who are retained in the ADF after MECRB action are to have their UMR clearly annotated:

'Member has undergone Splenectomy'

25. This need is based on the requirement for early laboratory diagnosis of the infection and the provision of early and vigorous treatment in the event that such members develop malaria. When members who have had a splenectomy serve in a malarious area, meticulous attention must be given to all aspects of malaria prophylaxis. When planning an operation, health planners should address the risk to splenectomised personnel and give guidance on the deployment of affected personnel.

SUMMARY

26. Malaria is a disease of particular military significance, which has the potential to impede seriously the effectiveness of entire formations. This HPD provides guidance for the prevention and management of malaria in ADF personnel. Close attention to the procedures outlined in this publication will minimise the effect of malaria on deployed ADF personnel.

W.P. RAMSEY
Brigadier
Director-General Defence Health Service

Annexes:
A. Australian Defence Force Malaria Chemoprophylaxis
B. Notification and samples required by Army Malaria Institute
C. Australian Defence Force malaria treatment protocols
D. Background information on malaria
E. Useful Malaria links

FILE: PE 99/5330 P1

DISTRIBUTION: DHS

CONTACT OFFICER: DCP

EARLIER HEALTH POLICY DIRECTIVE CANCELLED: Nil

REVIEW THREE YEARS FROM PUBLICATION OR REVIEW

ANNEX A TO
HPD 215

AUSTRALIAN DEFENCE FORCE MALARIA CHEMOPROPHYLAXIS

1. This annex details anti-malarial chemoprophylaxis for Australian Defence Force (ADF) personnel when travelling or posted to malarious areas. Chemoprophylaxis depends upon specific resistance, duration of exposure and medical indication. It includes medication:

a. to suppress all types of malaria while in malarious areas by eliminating parasites from the blood; and

b. to prevent vivax malaria after leaving malarious areas by eradicating parasites from the liver.

PROPHYLAXIS IN MALARIOUS AREAS

Deployment or visit to a malarious area for less than six months

2. The following regimens are to be followed for personnel deploying or visiting a malarious area for any period less than six months:

a. **Doxycycline.** Generally, Doxycycline should be used as firstline malarial prophylaxis in the ADF. 100mg daily with a meal beginning two days before deployment to malarious areas and continuing for two weeks after redeployment from malarious areas; or

b. **Mefloquine.** 250mg weekly beginning with loading doses of 250mg on each of seven, six and five days before deployment (total 750 mg) and then 250mg weekly during deployment and continuing for two weeks following redeployment (if Doxycycline is contraindicated). Mefloquine is not approved for use by ADF aircrew involved in flying operations; or

c. **Malarone** (not to be used for malarial prophylaxis until TGA approval has been given). However, if both Doxycycline and Mefloquine are contraindicated, the Malarone dosage to be used is one tablet (Atovaquone 250mg + Proguanil 100mg) daily beginning two days before deployment to malarious areas and continuing for two weeks after redeployment from malarious areas.

Deployment or posting to a malarious area for six months or more

3. The following regimens are to be followed for personnel deploying or visiting a malarious area for six months or more:

a. **Doxycycline.** Generally Doxycycline should be used as firstline malarial prophylaxis in the ADF. 50mg daily taken with a meal beginning two days before deployment to malarious areas and continuing for two weeks after redeployment from malarious areas. In addition Chloroquine phosphate 2 x 250 mg tablets (310mg of base), taken weekly on the same day of each week, beginning seven days prior to deployment and continuing for four weeks after redeployment from malarious areas. Also carriage of Malarone, (12 tablets) for standby treatment (*see* annex C) if medical care is not immediately available; or

b. **Mefloquine.** 250mg weekly beginning with loading doses of 250mg on seven, six and five days before deployment (total 750 mg) and then 250mg weekly during deployment and continuing for two weeks following redeployment (if Doxycycline is contraindicated). Also, carriage of Malarone (12 tablets) for standby treatment (*see* annex C) if medical care is not immediately available. Mefloquine is not approved for use by ADF aircrew involved in flying operations

Eradication following deployment to malarious areas

4. ADF personnel are required to take an eradication course following deployments to malarious areas. Exceptions are medical contraindications such as G6PD deficiency or known allergy to eradication agents, or imminent return to a malarious area with continuing use of malaria chemoprophylaxis (see below). The eradication course is commenced on the day of departure from the malarious area. It is taken concurrently with the continuation of chemoprophylaxis (as detailed in paragraphs 2. and 3. above).

5. Eradication courses are as follows:

a. Deployment to East Timor, Indonesia, Papua New Guinea, the Solomon Islands or Vanuatu: Primaquine phosphate 2 x 13.2 mg tablets (15mg of base) taken twice daily (with meals) for two weeks; or

b. Elsewhere: Primaquine phosphate 2 x 13.2mg tablets (15mg of base) taken once daily (with a meal) for two weeks.

Repetitive visits to malarious areas

6. For personnel making repetitive trips into malarious areas, malaria chemoprophylaxis may be modified to minimise the requirement for multiple Primaquine eradication courses. The following regimen is then to be followed:

a. Continue chemoprophylaxis as detailed in paragraph 2. above for a period of two weeks following redeployment; then

b. Commence Chloroquine phosphate 2 x 250 mg tablets (310mg of base) weekly (taken on the same day) starting on the last day of the two week post deployment course of chemoprophylaxis and continuing throughout the interval spent in a non- malarious environment.

c. Recommence a chemoprophylaxis regimen as in paragraph 2. above two days prior to re-entry into a malarious area (one-week prior with Mefloquine to include the three-day loading dose).

7. Eradication as detailed in paragraph 5. is to be undertaken when the repetitive visits/ deployments are completed. For aircrew frequently required to deploy to malarious areas, eradication is to be undertaken under the supervision of the Squadron Medical Officer once per calendar year when respite from flying duties can be programmed.

Side effects and contraindications of chemoprophylactic drugs

8. The decision on whether to use Doxycycline, Mefloquine, or Malarone as chemoprophylaxis should be made on the potential or known side effects and the likelihood of compliance by the individual.

9. **Doxycycline.** Generally Doxycycline should be used as first-line malarial prophylaxis in the ADF where possible. It is well tolerated when taken with food and the 50mg daily dose has been taken for many years by thousands of acne patients. Compliance may be a problem with Doxycycline compared to agents with less frequent administration for prophylaxis. Side effects are often self-limiting and disappear within the first week of prophylaxis. Side effects include nausea, abdominal cramps, oesophagitis, photosensitivity and superinfection.

10. Notable interactions with Doxycycline are antacids, penicillins, warfarin and methoxyflurane at anaesthetic doses. The use of the Penthrane (methoxyflurane) inhaler in first aid situations is authorised as concurrent medication with Doxycycline. Female personnel who use oral contraception should be advised of possible failure in contraception or menstrual control.

11. **Mefloquine.** Mefloquine has various side effects, including balance and gastrointestinal disturbances. Further adverse effects include sleep disturbance and mood disorders. Generally, these side effects will manifest themselves during the first three-day loading dose of Mefloquine.

12. Mefloquine has not been approved for use by aircrew when involved in flying operations.

13. **Malarone.** Malarone is a medication with few reported side effects. Mouth ulcers and gastrointestinal disturbances are not common. Malarone is not approved for aircrew when involved in flying operations.

14. **Primaquine.** Primaquine must not be used in personnel with G6PD deficiency. It can cause gastrointestinal distress that may be severe and may be potentiated by the concurrent use of Chloroquine. As for all derivatives of Quinine, photosensitivity is possible. Methaemoglobinaemia is a known adverse event, although its clinical significance is uncertain. As there are no data available for the effects of Primaquine on performance or high level tasking, aircrew and divers should not undertake flying or diving duties while on the Primaquine eradication course.

15. **Chloroquine.** Chloroquine is generally well tolerated. Side effects include gastrointestinal upset. Long term use (greater than five years continuous malaria prophylaxis) or 100g cumulative dose has been associated with the development of eye problems (deposits on the retina).

16. Fansidar and Maloprim are no longer to be used for malaria prophylaxis in the ADF. Paludrine is only now used in combination with other drugs, such as atovaquone (as Malarone) or chloroquine.

ANNEX B TO
HPD 215

NOTIFICATION AND SAMPLES REQUIRED BY ARMY MALARIA INSTITUTE

1. Malaria is a notifiable disease in all States and Territories of the Commonwealth of Australia. Defence Health Service (DHS) Medical Officers and all DHS facilities are to comply with this requirement (reference B).

2. In addition, all cases of malaria affecting Australian Defence Force personnel are to be notified to the Army Malaria Institute (AMI) on Form PM 040—*Central Malaria Register* (*see* appendix 1). Assistance with the completion of this form can be obtained from clinical staff at AMI by contacting the Institute on (07) 3332 4801 during office hours or 0411 024 289 after office hours.

3. Immediately after malaria diagnosis, as much as possible of Form PM 040 should be completed and faxed to AMI on (07) 3332 4800. After completion of treatment, the remaining sections of the form should be completed and the hard copies forwarded by mail or SDS. AMI will distribute Form PM 040 according to current directions.

4. The following samples are to accompany a Form PM 012—*Special Examination Request* to AMI:

a. Stained and unstained thick and thin blood films to confirm malaria and species diagnosis;

b. Any AMRAD/ ICT or other non-microscopic diagnostic tests performed;

c. Heparinised whole blood (7ml) samples (plasma separated from cells, if possible) collected after diagnosis (but before treatment) and forwarded in containers that can be maintained at 0–4°C for up to three days in transit. Drug analysis of these specimens may assist in monitoring the effectiveness of prior prophylaxis and/or treatment.

5. Ensure all samples are labelled with patient details and the time and date of collection. Where possible, serial samples obtained during treatment should also be forwarded to AMI for evaluation.

6. Samples are to be sent by courier according to standard NATA guidelines and should be planned to arrive, where possible, at AMI during normal office hours. The address for consigning samples is:

Parasitology Department
Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4051

7. Microscopy results will be available to clinicians within 24 hours of receipt of blood films to enable them to modify clinical management, if necessary.

Appendix:
1. Form PM 040—Central Malaria Register

APPENDIX 1 TO
ANNEX B TO
HPD 215

FORM PM 040—CENTRAL MALARIA REGISTER

MEDICAL-IN-CONFIDENCE ***(After first entry)***

PM 040
Revised Nov 2000

Department of Defence

Central Malaria Register

Number	
Rank	
Family name	
Given name(s)	
Date of birth	Sex

Notifying unit
Unit or ship
Address of present residence *(Including postcode)*

Encl/Folio

Previous malaria? *(Tick appropriate box)*
Yes ☐
No ☐

State or Territory health department notified? *(Tick appropriate box)*
Yes ☐ → If' Yes', specify State | Date
No ☐

Deployment and/or movement history

Country	Area	Date from	Date to

Present illness

Date of onset	Place of onset
Date of diagnosis	Diagnosing laboratory
Parasite species	Parasites and/or field *(Thick blood film)*

Prophylaxis *(Including post deployment eradication)*

Drug, dose and frequency	Date started	Date completed

Treatment of present illness

Drug, dose and frequency	Date started	Date completed

Adverse drug reactions *(Prophylaxis and/or treatment)*

Response to treatment *(Include parasitology and/or complications)*

Information provided by

Signature	
Printed name	
Rank	Contact phone number
Unit	Date

Distribution

Original ☐ *Army Malaria Institute*
Gallipoli Barracks
Enoggera QLD 4052

Duplicate ☐ *Unit Medical Record (UMR)*

Triplicate ☐ *ADFHR Navy*
ADFHR Army
ADFHR Air Force
(As applicable)

Stock No 7530-66-106-6686

MEDICAL-IN-CONFIDENCE ***(After first entry)***

ANNEX C TO
HPD 215

AUSTRALIAN DEFENCE FORCE MALARIA TREATMENT PROTOCOLS

1. Uncomplicated malaria can be treated in a limited inpatient facility or on an outpatient basis with careful monitoring of the response to treatment by both clinical and parasitological examination (with follow-up of the level of parasitaemia until no parasites are detected in thick blood films).

Treatment of vivax malaria

2. **Chloroquine.** 600mg base followed by 300mg base six hours later on the first day, then 300mg base on day two and again on day three, with a Primaquine eradication course (*see* annex B paragraph 5.).

3. Alternative regimens are:

a. **Malarone.** Four tablets (Atovaquone 250mg + Proguanil 100mg per tablet) as a single dose on three consecutive days followed by a Primaquine eradication course; or

b. **Mefloquine.** 750mg followed by 500mg six hours later, then 250mg a further six hours later, followed by an eradication course and careful observation for any neuropsychiatric effects.

Treatment of falciparum malaria

4. **Malarone.** Four tablets (Atovaquone 250mg+Proguanil 100mg per tablet) as a single dose on three consecutive days.

5. Alternative regimens are:

a. **Quinine.** 600mg (orally) every eight hours for three days with Doxycycline 100mg daily for 10 days commencing the same day as Quinine; or

b. **Mefloquine.** 750mg followed by 500mg six hours later, then 250mg a further six hours later, with careful observation for any neuropsychiatric effects.

Treatment of severe or complicated malaria

6. Whenever possible, specialist physician advice should be sought, as in addition to the possibility of falciparum-induced cerebral malaria, severe malaria is associated with shock, hyperthermia, hypoglycaemia, electrolyte imbalance, pulmonary oedema, severe diarrhoea and renal failure. Careful monitoring of appropriate parameters should be initiated and suitable corrections made.

7. Patients suffering severe or complicated malaria should be evacuated as soon as possible to an appropriate medical facility equipped to monitor and manage medical emergencies. The treatment of severe or complicated malaria includes:

a. loading dose of IV Quinine (dihydrochloride), 20mg/kg diluted to 10ml/kg in normal saline or five per cent Dextrose solution given over four hours; or

b. if intravenous or oral Quinine has already been given, administer IV Quinine 10mg/kg diluted in 10ml/kg of normal saline or five per cent Dextrose solution every eight hours until the patient can tolerate oral medication;

c. when the patient's condition improves sufficiently to initiate oral medication, change to oral Quinine 600mg eight hourly (beginning eight hours after the last dose of IV Quinine) for a total of three days Quinine treatment; and

d. add oral Doxycycline 100mg daily for 10 days as soon as patient is able to tolerate oral medication.

8. If oral Quinine or Doxycycline regimens are not well tolerated (eg severe cinchonism), following IV Quinine, administer regimens outlined in paragraph 4. or subparagraph 5b.

Precautions

9. Cardiac monitoring is necessary when infusing Quinine. Total doses of Quinine should not exceed 2000mg over a 24-hour period.

10. When converting from IV Quinine to oral Quinine, allow an interval of eight hours.

11. Allow an interval of 12 hours between doses of Quinine and Mefloquine if Quinine treatment has to be discontinued due to severe cinchonism.

Pregnancy

12. Pregnancy is a contraindication to deployment. Pregnant patients confirmed or suspected of being infected with malaria should be treated with Mefloquine (not Doxycycline or Malarone) as in subparagraph 5b.

ANNEX D TO
HPD 215

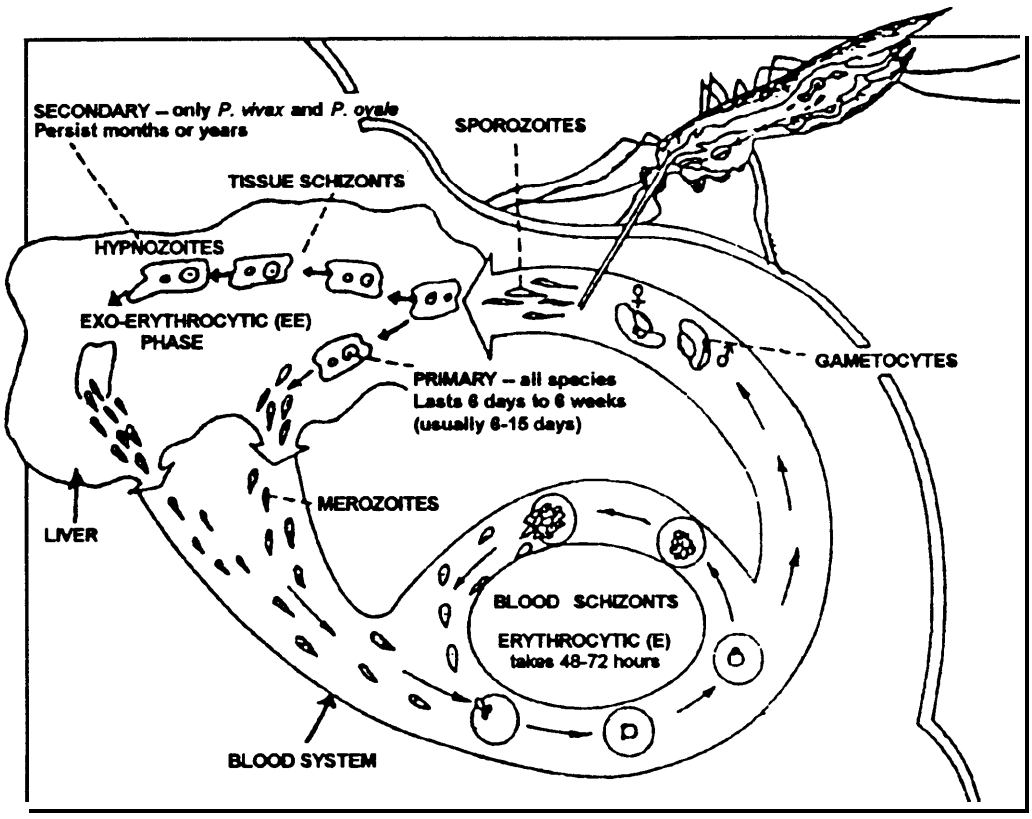
BACKGROUND INFORMATION ON MALARIA

Life cycle

1. An infective female anopheles mosquito, while feeding, injects sporozoites into the blood stream of the host. The sporozoites circulate for a short time before entering the liver cells (hepatocytes), where they multiply (by schizogony or asexual multiplication) forming numerous merozoites. After one to four weeks parasites are released from the liver into the blood stream and invade red blood cells. These intra-erythrocytic parasites undergo multiplication by asexual division eventually rupturing the red cells and rapidly re-invading other healthy red cells.

2. Asexual parasite maturation is often synchronous (48–72 hour cycle) accounting for the patterns of chills and fever that are characteristic of malaria. Sexual differentiation of intra-erythrocytic parasites leads to the formation of male and female gametocytes, which can be taken up by an Anopheline mosquito feeding on the infected person. Fertilisation in the stomach of the mosquito leads to the formation of ookinetes. These invade the body of the mosquito forming an oocyst on the stomach wall. Sporozoites develop within the oocysts and eventually, after rupture of the oocyst, pass to the salivary glands to be stored. The sporozoites are injected into another host when the mosquito next feeds, and so the cycle continues.

THE LIFE CYCLE OF PLASMODIUM VIVAX.



Types of malaria

3. For practical purposes there are two main types of malaria:

a. **Falciparum malaria.** Falciparum malaria causes illness with complications, including cerebral malaria, which is often fatal. There are no residual liver stages with this type of malaria and, once eradicated from the blood, there are no relapses.

b. **Vivax malaria.** Vivax malaria causes acute disease or chronic disability. While not usually fatal, this type may develop residual liver stages (hypnozoites) which can cause a series of relapses of the disease well after initial treatment of the disease.

4. Other types of malaria include ovale and malariae. These are less common. Ovale malaria may persist for a number of years, similar to vivax malaria.

Distribution

5. Malaria is endemic or epidemic in most tropical regions including many countries close to Australia. Appendix 1 indicates the distribution of malaria.

Clinical epidemiology

6. In endemic areas (*see* appendix 1) inhabitants develop a degree of immunity. If malaria transmission is intense throughout the year, most indigenous adults are able to develop sufficient immunity to suppress high levels of parasitaemia and severe clinical disease. In malarious areas with lesser, seasonal, focal or otherwise erratic transmission, symptomatic infections are more common. Malaria endemicity may alter with events such as population movement, climatic changes, deforestation, agricultural practices and other forms of land development, and urbanisation.

7. International air travel may introduce malaria into areas from which it has been previously eradicated or not existed. Such cases are often misdiagnosed. This so-called ‘imported malaria’ may be caused by a primary case (with the parasite contracted overseas) or a secondary case (contracted locally). Secondary cases may be due to an introduced Anopheles mosquito carrying the parasite, local Anopheles mosquitoes infected from recently arrived travellers with malaria, or malaria-infected blood (transfusions, shared needles, etc.).

Parasite resistance

8. Parasite resistance to available antimalarials continues to be a problem in both the chemoprophylaxis and treatment of malaria. There are no anti-malarial medications currently available that provide absolute protection. For this reason, use of prophylactic medication forms only part of the risk management of malaria. The most important aspect of malaria risk management is avoidance of exposure to the vector. Reference A outlines these measures in detail.

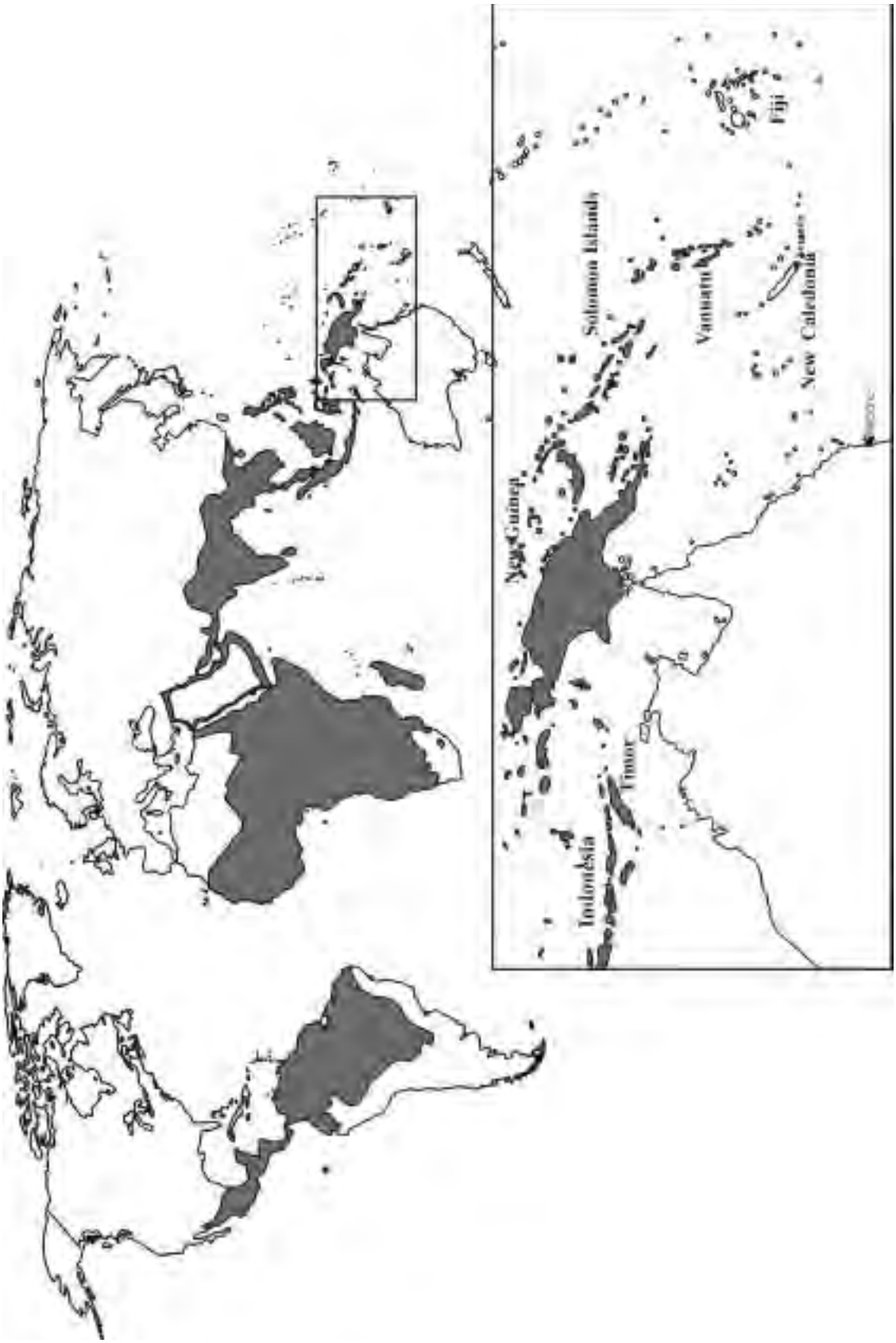
9. The prevalence and degree of parasite resistance to different drugs varies considerably from area to area. Resistance varies from acute infection, despite prophylaxis and treatment with anti-malarial drugs, to subclinical infection during prophylaxis. Consequently, infection with malaria is still possible, despite compliance with chemoprophylaxis. This emphasises the importance of early, correct diagnosis and adequate follow-up in the management of malaria.

10. Due to the possibility of resistant falciparum malaria or relapsing vivax malaria, personnel returning from malarious areas who develop any illness, especially with a fever, should advise their medical practitioner of their travel. Acute attacks of falciparum malaria will occur within a few weeks after return from overseas. On the other hand, the first episode of vivax malaria may not occur until several months or over a year following departure from a malarious area.

Appendix:
1. Distribution of malaria

APPENDIX 1 TO
ANNEX D TO
HPD 215

DISTRIBUTION OF MALARIA



ANNEX E TO
HPD 215

USEFUL MALARIA LINKS

1. Up to date references for areas of malaria endemicity and resistance can be obtained from:

a. The Army Malaria Institute.

b. The Defence Health Service Branch.

c. The CDC 'Yellow Book', www.cdc.gov/travel/

d. World Health Organisation, www.who.int/health-topics/malaria.htm.

e. *Severe and Complicated Malaria, 1990. Transactions of the Royal Society of Tropical Medicine and Hygiene*, 84 (Supplement 2), 1–65.

f. *Management of Severe and Complicated Malaria—A Practical Handbook*, 1991. World Health Organisation, Geneva

CURRENT HEALTH POLICY (DEFENCE HEALTH MANUAL) ON MALARIA (2013)

UNCLASSIFIED

CHAPTER 7

MALARIA

This policy has been transferred from extant HD 215 dated 29 JAN 2013. Only format and editorial amendments have been made. No substantive change has been made to the content or intent of this policy in the conversion.

INTRODUCTION

7.1 Malaria is a serious and sometimes fatal disease caused by a group of parasites of the Plasmodium family. Malaria is a disease of particular military significance, which has the potential to seriously impact on the effectiveness of Defence members operationally deployed to locations in the Asia-Pacific region and other tropical areas. Compliance with preventive measures will significantly reduce the risk of contracting the disease. Although malaria results in a significant number of deaths worldwide, it is a curable disease if diagnosed and treated promptly and correctly.

7.2 The disease remains widely distributed throughout the tropics and subtropics. Previously malaria was endemic to some areas of Europe, North Asia, North America and Australia. The disease was eradicated from Australia in the 1950s, though the potential for reintroduction exists in malaria receptive areas north of 19 degrees South latitude (between Townsville, Queensland and Derby, Western Australia).

AIM

7.3 This policy details measures to be taken in Defence to prevent personnel contracting malaria and the clinical and administrative management of the disease when it occurs.

SCOPE

7.4 This policy is applicable to Defence health personnel and provides information for members proceeding to malarious areas. This policy is not intended to provide guidance on the treatment of complicated malaria. Complicated malaria is a medical emergency for which specialist physician advice should be urgently sought.

POLICY

Definitions

7.5 For the purposes of this policy the following definitions apply:

a. **Prophylaxis.** Prophylaxis is any measure aimed at the prevention of a disease or condition

b. **Chemoprophylaxis.** The use of a drug or medication to prevent the development of a disease

c. **Vector.** A vector is an insect or other organism that transmits a pathogen. In the case of malaria, the vector is the Anopheles mosquito

d. **Repeated trips.** The term repeated trips applies to the situation where a member returns to a malarious area for longer than one week within one month of departure from a malarious area

e. **Aircrew.** Aircrew occupations are listed in DHM Vol 2 Part 6 Chapter 3[72], annex E

f. **Temporarily medically unfit (TMU).** TMU is a generic term used to indicate a Defence aircrew or Joint Battlefield Airspace Controller (JBAC) member is unfit for their specialist duty, but may be fit for alternate ground-based duties. TMU encompasses both Temporarily medically unfit for flying for aircrew occupations and TMU for Controlling Duties for JBAC members.

Prevention

7.6 Malaria prevention involves the following general measures:

a. risk assessment

b. prevention of mosquito-borne diseases

c. chemoprophylaxis.

7.7 Details on malaria prevention are in annex A.

Diagnosis of malaria

7.8 Malaria is one of the most common endemic diseases of tropical and subtropical areas. It is characterised by fever primarily in the acute and sub-acute stages. More chronic infections may present with anaemia and splenomegaly. However, as one or more organ systems may be involved, malaria can have other clinical presentations and an incorrect diagnosis may be made. Consequently, malaria must always be considered in the diagnosis of any illness occurring in a person in a malarious area, or who has visited a malarious area within the past year.

7.9 It is imperative to make an early diagnosis because any delay in treatment can be fatal, especially if the patient is infected with falciparum malaria. Since treatment varies according to the type of malaria, species diagnosis should be established as soon as possible. If there is any doubt about species identity, presumptive treatment for falciparum malaria should be started without delay.

7.10 Guidance on the diagnosis of malaria is in annex B.

Treatment of malaria

7.11 The treatment of malaria varies according to the species of parasite responsible for the infection. With the continuing spread of parasite resistance to anti-malarial agents, there is no universal regimen for the treatment of malaria. Malaria treatment regimens approved for use in Defence are in annex C.

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[72] DHM Vol 2 Part 6 Chapter 3

http://intranet.defence.gov.au/home/documents/data/ADFPUBS/DHM/volume2/part6/03.PDF

Eradication course and Glucose-6-Phosphate Dehydrogenase deficiency

7.12 On departure from a malarious area, Defence members are required to undertake an eradication course of medication in order to eliminate any residual parasites that remain in the liver. Eradication courses are detailed in annex A.

7.13 Primaquine phosphate is the only current drug for eradication of malaria. Primaquine can cause haemolytic episodes in individuals with a Glucose-6-Phosphate Dehydrogenase (G6PD) enzyme deficiency. G6PD deficiency occurs in some ethnic groups more commonly than others. Such groups include black Africans, Papua New Guineans, and individuals of Mediterranean (Greek and Italian) and Southeast Asian origin. It is not possible, however, to exclude any racial group from being at risk of this trait. All entrants to the Australian Defence Force (after 01 January 1994) are tested for G6PD deficiency. The Unit Medical Record (UMR) or electronic health record must contain a pathology result stating the outcome of the test, which must also document the date and result of the test. Where the G6PD status is not recorded, Defence members posted or deployed to a malarious area are to be tested prior to deployment, with the date and result recorded in the members' defence health record.

7.14 Once a test has been performed and the result recorded, no further testing for G6PD deficiency is required for subsequent deployments or postings.

Members at special risk during deployment or overseas posting to Malarious areas

7.15 **Pregnancy.** The risk to both the prospective mother and the foetus is significantly increased when pregnancy is complicated by malaria. The health care provider conducting the pre-deployment health assessment or overseas medical examination is to inform all servicewomen and female dependants of members with child bearing potential of the additional risks associated with malaria and pregnancy. Details of management of pregnant women in malarious areas are in appendix A4.

7.16 **Splenectomy.** Splenectomy is not an absolute contraindication for deployment to a malarious area. However, members who have undergone a splenectomy should be warned that they might be at greater risk of complications from malaria which could lead to severe disease. Management of asplenic personnel is to be in accordance with DHM Vol 2 Part 9 Chapter 12[73] - Management of members of the Australian Defence Force with absent or dysfunctional spleen.

[73] DHM Vol 2 Part 9 Chapter 12

http://intranet.defence.gov.au/home/documents/data/ADFPUBS/DHM/volume2/part9/12.PDF

Army Malaria Institute

7.17 The Army Malaria Institute (AMI) at Gallipoli Barracks Enoggera (Telephone (07) 3332 4801 and after hours 0411 024 289) is responsible for ensuring that the best possible protection is available for Defence members against malaria and other mosquito-borne diseases. To achieve this, the AMI is actively involved in various aspects of research from diagnosis and drug evaluation to field-testing of equipment and repellents. In addition, the AMI provides the following malarial services to Defence:

a. diagnostic assistance

b. clinical management advice

c. operational preparation advice

d. in-country malaria surveillance and risk assessment

e. maintenance of the Central Malaria Register

f. plasma concentrations of anti-malarial drugs

g. drug sensitivity testing of malarial parasites

h. evaluation of anti-malarial drugs

i. training of Preventive Medicine and Pathology personnel in malaria, arbovirus and entomological diagnostic techniques.

Notification of Malaria cases

7.18 Malaria is a notifiable disease in all states and territories of Australia. In malaria-receptive areas (ie north of latitude 19 degrees South) notification should be made immediately by telephone to the state or territory public health authority for appropriate public health precautions to be initiated. All health personnel are to comply with state/territory and Commonwealth reporting requirements in accordance with DHM Vol 2 Part 3 Chapter 14[74] - Notifiable condition reporting in the Australian Defence Force.

7.19 In addition, all confirmed or suspected cases of malaria in Defence members, or in their dependants, (whilst on posting to malarious areas) are to be reported to AMI on Form PM 040 - Central Malaria Register. Annex D details notification and samples required by AMI.

7.20 Monthly statistics on all Defence malaria cases are to be forwarded by AMI to the Directorate of Military Medicine at Joint Health Command.

[74] DHM Vol 2 Part 3 Chapter 14

http://intranet.defence.gov.au/home/documents/data/ADFPUBS/DHM/volume2/part3/14.PDF

Medical Employment Classification implications

7.21 Medical Employment Classification Review (MECR) is not required following a diagnosis of malaria unless absence from duty or employment restrictions extend beyond the defined time frames for MECR, as defined in:

a. Defence Instruction (General) Personnel 16-15[75] - Australian Defence Force Medical Employment Classification System

b. DHM Vol 2 Part 6 Chapter 3[76] - Medical Employment Classification System.

Additional information

7.22 Background information on malaria is listed in annex E and useful malaria links are listed in annex F.

SUMMARY

7.23 This policy provides guidance for the prevention and management of malaria in Defence members. Close attention to the procedures outlined in this chapter will minimise the effect of malaria on deployed Defence members.

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[75] Defence Instruction (General) Personnel 16-15

http://intranet.defence.gov.au/home/documents/data/cancelled/instructions/dig/personnel/GP16_15_ORIG.pdf

[76] DHM Vol 2 Part 6 Chapter 3

http://intranet.defence.gov.au/home/documents/data/ADFPUBS/DHM/volume2/part6/03.PDF

Annexes:

7A Malaria prevention
7B Diagnosis of malaria
7C Malaria treatment regimes
7D Notification and samples required by the Army Malaria Institute
7E Background information on malaria
7F Useful malaria links

ANNEX 7A

MALARIA PREVENTION

1. Malaria prevention should involve the following general measures:

a. risk assessment

b. prevention of mosquito-borne diseases

c. chemoprophylaxis.

Risk assessment

2. Health intelligence relevant to the anticipated area of operations should be evaluated carefully as part of pre-deployment preparations. Malaria transmission risks vary according to the geographic location (including urban/rural), season, climatic conditions, and time of day. For example, during previous Australian Defence Force operations in East Timor, the Batugade and Oecussi regions were high-risk areas, whereas the centre of Dili was a low risk area for malaria. Similarly the north coast of Papua New Guinea is generally a much higher risk area for malaria infection than the city of Port Moresby.

Prevention of mosquito-borne diseases

3. Transmission of mosquito-borne disease can be prevented by breaking any link in the chain of infection, such as eliminating or treating the source, eliminating the vector, or protecting the host from infection. In many deployed environments, source or vector elimination is impractical. However, there are means available to protect Service members against mosquito-borne diseases. Measures for prevention of mosquito-borne diseases are in appendix A1.

Chemoprophylaxis

4. The decision as to which drug regimen to use depends on the likelihood of compliance with drug ingestion, the potential or known side effects of the drug(s), and the efficacy of the regimen. Prophylaxis consists of medication to eliminate:

a. Plasmodium (P.) falciparum, P. vivax, P. malariae and P. ovale from the blood during deployment to a malarious area

b. P. vivax and P. ovale from the liver at the end of deployment in a malarious area.

5. Anti-malarial chemoprophylaxis for Defence members and dependants when travelling or posted to malarious areas are detailed in appendix A2. Details of drug effects and contraindications are in appendix A3. The use of anti-malarial chemoprophylaxis during pregnancy is addressed in appendix A4.

Appendicies:

7A1 Prevention of mosquito borne diseases

7A2 Anti-malarial chemoprophylaxis

7A3 Drug effects and contraindications

7A4 Prevention of malaria and pregnancy

APPENDIX 7A1

PREVENTION OF MOSQUITO BORNE DISEASES

1. Transmission of mosquito-borne disease can be prevented by breaking any link in the chain of infection, such as eliminating or treating the source, eliminating the vector, or protecting the host from infection. In many deployed environments, source or vector elimination is impractical. However, there are means available to protect Defence members against mosquito-borne diseases. These include protection against mosquito-borne diseases at three levels - individual, unit, and area.

Individual protective measures

2. The most important countermeasures are those that prevent the individual being bitten by mosquitoes in the first place. Individual protective measures are easily taught to Defence members but they must be regularly refreshed, reinforced and stringently supervised by leaders, if they are to be effective. There are no substitutes for individual measures. Unit and area defences are to be regarded only as supplementary measures. Individual protective measures include:

a. **Properly wearing the uniform.** This will reduce contact with biting mosquitoes. Between dusk and dawn, long-sleeved shirts should be worn with sleeves rolled down. The use of singlets or T-shirts as outer garments should be prohibited during this period. Trousers should be tucked into boot tops. All these measures limit the amount of exposed skin that could attract biting mosquitoes

b. Permethrin/N,N-Diethyl-M-Toluamide (DEET) system:

(1) The permethrin/DEET repellent system is the cornerstone of personal protection for Defence members against mosquito-borne disease. The method combines a chemical repellent applied to the skin with another repellent applied to the clothing, to prevent insects such as mosquitoes from biting exposed skin or biting through clothing. The permethrin/DEET repellent system treats field uniforms, mosquito nets and tentage with an insecticide (permethrin), in combination with the application of an insect repellent (DEET) to exposed areas of the skin

(2) With most species, permethrin works by killing mosquitoes on contact with the treated fabric. Permethrin is a synthetic pyrethroid insecticide that is very toxic to insects such as mosquitoes. However, it exhibits very low toxicity to humans. It is used at a specific concentration to treat field uniforms, mosquito nets and tentage. The only product currently approved for this purpose is Perigen® 500 (Perigen Defence, NSN 6840–66–135–2075). This is an emulsifiable concentrate containing 50 per cent permethrin, an alcohol based solvent and some emulsifiers. A water emulsion of the concentrate is prepared, and uniforms and mosquito nets are dipped in the solution. Tents are treated using spray equipment

(3) DEET is used for skin application in the permethrin/DEET insect repellent system. The approved formulation of DEET for use by Defence members is as follows: Insect Repellent Personal 75 mL, Insect Arthropod Repellent Lotion (NSN 6840–66–106–0247). This is a 75 mL flexible plastic screw-top tube containing 35 per cent DEET. DEET is applied to exposed skin surfaces whenever there is a risk of

insect bites. DEET is not applied to skin already covered by permethrin-treated field uniform clothing. Some commercially available insect repellents do not have the required DEET concentration to provide the optimum protection under the permethrin/DEET system

c. **Mosquito nets.** Mosquito nets must be used to protect sleeping Defence members because the repellent will not remain effective throughout the night, when most vectors, particularly mosquitoes, are biting. Even combatants sleeping on the ground or in foxholes must use a mosquito net. The four corners can be suspended on sticks less than two feet long, or tied to low vegetation. The sides can be shortened as necessary by taping, hemming, or rolling. After entering the mosquito net, the Defence member should tuck the sides under the air mattress or groundsheet.

Unit protective measures

3. Commanders must emphasise individual protective measures in training and strictly enforce their use during deployment. Educating unit Defence members on the consequences of malaria and other mosquito-borne diseases promotes voluntary compliance with individual protective measures, including chemoprophylaxis. Expeditious isolation and evacuation of suspected disease victims is critical. The unit should also treat mosquito larval habitats in and around the unit.

4. Naval units that are engaged in inshore littoral operations (eg survey, mine countermeasure, patrol and interdiction) that require repeated contact with malarious shorelines also require insecticide spraying of upper deck areas and all non-airconditioned spaces at repeated intervals. Attention must be paid to areas that are susceptible to fresh water pooling, as these reservoirs may foster mosquito breeding. AMI should be consulted to determine frequency of spraying.

Area protective measures

5. Appropriately equipped preventive medicine and environmental health units are to provide mosquito control measures on an area basis.

APPENDIX 7A2

ANTI-MALARIAL CHEMOPROPHYLAXIS

Pre-departure briefing

1. Since no antimalarial drug or drug combination is entirely safe or free of side-effects, prior to deployment Defence members must be informed about the importance of taking their prophylactic regimen and the possible adverse reactions. Details of drug effects and contraindications are in appendix A3. They are to be advised to contact a Medical Officer (MO) or Nurse Practitioner (NP) if they develop any unusual symptoms whilst taking their prophylaxis. Additionally, Defence members are to be briefed that extended usage of antimalarial drugs is not officially endorsed by the drug manufacturers or the Therapeutics Goods Administration. However, there is clinical evidence and experience from other Western militaries, including the United States and United Kingdom Defence Forces, supporting the continuous use of antimalarials for up to two years while on deployment. Although there are small risks of adverse side effects, the consequences of contracting malaria are far more severe and in the worst case, could be fatal. Overall, the benefits of using extended regimens of antimalarial drugs in Defence members outweigh the risks of failing to provide protection against malaria. Details of pre-departure briefings are to be recorded on the member's health record.

Chemoprophylaxis regimens for deployment/travel to a malarious area for less than six months

2. Within the Australian Defence Force doxycycline is the first-line drug for malaria prophylaxis. In operational areas with poor health infrastructure, doxycycline's antibiotic properties also prevent typhus, leptospirosis, and some gastro-intestinal, urinary tract and skin infections. The combined antimalarial and antibiotic effects confer additional protection while on deployment. Proguanil/Atovaquone combination (Malarone™), an approved drug combination for malaria prophylaxis, is the preferred second-line drug for individuals who are intolerant of doxycycline. Mefloquine (Lariam®) has also been used for Defence members who are unable to take doxycycline. Due to the wide-spread public perception of severe mefloquine adverse events, mefloquine is best used only by those who have previously tolerated the medication. Any Defence member starting mefloquine for the first time is to be warned about the possibility of severe central nervous system adverse effects which means mefloquine is contraindicated in many military occupations. Refer to paragraph 16 for malaria prophylaxis regimens for Aircrew and Joint Battlefield Airspace Controllers (JBAC).

3. The following dose regimens are recommended:

a. **Doxycycline 100 milligram (mg) per tablet.** One tablet daily beginning two days before deployment to a malarious area and continuing for two weeks after leaving the malarious area. Gastrointestinal adverse events are very common if doxycycline is taken on an empty stomach and are considerably decreased by taking doxycycline with food and water

b. **Atovaquone 250 mg + proguanil 100 mg per tablet (Malarone™).** One tablet daily beginning two days before deployment to a malarious areas and continuing for one week after leaving a malarious area. Potential for gastrointestinal adverse events exist but are only frequently seen with treatment courses which are four times the chemoprophylaxis dose

c. **Mefloquine hydrochloride 250 mg per tablet (Lariam®).** A loading dose of one tablet on each of seven, six and five days before deployment (total three tablets) and then one tablet per week during deployment and for two weeks after leaving the malarious area. The loading dose is given to achieve adequate drug levels during the initial period of deployment and to provide early warning of any potential intolerance to the drug. Prescribing of mefloquine is conditional upon the following:

(1) Defence members on mefloquine must be advised to immediately contact their MO or NP if they experience anxiety, depression, restlessness or confusion because these symptoms may be prodromal for more serious events. In these cases, the drug must be discontinued and replaced by doxycycline or Malarone™

(2) Mefloquine should not be used by Defence members with a previous history of neuropsychiatric illness or epileptic seizures

(3) The drug is not to be used by divers, aircrew or JBACs

(4) Mefloquine should not be used in Thailand, Cambodia, Burma or other areas where parasites have become resistant to the drug.

4. All antimalarial drugs should be taken with a substantial meal to avoid side effects and/or to ensure optimum absorption from the gastrointestinal tract.

5. Defence members should contact an MO or NP if they develop any unusual symptoms while they are taking any one of the three prophylactic regimens. Approximately 5–10 per cent of Defence members do not tolerate doxycycline due to gastrointestinal adverse events and require a different malaria chemoprophylaxis.

Deployment to a malarious area for greater than six months

6. The safety of continuous long term use of doxycycline for malaria chemoprophylaxis has not been adequately studied. However, several dermatologic studies using similar antibiotics (minocycline and tetracycline) and anecdotal information regarding the use of doxycycline for long term treatment of acne indicate that 100 mg of doxycycline can be safely taken on a daily basis for periods of 4–12 months continuously. The British National Formulary and other studies suggest adequate safety for up to two years. At this time continuous use of doxycycline is not recommended to exceed two years.

7. An alternative regimen which can be considered for long term treatment:

a. **First six months.** One tablet of doxycycline 100 mg per tablet daily

b. **Following three months.** One tablet of atovaquone 250 mg + proguanil 100 mg per tablet daily

c. **Following three months.** One tablet of doxycycline 100 mg per tablet daily

d. **For deployments exceeding one-year.** Three-month alternating cycles of Malarone™ and doxycycline (as above) are to be used, after the initial six months of doxycycline. Experience with the individual components of Malarone™ suggest a high level of confidence in their safety for long-term use, however, experience with their use in combination is lacking. Therefore the requirement to use Malarone™ for greater than six months should be considered on a case by case basis in consultation with the Army Malaria Institute (AMI).

8. For Defence members on mefloquine or chloroquine as the primary chemotherapeutic agent continue treatment for up to two years provided there are no adverse effects found at each routine three monthly health check, (see paragraph 10.). Additionally, each of the conditions outlined in paragraph 3.c. are to apply.

9. The risks involved with prolonged continuous chemoprophylaxis should be weighed against the necessity to maintain Defence members in a high risk exposure area. Additional consideration may be given to seasonal variations in determining the treatment profile. In some areas, due to mosquito life cycles, the actual risk of contracting malaria may be minimal when mosquito counts are low. If indicated, chemoprophylactic treatment may be halted during low risk periods, as directed in the health support plan from the mounting headquarters for the operational deployment, in consultation with the AMI.

Monitoring of Defence members taking malaria chemoprophylaxis

10. During the course of malaria prophylaxis Defence members are to be monitored:

a. **At least once every three months.** All Defence members are to be reviewed by an MO or NP for any adverse drug reaction and compliance with the drug regimen.

b. **At least every six months.** Evaluation of hepatic function should be performed during prolonged prophylaxis with any antimalarial drug.

11. Details of all health reviews are to be recorded on the Defence member's UMR.

Post-deployment eradication

12. Defence members are required to take an eradication course following deployments to malarious areas, except in the following circumstances:

a. deployment to Central Africa, West Africa and Haiti where there is little or no vivax malaria

b. medical contraindications such as Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency or known allergy to primaquine

c. imminent return to a malarious area with continuing use of malaria chemoprophylaxis

d. confirmation of pregnancy (see appendix A4)

e. extremely short (< 7 days) periods in a malarious area when the effective exposure to infected mosquitoes is known to be very low (eg Port Moresby, Papua New Guinea).

Eradication course

13. The eradication course is primaquine phosphate 13.2 mg (7.5 mg base) per tablet, taken as two tablets twice a day (with meals) for two weeks. The intent is to give 30 mg of primaquine base daily for 14 days. Defence members who tolerate primaquine poorly due to gastrointestinal adverse events may receive the same total dosage of medication given by either increasing the frequency of administration (eg 7.5 mg base four times a day instead of 15 mg base twice daily) or spreading the same total dosage of medication over greater than 14 days (eg 15 mg base once daily for 28 days). The eradication course is commenced on the day of departure

from the malarious area. It is taken concurrently with the continuation of chemoprophylaxis (as detailed in paragraph 3).

14. There is no alternative to primaquine for eradication of liver stage parasites. G6PD deficient Defence members are to be informed of the risk of relapsing malaria and advised of the requirement to seek medical care without delay if a fever develops. Some exceptions on primaquine use in G6PD deficient persons exist and expert medical advice needs to be sought prior to any G6PD deficient person being given primaquine or a drug with a known haemolytic potential. AMI must be contacted prior to any administration of primaquine to a person with G6PD deficiency. If a member develops infection with P. vivax or P. falciparum, prophylaxis with doxycycline or chloroquine can also be taken for several months in order to suppress relapses as they occur. For eradication regimes for pregnant women, see appendix A4.

Repeated visits to malarious areas

15. For Defence members making repeated trips to a malarious area, malaria chemoprophylaxis may be modified to minimise the requirement for multiple primaquine eradication courses. The following regimen is to be followed:

a. chemoprophylaxis with doxycycline (for two weeks), Malarone™ (for one-week) or mefloquine (two weeks) as detailed in paragraph 3 following departure from malarious area

b. any intervening febrile episode needs to be investigated as possible malaria

c. two days prior to re-entry into a malarious area recommence chemoprophylaxis as in paragraph 3 (one-week prior in the case of mefloquine to include the three-day loading dose)

d. primaquine eradication should be undertaken upon return to home base for a period longer than 30 days.

Use of antimalarials by Aircrew and Joint Battlefield Airspace Controllers

16. Aircrew and JBAC personnel travelling or deploying to a malarious area for periods longer than one week, are to take antimalarial chemoprophylaxis as follows:

a. Doxycycline is the first-line medication for antimalarial chemoprophylaxis unless contraindicated, unless a significant adverse effect to doxycycline is documented, or unless the Operation Health Support plan directs otherwise. Defence members in aviation related occupations taking doxycycline are to be made Temporarily Medically Unfit (TMU) for an initial full ground trial period of two days. Satisfactory completion of a doxycycline ground trial should be recorded on the front cover of the member's UMR prior to the resumption of flying or controlling duties. Adverse events are similarly to be noted. Defence members having satisfactorily completed an initial doxycycline ground trial have no further TMU requirement for subsequent courses. They are permitted to fly or control aircraft for the duration of their doxycycline chemoprophylaxis

b. Malarone™ (atovaquone/proguanil) is to be offered to Defence members in aviation related occupations who are unable to take doxycycline for the reasons above. Defence members in aviation related occupations taking Malarone™ are to be made TMU for an initial full ground trial period of two days. Satisfactory completion of a Malarone™ ground trial should be

recorded on the front cover of the member's UMR prior to the resumption of flying or controlling duties. Adverse events are similarly to be noted. Defence members having satisfactorily completed an initial Malarone™ ground trial have no further TMU requirement for subsequent courses. They are permitted to fly or control aircraft for the duration of their Malarone™ chemoprophylaxis

c. Chloroquine is no longer used as single chemoprophylaxis agent due to its lack of efficacy and availability.

17. Aircrew and JBAC personnel who inadvertently receive mefloquine (Lariam®) for chemoprophylaxis or must receive it for treatment of malaria are to be classified TMU for four weeks following cessation of drug administration.

18. Primaquine eradication for Aircrew and JBAC personnel. Aircrew and JBAC personnel taking an initial course of primaquine for eradication of liver parasites are to be made TMU for a seven-day ground trial. All personnel must be tested for G6PD and have a documented G6PD level in the normal range before primaquine is prescribed. If no adverse events are noted during the ground trial, personnel may resume flying or controlling duties while completing the remainder of their initial course. Satisfactory completion of a primaquine ground trial should be recorded on the member's UMR prior to the resumption of flying or controlling duties. Adverse events are similarly to be noted. Personnel having satisfactorily completed an initial primaquine ground trial will have no further TMU requirement for subsequent courses. They are permitted to fly or control aircraft for the duration of future primaquine eradication courses.

19. **Repeated visits to malarious areas.** For Aircrew and JBAC personnel making frequent, repeated trips into malarious areas, malaria chemoprophylaxis may be modified to minimise the requirement for multiple eradication courses. The regimen to be used is as follows:

a. continue chemoprophylaxis with doxycycline (for two weeks) or Malarone™ (for one week) as detailed in paragraph 3 following departure from malarious area

b. any intervening febrile episode needs to be investigated as possible malaria

c. two days prior to re-entry into a malarious area recommence chemoprophylaxis as in paragraph 3.

20. If significant adverse events are noted, personnel are to remain TMU while advice is sought from the AMI.

21. Primaquine eradication should be undertaken upon return to home base for a period longer than 30 days.

Pregnancy

22. The risk of using various antimalarial drugs in pregnancy is addressed in appendix A4.

Dependants of serving members posted overseas

23. Adult dependants of members posted overseas to malarious areas should take the same chemoprophylactic agents as recommended for Defence members. They should be encouraged to address these recommendations with their Health Care Provider.

24. Female dependants who are pregnant or considering falling pregnant are to be managed as per appendix A4.

25. Children under 10 years of age require special consideration as doxycycline is contraindicated owing to significant side effects, including permanent discolouration of teeth and bones. It is very difficult to correctly administer malaria chemoprophylaxis to young children and there are very little data supporting the use of chemoprophylaxis drugs in children < 10 kg. Families deploying to high risk malaria areas should give due consideration to options which allow young children to remain in Australia. If chemoprophylactic drugs are to be used in children:

a. For children weighing greater than 11 kg, first line treatment is Malarone™. A paediatric formulation of Malarone™ is available, with tablets containing atovaquone 62.5 mg + proguanil 25 mg. The dosage regimen is based on the child's weight:

   (1) 11–20 kg: one paediatric tablet or one-quarter of an adult tablet daily

   (2) 21–30 kg: two paediatric tablets or one-half of an adult tablet daily

   (3) 31–40 kg: three paediatric tablets or three-quarters of an adult tablet daily

   (4) > 40 kg: one adult tablet daily

b. For newborns up to the age of three months, careful protection against mosquito bites is required, using insecticide-treated mosquito netting and insect repellents.

APPENDIX 7A3

DRUG EFFECTS AND CONTRAINDICATIONS

1. All antimalarial drugs have side effects and contraindications and are tolerated differently by different people. They should all be taken with food and water to avoid side-effects and to ensure optimum absorption from the gastrointestinal tract.

2. **Doxycycline.** In general, doxycycline should be used as first-line malarial prophylaxis in Defence. Tetracyclines are safe to use and have been used long-term by millions of people for treatment of acne. Possible side effect issues include:

a. Gastrointestinal intolerance which can usually be minimised by taking doxycycline with food and plenty of fluids and not lying down within one-hour after taking the drug

b. Tetracycline photosensitivity mediated in the long wavelength of the ultraviolet spectrum. Broad-spectrum sunscreens should be used with a sun protection factor of at least 30

c. Superinfection with non-susceptible organisms resulting in enterocolitis or monilial overgrowth in the anogenital region. If this occurs, appropriate treatment should be instituted and a change to alternative prophylaxis is warranted

d. Increased intracranial pressure can be a very rare adverse event associated with the use of tetracyclines. Anyone complaining of a new headache after starting doxycycline prophylaxis should be examined carefully for decreased visual acuity and papilloedema. The outcome is generally good if the condition is recognised early, before vision has been seriously affected

e. Drug interactions may be seen with antacids containing aluminium, calcium or magnesium, iron preparations, penicillins, warfarin and methoxyflurane at anaesthetic doses. Penthrane (methoxyflurane) inhalers in first aid situations can be used concurrently with doxycycline

f. Oral contraceptive pill interactions. Females who use oral contraception should be advised of possible failure in contraception or menstrual control and advised to use an alternative form of contraception. Additionally, there are adverse side effects on the foetus with doxycycline use during pregnancy (see appendix A4).

3. **Malarone™ (atovaquone/proguanil).** Few side effects have been reported so far, although gastrointestinal intolerance may be common when taking treatment courses requiring four times the chemoprophylaxis dose. Neuropsychological symptoms are infrequent and no more common than with doxycycline. Neurocognitive testing by three laboratories revealed no adverse effects following Malarone™ administration.

4. **Mefloquine (Lariam®).** Mefloquine has been taken by over 20 million people worldwide. Since mefloquine is the only drug that can be taken weekly to prevent drug-resistant falciparum malaria, compliance is likely to be better under operational conditions which are not conducive to daily medication. If a person has tolerated mefloquine chemoprophylaxis previously, it is nearly unknown that they would subsequently have severe adverse events when mefloquine is again used for chemoprophylaxis at appropriate dosages. Possible side effect issues with mefloquine are:

a. **Frequently reported adverse events.** The most frequently reported adverse events are nausea, vomiting, loose stools, abdominal pain, dizziness, loss of balance, headache, and sleep disorders including very vivid dreams. These are usually mild and will often manifest themselves during the initial three-day loading dose. These symptoms often decrease or disappear with continued use

b. **Neuropsychological.** The main problem with mefloquine is that severe neuropsychological effects have been observed in a very small proportion of people taking the drug:

(1) **Mild symptoms.** Complaints of dizziness, sleeplessness, strange or vivid dreams, or anxiety may be reported by about one-third of patients using the drug. Women travellers with a low body mass index report more neuropsychological effects in controlled as well as questionnaire-based studies. For this reason, women should be made aware that they are at greater risk than men of developing neuropsychological problems with mefloquine use

(2) **Severe symptoms.** Gross evidence of neurotoxicity is rare in travellers on mefloquine prophylaxis. More severe events, such as seizures and psychoses, are more common in individuals with a previous history of psychiatric disease. This implies that every effort should be made to identify individuals with a strong risk of relapse following mefloquine use and prescribe alternative malaria prophylaxis for them. Mefloquine should not be given to individuals with active depression, a recent history of depression, generalised anxiety disorder, schizophrenia or other major psychiatric disorders, or with a history of convulsions. If acute anxiety, depression, restlessness or confusion occur during prophylaxis, these could be prodromal for a more serious event. In these cases mefloquine should be discontinued immediately and an alternative drug should be substituted. Because of the long half-life of the drug, adverse reactions to mefloquine may persist for several weeks after the last dose

(3) Caution should be exercised with regard to activities requiring alertness and fine motor coordination such as driving and operating machinery. Mefloquine is not approved for use by Aircrew and Joint Battlefield Airspace Controllers personnel.

5. **Primaquine.** Primaquine must not be used in Defence members with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency except in specific circumstances as detailed in annex A, appendix 2, paragraph 14. Possible side effect issues in those with normal G6PD levels are:

a. it can cause gastrointestinal distress that may be severe and may be potentiated by the concurrent use of chloroquine. Taking primaquine with food usually minimises gastrointestinal adverse events

b. as for all derivatives of quinine, photosensitivity is possible

c. Methaemoglobinaemia is a known adverse event, although its clinical significance is uncertain.

6. **Chloroquine.** Chloroquine is generally well tolerated but of very limited availability in Australia. Side effects include headache, dizziness and gastrointestinal upset. Long-term use (greater than five years continuous malaria prophylaxis) or 100g cumulative dose has been associated with the development of eye problems (deposits on the retina).

APPENDIX 7A4

PREVENTION OF MALARIA AND PREGNANCY

1. The risks to both the prospective mother and the foetus are significantly increased when pregnancy is complicated by malaria. Malarial parasites have the ability to concentrate in placental tissue resulting in reduced blood flow through the placenta and a high likelihood of miscarriage or stillbirth. Surviving offspring are likely to have low birth weights with an associated risk of neonatal death. There is also an increased risk of maternal death. Chemoprophylactic drugs also may pose a significant risk to the foetus.

2. Therefore no chemoprophylactic drug regimen is suitable for use in pregnancy unless the risk of contracting the disease outweighs the risk for foetal complications due to medication use. In general, pregnant women should avoid any travel to malarious areas. Should the need arise, each case should be reviewed individually in consultation with the Army Malaria Institute and obstetric specialist, to determine risk versus benefit.

3. Women of childbearing age are to be managed as follows:

a. Posting to malarious areas. Pregnant servicewomen are not to be posted to malarious areas

b. Servicewomen planning pregnancy during or after posting to a malarious area. Servicewomen should strongly consider not falling pregnant whilst overseas in a malarious area and consistently use a reliable means of contraception

c. Servicewomen who become pregnant while in a malarious area. Servicewomen who become pregnant during deployments or postings to malarious areas are to be evacuated out of the area at the earliest opportunity. Pending evacuation, maximum effort needs to be made to protect the individual from exposure to malaria vectors. Specific issues related to pregnancy in a malarious area are addressed in this policy. DHM Vol 2 Part 9 Chapter 3[77] —Management of pregnant members in the Australian Defence Force provides general guidance on the administrative management of pregnant service women.

4. Joint Health Command recommends that pregnant women avoid travelling to or residing in malarious areas. Dependants of members posted overseas to malarious areas should strongly consider not falling pregnant, or may consider returning to Australia in the event of pregnancy, due to the risk of malaria complications and the side effect of chemoprophylactic medications. Pregnant dependants who choose to travel to or reside in a malarious area, do so at their own risk.

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Prevention

5. If a dependant who is pregnant or is planning pregnancy elects to travel to or reside in a malarious area, strict precautions should be taken to reduce the risk of developing malaria by preventing mosquito bites. Care should be taken not to exceed the recommended dosage of insect repellents.

6. **Chemoprophylaxis.** It is recommended that women taking malaria chemoprophylaxis avoid becoming pregnant. However, should a woman become pregnant and not be able to be removed from a high exposure risk area, the use of chemoprophylaxis during pregnancy may be justified if the small risk to the foetus is outweighed by the benefit to the mother and the foetus. It is preferable to avoid all antimalarials during the first trimester. However, if necessary the following guidelines may help determine treatment:

a. The following prophylaxis may be taken during pregnancy with caution although both drugs are listed as category D drugs for pregnancy (drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage):

(1) Chloroquine has been associated with a small risk for neurologic disturbances in the foetus; however, it has been used more than any other antimalarial in pregnancy both for prophylaxis and treatment and its use may be justified if the risk for malaria is high. Chloroquine is no longer routinely available in Australia

(2) Mefloquine™ may be given safely during the second and third trimester, but there is limited information on its safety during the first trimester and the drug may cause serious birth defects during this period

b. The following drugs are either not safe to take during pregnancy or there is insufficient information available to assess their safety. Therefore pregnant women should NOT take the following medications, except for specific use in the case of pending evacuation from the malarious area in accordance with paragraph 9:

(1) Doxycycline should not be used in any phase of pregnancy or while breastfeeding due to the potential of permanent staining of bones and teeth

(2) **Malarone™.** The individual components have been safely used during pregnancy, however, there is not enough information or experience to recommend the use of the drug combination during pregnancy

(3) **Primaquine.** Since it is not possible to ascertain foetal Glucose-6-Phosphate Dehydrogenase status, eradication courses of primaquine should not be given to women until after delivery

(4) Mefloquine™ during the first trimester.

7. In particular, pregnancy should be avoided for three months after stopping mefloquine and one week after stopping doxycycline due to the potential of drug induced foetal malformations.

Confirmation of pregnancy

8. Pregnant dependants who remain in a malarious area while pregnant should continue to take malaria chemoprophylaxis, except for where the medication is contraindicated, as per paragraph 6.b. A servicewoman who becomes pregnant while taking malaria chemoprophylaxis should be evacuated from the malarious area as soon as possible.

9. Pregnant women should cease chemoprophylaxis as follows:

a. Mefloquine™ should be continued until four weeks post deployment if evacuation occurs in the short-term

b. Doxycycline should be stopped on confirmation of pregnancy due to its ability to stain developing teeth and bones. The expectant mother is to be informed of the risk of malaria versus the unknown risk of drug induced teratogenicity. Unless the risk of exposure to malaria is very high, such as for sub-Saharan Africa, discontinuation of chemoprophylaxis may be appropriate pending removal from the endemic area

c. **Malarone™.** There is little data on the use of Malarone™ during pregnancy but the component drugs are thought to be relatively safe for short-term use during pregnancy. Medication with Malarone™ should cease on return to Australia.

10. **Eradication program.** Primaquine is unsafe for pregnant women and there is no alternative to primaquine for eradication of liver stage parasites. Pregnant women are to be informed of the risk of relapsing malaria, the possibility of fever-induced premature labour, and advised of the requirement to seek medical care without delay if symptoms of malaria develop. If an eradication program is considered it should not be administered until after delivery. If vivax malaria develops or there is a high risk of an adverse outcome to the pregnancy, such as preterm labour, weekly chloroquine suppression should be taken during the remainder of the pregnancy and a primaquine eradication regimen taken post-delivery, as defined in annex A, appendix 2, paragraph 13.

11. In all cases the mother is to be informed that the newborn should be checked within the first week of life for congenital malaria, which is a risk in any women known to have had malaria parasites at any time during pregnancy.

ANNEX 7B

DIAGNOSIS OF MALARIA

1. Malaria is one of the most common endemic diseases of tropical and subtropical areas. It is characterised by fever primarily in the acute and sub-acute stages. More chronic infections may present with anaemia and splenomegaly. However, as one or more organ systems may be involved, malaria can have other clinical presentations and an incorrect diagnosis may be made. Consequently, malaria must always be considered in the diagnosis of any illness occurring in a person in a malarious area, or who has visited a malarious area within the past year.

2. It is imperative to make an early diagnosis because any delay can be fatal, especially if the patient is infected with falciparum malaria. Since treatment varies according to the type of malaria, species diagnosis should be established as soon as possible. If there is any doubt about species identity, presumptive treatment for falciparum malaria should be started without delay.

3. Definitive parasitological diagnosis is usually established by examining suitably prepared thick and thin blood films. Competence and experience are required in the assessment of these films, as the number of parasites may be low and morphology variable. Since parasites may not be present in the peripheral blood at the time that the slide is taken, another slide should be examined 24 hours later. Skilled staff using light microscopy may make rapid estimates of the level of parasitaemia, the level of anaemia and the presence of other blood parasites. The quality of the blood slides is very important in reaching a correct diagnosis. In some instances, poor technique or inexperienced personnel reading the slides may compromise the accuracy of reporting. Allowances should be made for this and, if necessary, multiple repeated slides should be examined over two–three days.

4. Parasitological Diagnosis can also be performed using malaria Rapid Diagnostic Test (RDT) devices when accurate diagnosis by microscopy is not available. These immunochromatographic tests for detecting specific malaria antigens are less time consuming and require less training than malaria microscopy. Hence, they are especially useful during field deployments or when peripheral medical facilities are not supported by a laboratory. At least 50 branded RDTs and 150 different products are now commercially available; some of them detect Plasmodium falciparum (P. falciparum) only, while others detect P. falciparum plus one or more other plasmodial species, or pan Plasmodium species. The major target antigens in RDTs for P. falciparum are histidine rich protein 2 (PfHRP2), lactate dehydrogenase (pLDH), and aldolase, while target antigens for P. vivax and pan plasmodium are LDH and aldolase. Compared to thick film microscopy, good quality RDTs show a similar sensitivity in detecting P. falciparum but most are less sensitive in detecting P. vivax.

5. Several issues associated with using malaria RDTs should be noted:

a. The quality (sensitivity, specificity, heat stability) of RDTs varies significantly. World Health Organisation (WHO) tests and updates the test results of a large number of RDT products providing a guide for procurement of RDTs. Several RDTs demonstrated consistent detection of malaria at low parasite densities (200 parasites/microlitre), have low false positive rates, are stable at tropical temperatures, are relatively easy to use, and can detect P. falciparum, P. vivax infections, or both. These quality RDTs will be catalogued and are to be used. Prior to cataloguing, advice may be sought

from the Directorate of Health Materiel Logistics and Pharmacy in Joint Health Command

b. Like microscopy diagnosis, a negative test result does not always exclude malaria with certainty as there may be insufficient parasites to register a positive result. If necessary multiple repeated tests should be examined over two–three days

c. The HRP2 antigen is not present in a high proportion of P. falciparum in South American countries. HRP2 detecting RDTs should not be used for diagnosing P. falciparuminfections for personnel deployed to or returned from South American countries

d. Since the HRP2 antigen can persist in patients' blood for several weeks after elimination of parasitised red blood cells, HRP2-based RDTs are not suitable for monitoring treatment outcomes

e. Appropriate further investigation of all negative cases should be considered

f. A quality assurance program is recommended, which involves testing the RDT kits upon receipt and periodically during the storage period (some kits require transport and storage at 4° Centigrade)

g. The used RDTs may serve as a source of parasites for verification of diagnosis by genetic amplification tests. A guide for use of malaria RDTs is available in WHO website[78].

6. **Clinical manifestations.** In situations where a laboratory capability is not available Medical Officers and Nurse Practitioners will be required to make a diagnosis based on symptoms alone. The first symptoms of malaria are non-specific: the lack of a sense of wellbeing, headache, fatigue, abdominal discomfort and muscle aches followed by fever. In some instances, a prominence of headache, chest pain, abdominal pain, arthralgia, myalgia, or diarrhoea may suggest another diagnosis. Although the headache may be severe in malaria, there is no neck stiffness or photophobia resembling that in meningitis. While myalgia may be prominent, it is not usually severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common.

7. The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, represent a relatively unusual initial manifestation and suggest infection with P. vivax or P. ovale. The fever is irregular at first (that of falciparum malaria may never become regular); the temperature of non-immune individuals and children often rises above 40 degrees centigrade in conjunction with tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalised seizures are specifically associated with falciparum malaria and may herald the development of cerebral disease.

8. Many clinical abnormalities have been described in acute malaria, but most patients with uncomplicated infections have few abnormal physical findings or symptoms other than fever, malaise, mild anaemia and (in some cases) a palpable

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[78] Use of Malaria Rapid Diagnostic Tests

http://www.rollbackmalaria.org/toolbox/tool_Use OfMalariaRDTs.html.

spleen. Anaemia is quite common among young children living in areas with stable transmission, particularly where there is parasite resistance to chloroquine or other drugs. Splenic enlargement is very common among otherwise healthy individuals in malaria-endemic areas and reflects repeated infections; however, in non-immune individuals with malaria, the spleen takes several days to become palpable. Slight enlargement of the liver is also common, particularly among young children. Mild jaundice is common among adults; it may develop in patients with otherwise uncomplicated falciparum malaria and usually resolves over two to three weeks.

9. Malaria is not associated with a rash like those in meningococcal septicaemia, typhus, enteric fever, viral exanthemas, and drug reactions. Petechial haemorrhages in the skin or mucous membranes (features of viral hemorrhagic fevers and leptospirosis) develop only rarely in severe falciparum malaria.

10. **Cerebral malaria.** Coma is a characteristic and ominous feature of falciparum malaria. Cerebral malaria manifests as a diffuse symmetric encephalopathy; focal neurologic signs are unusual. Although some passive resistance to head flexion may be detected, signs of meningeal irritation are lacking. The eyes may be divergent and pout reflex is common, but other primitive reflexes are usually absent. The corneal reflexes are preserved except in deep coma. Muscle tone may be either increased or decreased. The tendon reflexes are variable, and the plantar reflexes may be flexor or extensor; the abdominal and cremasteric reflexes are absent. Flexor or extensor posturing may be documented. Approximately 15 per cent of patients have retinal haemorrhages; with pupillary dilatation and indirect ophthalmoscopy, this figure increases to 30 to 40 per cent. Other fundoscopic abnormalities include discrete spots of retinal opacification (30–60 per cent) papilloedema (eight per cent among children, rare among adults), cotton wool spots (less than five per cent), and decolourisation of retinal vessels or segment of vessels (occasional cases). Convulsions, usually generalized and often repeated, occur in up to 50 per cent of children with cerebral malaria. More covert seizure activity is also common, particularly among children, and may manifest as repetitive tonic-clonic eye movements (see Harrison's Principles of Internal Medicine[79], 18th edition).

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[79] Harrison's Principles of Internal Medicine, 18th edition
http://accessmedicine.mhmedical.com/book.aspx?bookId=331

ANNEX 7C

MALARIA TREATMENT REGIMENS

1. Patients with uncomplicated malaria can be treated as inpatients or outpatients, with careful monitoring of their response to treatment, by both clinical and parasitological examination, with follow-up of the level of parasitaemia until no parasites are detected in thick blood films. Asplenic patients should be monitored carefully as in-patients, as they may develop complications suddenly.

Treatment of vivax malaria

2. The primary regimen for treating vivax malaria is:

a. Artemether 20 mg + lumefantrine 120 mg per tablet (Riamet®). Four tablets followed by four tablets at eight hours, 24 hours, 36 hours, 48 hours and 60 hours (total dose = 24 tablets). Each dose to be taken immediately after food

b. Chloroquine is no longer routinely used for vivax malaria due to likelihood of resistant parasites from Melanesia and limited availability of the medication.

3. Alternative regimens are:

a. Atovaquone 250 mg + proguanil hydrochloride 100 mg per tablet (Malarone™).Four tablets taken once a day for three consecutive days, followed by a primaquine eradication course. The daily dose of Malarone™ should be taken with food or a milky drink at the same time each day

b. Mefloquine hydrochloride 250 mg base per tablet (Lariam®). Three tablets followed by two tablets six to eight hours later, followed by a primaquine eradication course. Although an approved treatment for vivax malaria, the potential for neuropsychiatric adverse events when giving treatment dosages of mefloquine makes this regimen the least preferred option which should not be used without specialist consultation.

Treatment of falciparum malaria

4. The primary regimen for treating falciparum malaria is:

a. Artemether 20 mg + lumefantrine 120 mg per tablet (Riamet®). Four tablets followed by four tablets at eight hours, 24 hours, 36 hours, 48 hours and 60 hours (total dose = 24 tablets). Each dose to be taken immediately after food.

5. Alternative regimens are:

a. Atovaquone 250 mg + proguanil hydrochloride 100 mg per tablet (Malarone™).Four tablets once a day for three consecutive days. The daily dose should be taken with food or a milky drink at the same time each day

b. Mefloquine hydrochloride 250 mg base per tablet (Lariam®). Three tablets followed by two tablets six to eight hours later, with careful observation for any neuropsychiatric effects. Although an approved treatment for falciparum malaria, the potential for neuropsychiatric adverse events when giving treatment dosages of mefloquine makes this regimen the least preferred option which should not be used without specialist consultation.

Treatment of severe or complicated malaria

6. Severe or complicated malaria is a medical emergency which requires urgent treatment. Whenever possible, specialist physician advice should be sought, as in addition to the possibility of falciparum-induced cerebral malaria, severe malaria is associated with shock, hyperthermia, hypoglycaemia, electrolyte imbalance, pulmonary oedema, severe diarrhoea and renal failure. Careful monitoring of appropriate parameters should be initiated and suitable corrections made. Most of the cerebral malaria patients who die, do so in the first 24–48 hours necessitating very rapid institution of effective treatment. Intravenous artesunate is the treatment of choice for severe malaria. Artesunate is available through the Therapeutic Goods Administration Special Access Scheme.

7. Artesunate is of limited availability outside large hospitals in capital cities and its quality from developing world sources outside of Australia cannot be guaranteed. Lack of artesunate should not delay treatment if the less preferred intravenous quinine is the only medication available. Patients suffering severe or complicated malaria should be evacuated as soon as possible to an appropriate medical facility, equipped to monitor and manage medical emergencies. The treatment of severe or complicated malaria includes:

a. Intravenous (IV) artesunate. 2.4 mg/kg IV immediately and then repeated at 12 and 24 hours. Daily intravenous doses 2.4 mg/kg should continue to be given until the patient can tolerate oral medications

b. Intravenous (IV) quinine (Quinine dihydrochloride six per cent) may be given if artesunate is unavailable but it is definitely second choice as controlled trials have demonstrated clear artesunate superiority when both artesunate and quinine have been tested together. Cardiac monitoring in an intensive care unit is necessary when infusing quinine. Total doses of quinine should not exceed 2000 mg over a 24-hour period:

   (1) Loading dose of 20 mg/kg (up to a maximum of 1400 mg) diluted in 10 mL/kg of five per cent Dextrose solution or normal saline infused slowly over four hours. As a guide, Quinine dihydrochloride six per cent injection vials is presented as 600 mg/10 mL and should be diluted in 500 mL of five per cent Dextrose solution or normal saline. A loading dose is not required if antimalarials have been given during the previous 24 hours

   (2) Maintenance dose of 10 mg/kg (up to a maximum of 700 mg) diluted in 10 mL/kg of normal saline or five per cent Dextrose solution infused slowly every eight to 12 hours until the patient can tolerate oral medication. The maintenance dose should be commenced eight to 12 hours after the loading dose

   (3) If IV quinine is required for more than 48 hours the maintenance dose of quinine should be reduced to 5 mg/kg to avoid accumulation

c. Artemether 20 mg + lumefantrine 120 mg per tablet (Riamet®). Should be given once the recovered patient can tolerate oral medications in order to complete curative treatment. Four tablets followed by four tablets at eight hours, 24 hours, 36 hours, 48 hours and 60 hours (total dose = 24 tablets). Each dose to be taken immediately after food.

8. In an emergency field situation when no intravenous medications are available, there is limited information indicating that crushed antimalarials delivered by nasogastric tube to a comatose patient may work but it is only to be considered as an emergency intervention to be used when there are no other options.

Drug side effects and contraindications

9. **Chloroquine.** Minor side effects such as headache, dizziness and gastrointestinal disturbances may occur. Pruritus is relatively more common in dark-skinned patients. There have been rare reports of toxic epidermal necrolysis, erythema multiforme and Steven-Johnson syndrome.

10. **Riamet®.** Symptoms and side effect issues associated with malaria treatment include:

a. Headache, dizziness, sleep disorders, abdominal pain and nausea. They are usually mild in nature and not necessarily related to treatment with the drug, but to the underlying disease

b. Since a fatty meal greatly enhances the absorption of both components of Riamet®, patients should be encouraged to take their medication with food as soon as they can tolerate it

c. Riamet® should not be given to patients who are taking any drug that inhibits cytochrome enzyme CYP3A4 (eg erythromycin, ketoconazole, cimetidine) or cytochrome enzyme CYP2D6 (eg flecainide, metoprolol, imipramine). Other contraindications include the concurrent or recent use of drugs such as quinine, quinidine or halofantrine, which prolong the QT interval.

ANNEX 7D

NOTIFICATION AND SAMPLES REQUIRED BY THE ARMY MALARIA INSTITUTE

1. Malaria is a notifiable disease in all states and territories of the Commonwealth of Australia. In addition to the requirement for Joint Health Command Medical Officers and all Australian Defence Force health facilities to comply with the requirement for reporting malaria, as detailed in DHM Vol 2 Part 3 Chapter 14[80] — Notifiable Condition Reporting in the Australian Defence Force, all confirmed or suspected malaria cases in Defence members or their dependants (whilst on posting to malarious areas) must be reported to the Army Malaria Institute (AMI).

2. If a febrile illness is confirmed to be malaria, treatment is to be initiated immediately and AMI is to be contacted without delay. All available information is to be provided on Form PM 040[81]—Central Malaria Register and the partially completed Form PM 040 faxed to AMI on (07) 3332 4800. After the completion of treatment, the remaining sections of the form are to be completed and the hard copies forwarded by mail or Signals Dispatch Service. AMI will distribute Form PM 040 according to current directives. Form PM 040 is also to be completed in all cases of febrile illness in Defence members who are located in, or have recently returned from a malarious area. Assistance with the completion of this form can be obtained from clinical staff at the AMI by contacting the Institute on (07) 3332 4801 during office hours or 0411 024 289 after office hours.

3. Where practicable, two stained and two unstained thick and thin blood films taken prior to treatment are to be sent to AMI (accompanied by Form PM 527–2[82]— Pathology Request) to confirm malaria infection and species diagnosis. The blood is best obtained prior to any treatment, but if that is not possible, indicate at what time post medication (eg post four-hour) the blood was obtained.

4. Contact AMI for assistance with technical aspects of correct preparation of thick and thin blood films. Assistance with technical aspects of correct preparation of thick and thin blood films may be accessed at the following site:

CDC - DPDx[83]

5. Any Immunochromatographic Rapid Diagnostic Test used in the diagnosis is also to be forwarded to AMI.

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[80] DHM Vol 2 Part 3 Chapter 14

http://intranet.defence.gov.au/home/documents/data/ADFPUBS/DHM/volume2/part3/14.PDF

[81] Form PM 040

http://intranet.defence.gov.au/cgi-bin/hive/hive.cgi/PM040.itp?HIVE_SESSION=tnrehbbigsqn/127.0.0.1&HIVE_PROD=0&HIVE_REQ=2001&HIVE_REF=hii%3a22801&HIVE_RET=ORG/PM040.itp

[82] Form PM 527-2

http://intranet.defence.gov.au/cgi-bin/hive/hive.cgi/PM527-2.itp?HIVE_SESSION=tnrehbbigsqn/127.0.0.1&HIVE_PROD=0&HIVE_REQ=2001&HIVE_REF=hii%3a22865&HIVE_RET=ORG/PM527-2.itp

[83] CDC – DPDx http://www.cdc.gov/dpdx/

6. All samples are to be labelled with the patient's details and the time and date of collection.

7. Blood films are to be sent by courier according to standard International Air and Transport Association guidelines.

8. If further diagnostic uncertainty exists, blood samples can be tested using molecular methods (polymerase chain reaction or Polymerase Chain Reaction) at AMI. A microtainer of citrate or heparin or Ethylenediaminetetraacetic acid anti-coagulated blood is preferred. Alternatively, a drop of blood can be spotted on a filter paper, air dried and sent in a plastic bag. Both microtainer and filter paper can be sent to AMI at room temperature, or at 4 degrees celsius.

9. The address for consigning samples is:

Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4051

10. Microscopy results will be available to clinicians within 24 hours of receipt of blood films, to enable them to modify clinical management, if necessary. Even when clinical laboratory staff are confident of species diagnosis, blood smears are to be forwarded to AMI for confirmation.

ANNEX 7E

BACKGROUND INFORMATION ON MALARIA

Life cycle

1. An infective female Anopheles mosquito, while feeding, injects sporozoites into the blood stream of the host. The sporozoites circulate for a short time before entering the liver cells (hepatocytes), where they multiply asexually, forming numerous merozoites. After about one week (rarely up to four weeks) parasites are released from the liver into the blood stream and invade red blood cells. These intra-erythrocytic parasites undergo multiplication by asexual division over the next 48 hours, eventually rupturing the red cells and rapidly re-invading other healthy red cells.

2. After one or two asexual blood cycles, parasite densities reach the pyrogenic threshold of 10–100 parasites per microlitre of blood. This usually manifests itself by the onset of chills and fever lasting several hours. Fever usually subsides with the onset of sweating, but recurs every time more parasites are released from red cells. Asexual parasite maturation is often synchronous, accounting for the characteristic pattern of chills and fever every second day. It is unusual for a non-immune Defence member who has a genuine malaria infection not to be quite ill with a high fever unless the Defence member has been partially treated previously to suppress parasitemia.

3. Sexual differentiation of intra-erythrocytic parasites leads to the formation of male and female gametocytes, which can be taken up by an Anopheles mosquito feeding on the infected person. Fertilisation in the stomach of the mosquito leads to the formation of ookinetes. These invade the body of the mosquito forming an oocyst on the stomach wall. Sporozoites develop within the oocysts and eventually, after rupture of the oocyst, pass to the salivary glands to be stored. The sporozoites are injected into another host when the mosquito next feeds, and so the cycle continues.

Types of malaria

4. There are four types of human malaria, the two most common being:

a. **Falciparum malaria.** Falciparum malaria can progress rapidly to cause illness with complications, including cerebral malaria, which is often fatal. There are no residual liver stages with this type of malaria and, once eradicated from the blood, there are no relapses

b. **Vivax malaria.** Vivax malaria causes acute disease or chronic disability. While not usually fatal, this type often develops residual liver stages (hypnozoites) which remain dormant for weeks or months after initial treatment of the disease. These liver stages can cause further acute episodes of malaria or relapses whenever they awaken, producing a large number of parasites, which are then discharged from the liver into the blood stream.

5. Other types of malaria include ovale and malariae. These are much less common than falciparum or vivax malaria. Ovale and malariae malaria may persist for a number of years, similar to vivax malaria.

Epidemiology

6. Malaria is endemic or epidemic in most tropical regions, including many countries close to Australia. Saibai Island in the Torres Strait is within sight of highly malaria endemic areas.

7. In endemic areas (see World Health Organisation, International Travel and Health Publication 2012[84]) inhabitants develop a degree of immunity to the disease. If malaria transmission is intense throughout the year, most Indigenous adults are able to develop sufficient immunity to suppress high levels of parasitaemia and severe clinical disease. Malaria immunity is rapidly lost in those leaving an endemic area. In malarious areas with lesser, seasonal, focal or otherwise erratic transmission, symptomatic infections are more common. Malaria endemicity may alter with events such as military hostilities, population movement, climatic changes, tsunamis, deforestation, agricultural practices and other forms of land development, and urbanisation.

8. International air travel may introduce malaria into areas from which it has been previously eradicated or never existed. Such cases are often misdiagnosed. This so-called 'imported malaria' may be caused by a primary case (with the parasite contracted overseas) or a secondary case (contracted locally). Secondary cases may be due to an introduced Anopheles mosquito carrying the parasite, local Anopheles mosquitoes infected from recently arrived travellers with malaria, or malaria-infected blood (transfusions, shared needles, etc).

Parasite resistance

9. Parasite resistance to available antimalarials continues to be a problem in both the prophylaxis and treatment of malaria. None of the current drugs or drug combinations provides absolute protection. For this reason, use of prophylactic medication forms only part of the risk management of malaria. The most important aspect of malaria risk management is avoidance of exposure to the vector mosquito.

10. The prevalence and degree of parasite resistance to different drugs varies considerably from area to area. Consequently, Defence personnel can become ill with malaria despite compliance with chemoprophylaxis. This emphasises the importance of early, correct diagnosis and adequate follow-up in the management of malaria.

11. Due to the possibility of drug-resistant falciparum malaria or relapsing vivax malaria, personnel returning from malarious areas who develop any illness, especially with a fever, should advise their doctor of their recent travel. Acute attacks of falciparum malaria will occur within a few weeks after return from overseas. On the

[84] WHO International Travel and Health Publication http://www.who.int/ith/en/

other hand, the first episode of vivax malaria may occur more than a month, several months, or even more than a year following departure from a malarious area.

12. The world distribution of malaria is available in Centre for Disease Control and Prevention. Travellers' Health at: Malaria - Chapter 3 - 2016 Yellow Book | Travelers' Health | CDC[85].

[85] Malaria – Chapter 2 – 2016 Yellow Book
http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria

ANNEX 7F

USEFUL MALARIA LINKS

1. Up-to-date references for areas of malaria endemicity and resistance can be obtained from:

a. The Army Malaria Institute
http://drnet.defence.gov.au/vcdf/AMI/Pages/Welcome.aspx

b. The Joint Health Command
http://drnet.defence.gov.au/VCDF/JHC/pages/Home.aspx

c. The Centre for Disease Control and Prevention, 'Yellow Book'
http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014

d. World Health Organisation, International Travel and Health Publication 2012
http://www.who.int/ith/en/

e. Therapeutic Guidelines: Antibiotic (2010) version 14. Therapeutic Guidelines Ltd, Melbourne, Australia http://etg.tg.com.au/ip/desktop/index.htm

f. World Health Organisation: World Malaria Report 2015
http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf?ua=1

g. World Health Organisation: Guidelines for the treatment of malaria, Third edition, 2015
http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1

h. World Health Organisation: Malaria Rapid Diagnostic Test Performance Results of WHO product testing of malaria RDTs: Summary Rounds 1–3 (2008–2011) http://www.who.int/tdr/publications/tdr-research-publications/rdt3_summary.pdf

CHAPTER 11

GOVERNANCE

INTRODUCTION

11.1 Health governance ensures that health care conforms to relevant standards and guidelines. Commander Joint Health (CJHLTH) is the technical control authority for health materiel and is responsible for clinical governance. In addition to the supply chain governance structure, CJHLTH manages a health materiel governance system that comprises the following:

a. materiel integrity

b. health materiel committees

c. internal and external audit

d. stocktaking.

MATERIEL INTEGRITY

Health policy and procedures

11.2 CJHLTH issues health policy and procedures governing health materiel. All health practitioners must comply with health policy. Health policy includes the following:

a. Health policy that applies to the administration of the Australian Defence Force (ADF) is issued as a Defence Instruction (General) or a Defence manual.

b. Technical health policy, which applies only to health personnel, is issued as a health manual, health directive or health bulletin. Health manuals and directives promulgate enduring health policy. Health bulletins disseminate health policy that is short-term in nature.

c. Defence health doctrine and procedures provide general and technical health information for health personnel, commanders and staff deploying on operations.

11.3 Defence health practitioners are also to comply with community standards of practice, including standards, professional guidelines, codes of ethics and practice guidelines.

11.4 Services, Groups and Commands must ensure that health facilities have written procedures governing the implementation of health policy and the day-to-day management of health materiel.

Defective or substandard materiel

11.5 Health facilities and logistics elements must report all defective or unsatisfactory materiel in accordance with the Technical Regulatory Framework. Personnel who identify a Category 1 defect are to report the defect by raising **Form AC466**[91]—'Report on Defective or Unsatisfactory materiel (RODUM)—Land'. Any

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[91] http://intranet.defence.gov.au/webforms/form?ac446

user can raise a RODUM through the **RODUM website**,[92] or via web form submission by fax, phone (hotline) and message

11.6 Health facilities must report defective or substandard materiel promptly to enable promulgation of information, initiation of remedial action such as emergency recall, and provision of advice.

Incident reporting

11.7 Health incidents. Health practitioners must report health incidents with an actual or potential adverse outcome using **Sentinel**[93] and **Form AD441**[94]—'Health Incident Report'. If there is an incident that may also give rise to a claim against Defence for negligent advice or medical malpractice, the health practitioner must also complete a **Form AD088**[95]—'COMCOVER Notification Record' and forward the form to the Defence Insurance Office along with any documentation and correspondence (such as a letter of demand) relating to the incident.

11.8 **Pharmacy incidents.** In addition to the reporting requirements listed above, a pharmacist must also record pharmacy incidents in FRED Dispense (see Chapter 3—'Systems') using patient notes. Pharmacy incidents include administering or supplying incorrect medication, incorrect dosage of a medication or dispensing errors.

11.9 **Notifiable incidents.** Health practitioners must report all notifiable incidents in accordance with **Defence Instruction (General) Administrative 45–2**[96]—'Incident reporting and management'.

Adverse drug reaction reporting

11.10 Health practitioners must report actual and suspected adverse drug reactions to both the Therapeutic Goods Administration (TGA) and Joint Health Command (JHC).

11.11 The TGA manages the Australian Adverse Drug Reporting System. The **TGA website**[97] contains information on reporting adverse drug reactions to the TGA. If a health practitioner is unsure of the reporting requirement, they must contact the JHC Directorate of Health Materiel.

11.12 JHC monitors adverse drug reactions, particularly to vaccines and to drugs that are relevant to operational deployments. In addition to the substances listed on the TGA website, Defence health practitioners must notify the Directorate of Health Materiel Logistics and Pharmacy (DHMLP) of any adverse reaction to vaccines or drugs with a specific relevance to operations. Defence health practitioners must also notify DHMLP when a RODUM report relates to an adverse reaction to a particular medicine. All reports are to be submitted via email using the **Report of suspected**

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[92] http://vbmweb.sor.defence.gov.au/rodum

[93] http://whs.eas.defence.mil.au/sentinel.htm

[94] http://intranet.defence.gov.au/webforms/form?ad441

[95] http://intranet.defence.gov.au/webforms/form?ad088

[96] http://intranet.defence.gov.au/home/documents/data/ADFPUBS/DIG/_INTERIM%20DI%20ADMIN%2045_2.pdf

[97] http://www.tga.gov.au

adverse reaction to medicines or vaccines[98] (the 'Blue Card') to both of the following:

a. the Therapeutic Goods Administration[99]

b. DHMLP[100] in JHC.

COMMITTEES AND STAKEHOLDERS

Committees

11.13 CJHLTH has established a health materiel committee structure to manage governance, standards and performance outcomes. The committees enable consultation between the capability coordinator, stakeholders, enabling organisations and customers. The committees also provide a conduit for technical control and clinical authority between JHC, regions and local health care providers. Figure 11.1 depicts the health materiel committee structure.

11.14 **Joint Health Acquisition and Sustainment Review Board.** The Joint Health Acquisition and Sustainment Review Board provides both strategic oversight of the Health Capability Plan and direction regarding the materiel sustainment and acquisition agreements. CJHLTH and Head Land Systems Division in CASG co-chair the meetings, which are held twice every year to consider health materiel financing and performance and to provide direction to the Health Materiel Committee (HMC). The meetings also provide the foundation for CJHLTH reports on health materiel capability.

11.15 **Health Materiel Working Group (HMWG).** The Director-General Health Capability chairs the HMWG meetings, which are held quarterly. The HMWG considers strategic health materiel issues, such as governance, communication and resolution of outstanding strategic procurement issues. Standing agenda items for discussion at the HMWG include:

a. updates from HLTHSPO, Garrison Health Operations, DHMLP, the Services and Headquarters Joint Operations Command

b. updates from project management groups, subordinate committees, working groups and steering groups

c. review of Health Capability Plan, including emerging minor and major health materiel projects.

11.16 **Pharmacy and Therapeutics Committee.** The Pharmacy and Therapeutics Committee (PTC) has strategic responsibility for the ADF Medicines Formulary and evaluates the use of medicines in Defence. The PTC provides strategic advice, informs medicine policy, and reviews medicine quality and cost. The secretariat for the PTC is provided by DHMLP. The PTC meets quarterly to consider new products, prices, treatment protocols and other changes. Where applicable, the review also considers prime vendors' lists of contract-identified items to ensure suitable product availability.

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[98] http://tga.gov.au/safety/problems-medicines-forms-bluecard.htm

[99] adr.reports@tga.gov.au

[100] JHCPharmacy@defence.gov.au

11.17 **Health Materiel Performance Review.** The Director DHMLP and Director HLTHSPO co-chair a monthly Health Materiel Performance Review meeting. The meeting considers fleet management issues, including review of CASG performance against the agreed and funded objectives. The meeting reviews:

a. financial performance against the agreed targets (guidance)

b. performance against the agreed key result areas within the Materiel Sustainment Agreement product schedule for health.

c. performance against the agreed equipment procurement plan

d. risks to the agreed materiel sustainment activity from the supplier and customer perspectives

e. availability of contingency and repair pool items.

11.18 **Aeromedical Evacuation Equipment Working Group.** The Aeromedical Evacuation Equipment Working Group (AMEE WG) ensures medical and dental equipment for use on aircraft is certified airworthy prior to introduction into service. The AMEE WG informs the HMC of progress and issues that impact aeromedical evacuation capability.

11.19 **Pharmaceutical Integrated Logistics System Product User Group.** The Pharmaceuticals Integrated Logistics System Product User Group (PILSPUG) provides capability manager priorities for PILS sustainment and funding requirements to the Inventory Management User Requirements Group. The PILSPUG also considers interfaces with other health and logistics information systems. The PILSPUG reports to the HMC on PILS matters that could impact health material and/or health materiel budgets.

11.20 **Defence Health Policy Steering Group.** The Defence Health Policy Steering Group manages health policy and reports to the HMC on health policy that could impact health materiel.

11.21 **Local therapeutics committee.** Local therapeutics committees operate at the unit and regional levels and allow for communication from the local level through the regional level to the PTC. Local therapeutics committees generally comprise an officer from each of the following disciplines: medical, pharmacy, nursing, environmental/public health and other allied health. The committees meet quarterly to review the ADF Medicines Formulary, discuss therapeutic and diagnostic products, and make recommendations to the PTC. Minutes from local therapeutics committee meetings are to be forwarded to the DHMLP. A local therapeutics committee must at a minimum:

a. monitor management, use and efficacy of therapeutic substances

b. develop written procedures for the control of therapeutic substances appropriate to the health facility, including access control for the pharmacy and to stock held in wards, sickbays, emergency trolleys, treatment rooms and out-of-hours cupboards

c. identify those therapeutic substances that may be supplied or recommended by nurses and medics

d. determine the range of medicines and minimum and maximum stock levels held within wards, sickbays, emergency trolleys, treatment rooms and out-of-hours cupboards.

Stakeholders

11.22 There are diverse stakeholders in the committee structure for health materiel. Table 11–1 describes the representation of stakeholders within the committee structure.

Table 11–1 Committee representation

Committee	JHC	JLC	CASG	JOC	Navy	Army	Air Force	GHO	Other
Joint Health Acquisition and Sustainment Review Board	X	X	X					X	
HMWG	X	X	X	X	X	X	X	X	
PTC	X		X	X	X	X	X	X	X
AMEE WG	X		X		X	X	X		
PILSPUG	X		X					X	

AUDIT SYSTEM

11.23 Defence Health Manual **Vol 02 Part 01 Chapter 04**[101]—Clinical governance framework' describes the Defence clinical governance framework and the governance audit system for the internal and external audit of health facilities.

STOCKTAKING

11.24 Stocktaking is a logistics governance activity that identifies systemic weaknesses and ensures the Defence inventory is accurately captured on logistics information systems. Health facilities are to plan, conduct and report stocktakes in accordance with the **Defence Logistic Manual**[102] and Defence Instructions.

11.25 **Stocktake program.** Every health facility must load a stocktake program for each supply customer account (SCA) on the applicable logistics information system. The stocktake program must include:

a. a rolling stocktake program and assurance check program for health equipment

b. commodity-specific stocktakes and assurance checks, such as those specified for pharmaceuticals in Chapter 6-'Control of medicines'.

11.26 **Stocktake appointments.** Stocktaking is a physical count of assets to ensure the physical quantities match the register. Each health facility must maintain an authorised list of stocktake appointments. An independent stocktaker and a representative of the unit equipment manager conduct the stocktake. Other stocktake appointments include the following:

11.27 **Commander.** The commanding officer/officer commanding must develop the stocktake program and procedures and conduct stocktakes and assurance checks in accordance with the program.

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101 http://defweb.cbr.defence.gov.au/home/documents/data/ADFPUBS/DHM/volume2/part1/04.pdf

102 http://intranet.defence.gov.au/home/documents/departmental/manuals/deflogman/logman1.htm

11.28 **Governance manager.** The governance manager is to monitor the stocktake program and submit stocktake results and asset management reports.

11.29 **Inventory controller.** The inventory controller must conduct a 100 per cent stock take during each stocktake period.

11.30 **SCA custodial officers.** SCA custodial officers must conduct a 10 per cent monthly stocktake in accordance with the program, with completion of 100 per cent of items by November each year.

11.31 **Losses.** The Electronic Supply Chain Manual **V04S10C01**[103]— 'Stocktaking of Defence assets and inventory' describes the accounting mechanisms supporting stocktaking. This includes the requirement to investigate and establish liability for losses of public property.

ANNEX V

ADVERSE EVENT REPORTING IN AMI STUDIES 1999 – 2002

There were three trials and one treatment activity conducted by the ADF using mefloquine and tafenoquine between 1999 and 2002. The studies were the following:

- Evaluation of safety and adverse effects of mefloquine in the prophylaxis of malaria.
- Evaluation of the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prevention of malaria.
- Evaluation of tafenoquine for eradication of vivax malaria.
- Evaluation of tafenoquine for the treatment of malaria.

Adverse event reporting in the AMI studies

Adverse event reporting would be expected to be higher in a study as Adverse Events are specifically asked for, whereas post marketing surveillance relies on individuals initiating a report.

Evaluation of safety and adverse effects of Mefloquine in the prophylaxis of malaria

The following two tables describe the adverse events reported during the mefloquine and doxycycline study.

3 Adverse events, by body system, reported among Australian soldiers who withdrew from the mefloquine trial due to adverse effects of the drug*

Body system	First contingent withdrawals (*n* – 52)	Second contingent withdrawals (*n* – 23)
Gastrointestinal	6	4
Constitutional	9	9
Neuropsychiatric	42	20
Dermatological	3	3
Musculoskeletal	2	0

* Some participants reported more than one reason for withdrawing.

Table S1

4 Adverse events reported by Australian soldiers in the first contingent* after taking mefloquine (*n* = 536) or doxycycline (*n* = 388) for malaria prophylaxis in East Timor, Apr–Oct 2001

	Mild degree		Moderate degree		Severe degree	
	Mefloquine	Doxycycline	Mefloquine	Doxycycline	Mefloquine	Doxycycline
Sleep disturbance	128 (24%)	53 (14%)	33 (6%)	28 (7%)	2 (< 1%)	2 (< 1%)
Headache	53 (10%)	51 (13%)	17 (3%)	14 (4%)	1 (< 1%)	4 (1%)
Tiredness	72 (13%)	78 (20%)	20 (4%)	16 (4%)	0	1 (< 1%)
Nausea	86 (16%)	63 (16%)	22 (4%)	20 (5%)	4 (1%)	0

* Some participants reported more than one adverse event.

Table S2

Adverse event reporting for doxycycline was not conducted for the second contingent.

Reference - Kitchener SJ, Nasveld PE, Gregory RM, Edstein MD. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med J Aust 2005; 182 (4): 168-171.

Evaluation of the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prevention of malaria

The following two tables describe the adverse events reported during the tafenoquine and mefloquine study.

TABLE 3. Adverse events occurring in >5% of subjects on tafenoquine or mefloquine (prophylactic phase)[a]

Adverse event	No. (%) of subjects by AE severity and treatment group							
	Mild		Moderate		Severe		Total	
	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine
At least one AE	431 (88)	140 (86)	194 (39)	46 (28)	18 (4)	3 (2)	454 (92)	143 (88)
Gastrointestinal								
Gastroenteritis	109 (22)	36 (22)	80 (16)	17 (11)	6 (1)	0	182 (37)	51 (32)
Diarrhea	77 (16)	28 (17)	0	2 (1)	1 (<1)	0	77 (16)	30 (19)
Nausea	27 (6)	13 (8)	1 (<1)	0	0	0	28 (6)	13 (8)
Abdominal pain	19 (4)	11 (7)	5 (1)	3 (2)	1 (<1)	0	24 (5)	13 (8)
Vomiting	19 (4)	8 (5)	2 (<1)	1 (<1)	0	0	21 (4)	8 (5)
Musculoskeletal								
Injury	149 (30)	46 (28)	45 (9)	4 (3)	3 (<1)	2 (1)	178 (36)	49 (30)
Back pain	65 (13)	24 (15)	12 (2)	2 (1)	0	0	74 (15)	26 (16)
Arthralgia	52 (11)	17 (11)	9 (2)	1 (<1)	0	0	55 (11)	18 (11)
Respiratory								
URTI	97 (20)	30 (19)	6 (1)	2 (1)	0	0	101 (21)	32 (20)
Pharyngitis	24 (5)	2 (1)	2 (<1)	1 (<1)	0	0	25 (5)	3 (2)
Dermatological								
Rash	70 (14)	20 (12)	1 (<1)	1 (<1)	0	0	70 (14)	21 (13)
Fungal dermatitis	43 (9)	8 (5)	1 (<1)	0	0	0	44 (9)	8 (5)
Headache (constitutional AE)	59 (12)	18 (11)	2 (<1)	2 (1)	0	0	61 (12)	20 (12)
Viral infection	23 (5)	7 (4)	16 (3)	6 (4)	1 (<1)	0	39 (8)	13 (8)

[a] In total, there were 492 tafenoquine subjects and 162 mefloquine subjects. AE, adverse event; URTI, upper respiratory tract infection.

Table S3

TABLE 4. Neuropsychiatric events in subjects on tafeoquine or mefloquine (prophylactic phase)[a]

Adverse event	No. (%) of subjects by AE severity and treatment group					
	Mild		Moderate		Total	
	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine
Vertigo	22 (5)	7 (4)	0	1 (<1)	22 (5)	8 (5)
Somnolence	12 (2)	6 (4)	0	0	12 (2)	6 (4)
Abnormal dreams	7 (1)	2 (1)	0	0	7 (1)	2 (1)
Dizziness	5 (1)	2 (1)	0	0	5 (1)	2 (1)
Insomnia	4 (<1)	3 (2)	1 (<1)	0	5 (1)	3 (2)
Abnormal coordination	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Anxiety	2 (<1)	0	0	0	2 (<1)	0
Agitation	2 (<1)	0	0	0	2 (<1)	0
Euphoria	2 (<1)	0	0	0	2 (<1)	0
Tremor	2 (<1)	0	0	0	2 (<1)	0
Depression	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Paroniria	1 (<1)	0	0	0	1 (<1)	0
Amnesia	1 (<1)	0	0	0	1 (<1)	0

[a] In total, there were 492 tafenoquine subjects and 162 mefloquine subjects. There were no severe adverse events (AEs) of this type.

Table S4

Reference - Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. 2010 Feb;54(2):792-8.

Evaluation of Tafenoquine for eradication of vivax malaria trial adverse events

The following table describes the adverse events reported during the tafenoquine eradication study.

Table 2 Comparison of the rates of adverse events between healthy subjects administered 3 d courses of tafenoquine and a 14 d course of primaquine plus doxycycline for post-exposure vivax malaria prophylaxis

Adverse events (AE)[a]	Tafenoquine 400 mg od[b] (*n* = 242)	Tafenoquine 200 mg bid[c] (*n* = 161)	Tafenoquine 200 mg od[b] (*n* = 406)	Primaquine 7.5 mg tid[d] (*n* = 464)
Nausea	57, 5[e] (25.6)	28, 3 (19.3)	31, 1 (7.9)	43, 4 (10.1)
Abdominal distress	33, 9 (17.4)	14, 3 (10.6)	22, 4 (6.4)	14, 1 (3.2)
Diarrhoea	18, 5 (9.5)	22, 2 (14.9)	16, 3 (4.7)	8, 2 (2.2)
Reflux	14, 0 (5.8)	10, 0 (6.2)	2, 0 (0.5)	10, 0 (2.2)
Vomiting	7, 4 (4.5)	2, 2 (2.5)	1, 1 (0.5)	4, 1 (1.1)
Flatulence	4, 0 (1.7)	4, 0 (2.5)	2, 0 (0.5)	5, 0 (1.1)
Headache	17, 1 (7.4)	5, 0 (3.1)	3, 1 (1.0)	8, 1 (1.9)
Lethargy	5, 1 (2.5)	1, 2 (1.9)	7, 0 (1.7)	8, 0 (1.7)
Any GI AE	111 (45.9)	65 (40.4)	69 (17.0)	75 (16.2)
Tafenoquine concentrations (ng/ml)[f]				
With AE	619 ± 122 (*n* = 92)	631 ± 136 (*n* = 56)	317 ± 65 (*n* = 72)	
Without AE	609 ± 138 (*n* = 87)	630 ± 120 (*n* = 80)	321 ± 64 (*n* = 311)	

Values in parentheses are percentages.
[a] No. subjects with mild and moderate adverse events, respectively (% of subjects with combined mild and moderate adverse events).
[b] Once daily.
[c] Twice daily.
[d] Thrice daily for primaquine plus doxycycline 100 mg daily.
[e] One severe adverse event.
[f] Mean (± SD) plasma tafenoquine concentrations measured between 8 and 14 h after last drug administration on day 3.

Table S5

Reference - Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. 2010 Feb;54(2):792-8.

Evaluation of tafenoquine for the treatment of malaria

There were no serious adverse events reported in this study and no withdrawals because of adverse events. The eight-week regimen of tafenoquine was well tolerated.

Reference – Kitchener S, Nasveld P, Edstien M. Short report: Tafenoquine for the treatment of recurrent plasmodium vivax malaria. Am J Trop Med Hyg, 76(3), 2007, pp494-496

ANNEX W

PUBLISHED TAFENOQUINE STUDIES

Study	Year and country study conducted	SAEs	AEs	Efficacy	Ref
TQ Dose-ranging study 1999 (n=44) 300mg for 7 days (n=15); 500mg for 3 days repeated 1 week after initial dose (n=11), 1 dose 500mg (n=9) and CQ only (n=9)	1996-97 Thailand	No SAEs reported.	All treatment groups had mild, transient side effects consisting predominantly of headache, loose stools or diarrhea, nausea and abdominal discomfort. TQ patients complained more within 12 hour of dosing.	Risk of relapse was significantly lower for TQ patients. Incidence of relapse was reduced by 91% 2 relapses in TQ patients and 4 in the CQ group	(1)
Monthly TQ for Prophylaxis to P. vivax and MDR P. falciparum (n=205) Loading dose of 400mg TQ for 3 days followed by single monthly 400mg or placebo for five months	1998 Thailand	Nine SAEs reported. Placebo group appeared to have more SAEs (6 compared to three in TQ group). Fever was the most common SAE.	70.2% TQ group reported 1 or more AEs compared to 55.4% in the placebo group, with the same AEs as above. Slightly higher rates of AEs in TQ group that was open-doses compared to blinded doses.	22 P. vivax, 8 P. falciparum and 1 mixed occurred. Only 1 P. vivax occurred in the TQ group. TQ has a protective efficacy of 97% for all malaria (96% for P. vivax and 100% for P. falciparum)	(2)

Study	Year and country study conducted	SAEs	AEs	Efficacy	Ref
1500mg 3 days then 3-Dose TQ versus PQ (n=80) 300mg TQ per day for 7 days (n-18); 600mg TQ for 3 days (n=19); 600mg TQ single dose (n=18), 15mg per day 14 days PQ and CQ only (n=13)	1998-99 Thailand	No SAEs reported	600mg TQ single dose vomited 1 hour after administration. Same AEs as above study, except during CQ treatment all patients had neurological complaints (vertigo or headache) and 50% had gastrointestinal upsets. Higher proportion of gastrointestinal disturbances reported among TQ groups compared to PQ group	8 relapses in CQ group; 3 in PQ group and 1 in 600mg TQ single dose. Incidence of relapse reduced by 98.5% compared to CQ and 79.5% compared to PQ group	(3)
Post exposure prophylaxis (Bougainville 1998) 22.5mg PQ daily for 14 d, 400mg TQ daily for 3 d and 200 mg TQ base twice daily for 3 d	1998-99 Bougainville	No SAEs listed	TQ produced more AEs with gastrointestinal upset (nausea and abdominal pain) the most common. PQ 18%, TQ 400mg 41.4% and TQ 200mg 34%	PQ 4.2 % (n=214) and TQ 1.85% (n=378)	(4)

Study	Year and country study conducted	SAEs	AEs	Efficacy	Ref
Randomised, double blind, placebo-controlled trial in malaria endemic regions of Africa 1. Kassena-Nankana district of northeastern Ghana 13 weeks (TQ 045 1998) 2. Kenya 3 days and 13 weeks (n=223) (TQ 043 1997) 3. Kombewa in Western Kenya 24 weeks (TQ 030 2000)	1. 1998 Ghana 2. 1997 Kenya 3. 2000 Kenya	1. Nine AEs reported, no deaths and all considered to be unrelated to study drug (no breakdown of which drug caused the SAEs) 2. 2 SAEs with TQ due to incorrect G6PD status 3. Not reported	1. AEs reported 200mg TQ weekly 53-54% (n=57-58) and 250 mg MQ weekly 21-25% (n=46-54). Gastrointestinal, musculoskeltal and respiratory accounted for 52-70% of total AEs 2. Gastrointestinal upset more common in 400mg TQ (46%) per week compared to placebo group (17%) 3. 2.1% 200mg weekly TQ and 1% MQ 250mg MQ weekly	1. 200mg TQ weekly 85.6% (n=91) and 250 mg MQ weekly 85.7% (n=46) 2. 3 days 400mg only 68% efficacy; 86% efficacy in 200mg 3 days then 200mg 13 weeks; 89% efficacy 400mg 3 days then 400 mg 13 weeks 3. 95.8% 200mg TQ and 95.1% 250mg MQ	1. (5) 2. (6) 3. (7)
Three different regimes of TQ versus PQ post-exposure prophylaxis (n=1512) Over 3 days TQ - 400mg once daily, 200mg twice daily; 200mg once daily or 22.5mg PQ + 100mg doxy over 14 d	1999-2000 Bougainville East Timor	No SAEs reported	Most frequent AEs across all groups was nausea, abdominal distress and diarrhoea. However, the lower dose of TQ 200mg once daily produced AEs similar to PQ +Doxy	Relapse rate for Bougainville group was 1.2% for 200mg twice daily, 2.3% 400mg once daily and PQ+Doxy was 3.4% Relapse rate for East Timor group was 4.9% for 200mg once daily, 5.3% for 200mg twice daily and 11% for 400mg once daily and 10% for PQ + doxy	(8)

Study	Year and country study conducted	SAEs	AEs	Efficacy	Ref
Prophylaxis Study 6 months East Timor Weekly 200mg TQ (n=492) or 250mg MQ (n=162) for 6 months	2001 East Timor	21 severe AEs 4% TQ (n=18) and 2% MQ (n=3). The most common SAE was gastroenteritis 1.2% TQ and 0% MQ. 3.7% (n=18) TQ Arm and 3.1% (n=5) MQ Arm had SAEs	91.9% TQ and 88.3% MQ had reported one AE. No significant difference between the MQ or TQ arms. Most common AE was gastroenteritis and injury. Vortex keratopathy was found in 93.2% (n-74) in the TQ arm – all resolved in 12 months 13% (n=64) TQ Arm and 14.2% (n=23) MQ Arm reported neuropsychiatric AEs. The most common being vertigo, dizziness and various sleep disorders. No significant difference between treatment arms. 2.4% (n=15) TQ Arm and 1.9% (n=3) MQ Arm withdrew. 4 TQ subjects were withdrawn due to injury, 2 due to arthralgia. 3 TQ subjects withdrew for treatment related AEs (Abdominal pain, depression and hyperesthesia).	No symptomatic malaria infections occurred during the prophylactic phase in either TQ or MQ groups. 0.9% (n=4) in the TQ group and 0.7% (n=1) in the MQ group had P. vivax malaria. 16-20 weeks RTA	(9)

Study	Year and country study conducted	SAEs	AEs	Efficacy	Ref
3 day course of TQ monotherapy for the treatment of P. vivax (n=70). TQ 400 mg once daily for 3 days or 2500mg total dose of CQ for 3 days plus 15mg daily PQ for 14 days	2003-2005 Thailand	5 SAEs reported in TQ arm – increased methemoglobinemia at day 7	TQ monotherapy not recommended as it has a slower parasite, gametocyte and fever clearance rate compared to CQ/PQ. It could also increase resistance to this long-acting agent. Renal safety was assessed – one TQ patient had a change from baseline in serum creatinin but resolved spontaneously	At day 120 100% of TQ group has no relapse, 95% of CQ/PQ group had no relapse. Mean parasite, gametocyte and fever clearance was for TQ 82.5h, 49.1 h and 41.1 h, respectively. For CQ/PQ it was 40 h, 22.7h and 24.7 h, respectively. At day 28 clinical response rate was 93% for TQ due to underlying asymptomatic infections. AEs the same as the above AEs	(10)
Single dose tafenoquine (300mg) plus CQ (TQ+CQ) compared to chloroquine plus primaquine (CQ+PQ) and chloroquine alone (CQ)	2011-13 Peru Brazil Thailand India	QT prolongation most common (3% n=329) but similar rate across CQ+PQ (8% n=50), CQ (4% n=54) and TQ +CQ (2% n=225) arms. Difference versus CQ only TQ+CQ 54.5% and CQ+PQ 39.9%	Any adverse event similar across TQ+CQ 38%, CQ+PQ 32% and CQ alone 41%. Headaches most common AE. Diarrhoea incidence higher in TQ (600mg) +CQ group. No AEs lead to study withdraw, nor did any deaths). QT prolongation led to study drug discontinuation (one TQ (50mg), one PQ and one CQ alone).	Tafenoquine 300mg dose 89% compared to 77.3% for primaquine and 37.5% for chloroquine	(11,12)

Study	Year and country study conducted	SAEs	AEs	Efficacy	Ref
Open-label, randomized, parallel-group study to evaluate drug interactions between tafenoquine and two ACTs: dihydroartemisinin-piperaquine and artemether-lumefantrine 1. 300mg TQ plus dihydroartemisinin-piperquine 2. 300mg TQ plus artemether-lumefantrine	201? USA	Two SAEs -cardiac arrest in dihydroartemisinin-piperquine group that was drug related. Other SAE not drug related	Clinically -No apparent effect of the addition of tafenoquine on the number of patients experiencing AEs of any cause compared with ACTs alone. 58.3% for Dihydroartemisinin-piperquine, 54.2 for artemether-lumefantrine and 33.3% for TQ alone. Headache most common AE. Drug related AE – 4.2% AEs occurring in TQ alone subjects. Headache comme AE		(13)

Other Papers and Reviews

	Country	Title	Comment		Reference
Scientific Study	United Kingdom	Ophthalmic and Renal Effects of 200mg TQ Tafenoquine does not prolong QT interval at therapeutic concentrations (n=120)	No effect on night vision or other ophthalmic indices measured No difference between TQ or placebo in mean change in glomerular filtration rate after 6 months dosing. Tafenoquine was well tolerated		(14)
	Thailand	Plasma concentrations of TQ in Thai soldiers TQ Treatment Study (AMI)			(15,16)

	Country	Title	Comment		Reference
	Thailand	Gender differences in volunteers after TQ administration (AMI)			(17)
	In review Australia	Blood schizonticidal activity and safety of tafenoquine when administered as chemoprophylaxis to healthy, non-immune participants challenged with blood stage 7. Plasmodium falciparum: A randomized, double-blinded, placebo-controlled Phase 1b study.			(18)
Reviews	2017	Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis.			(19)
	In review	Tafenoquine and primaquine do not exhibit clinical neurologic signs associated with central nervous system lesions in the same manner as earlier 8-aminoquinolines			(20)

	Country	Title	Comment		Reference
		The blood schizonticidal activity of tafenoquine makes an essential contribution to its prophylactic efficacy in nonimmune subjects at the intended dose (200 mg).			(21)

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ANNEX X

INTERNATIONAL AND MILITARY GUIDELINES ON MALARIA PREVENTION

Jurisdiction	Reference	Recommendations
International		
Public Health England	*Guidelines for malaria prevention in travellers from the UK* (Last updated March 2018)	Doxycycline, atovaquone/proguanil, mefloquine all recommended for areas of chloroquine resistance.
International Association for Medical Assistance to Travellers (IAMAT)	*How to protect yourself against malaria* White Paper 2017 edition (accessed 08/07/2018)	For areas with chloroquine resistant P. falciparum: mefloquine, doxycycline or atovoquone/proguanil.
Centres for Diseae Control (CDC)	*https://www.cdc.gov/malaria/travelers/drugs.html* (Accessed 08/07/2018)	Atovaquone/proguanil, chloroquine, doxycycline, mefloquine, primaquine.
World Health Organization (WHO)	*WHO Model List of Essential Medicines* – Last updated Aug 2017 http://www.who.int/medicines/publications/essentialmedicines/en/	Doxycycline, mefloquine, chloroquine/proguanil (only in Central America for P.vivax)
Military		
Canada	*Surgeon General Taskforce Report on Mefloquine.* Government of Canada, June 2017	Individual choice of doxycycline, atovaquone/proguanil, or mefloquine after clinical assessment.
Czech Republic	Quoted in *Mental Health of Canadian Veterans: A Family Purpose. Report of the Standing Committee on Veterans Affairs*, House of Commons Canada, June 2017	Mefloquine offered.
Belgium	Quoted in *Mental Health of Canadian Veterans: A Family Purpose. Report of the Standing Committee on Veterans Affairs*, House of Commons Canada, June 2017	Mefloquine offered but Malarone and doxycycline preferred
Denmark	Quoted in *Mental Health of Canadian Veterans: A Family Purpose. Report of the Standing Committee on Veterans Affairs*, House of Commons Canada, June 2017	Mefloquine offered but Malarone and doxycycline preferred

Jurisdiction	Reference	Recommendations
France	Quoted in Ellis N (Chair). Mental Health of Canadian Veterans: A Family Purpose. Report of the Standing Committee on Veterans Affairs, House of Commons Canada, June 2017	Doxycycline preferred, but mefloquine offered.
Germany	Letter from German Surgeon General (Annex V)	Doxycycline, atovaquone-proguanil. Mefloquine no longer used
Ireland	Statements by Irish Minister of State at the Department of Defence to the Oireachtas Éireann	Mefloquine first line for deployments for sub-Saharan Africa
Netherlands	Quoted in *Mental Health of Canadian Veterans: A Family Purpose. Report of the Standing Committee on Veterans Affairs*, House of Commons Canada, June 2017	Mefloquine offered but Malarone preferred
Slovakia	Quoted in *Mental Health of Canadian Veterans: A Family Purpose. Report of the Standing Committee on Veterans Affairs*, House of Commons Canada, June 2017	Mefloquine offered
Sweden	Quoted in *Mental Health of Canadian Veterans: A Family Purpose. Report of the Standing Committee on Veterans Affairs*, House of Commons Canada, June 2017	Mefloquine offered
UK MoD	*An Acceptable risk? The use of Lariam for military personnel*. Defence Committee, Fourth Report of Session 2015 – 2016, 10 May 2016	Doxycycline and atovaquone-proguanil are considered first line chemoprophylaxis medications in chloroquine-resistant malaria risk areas. Mefloquine reserved for those with contraindications or intolerance to the above.
United States DoD	*Assistant Secretary of Defense for Health Affairs Memorandum: Guidance on Medications for Prophylaxis of Malaria,* 15 April 2013	Doxycycline and atovaquone-proguanil are considered first line chemoprophylaxis medications in chloroquine-resistant malaria risk areas. Mefloquine reserved for those with contraindications or intolerance to the above.