

Chapter 1

Introduction

Referral

1.1 On 19 June 2018, the Senate referred the following matter to the Senate Foreign Affairs, Defence and Trade References Committee for inquiry and report by 17 September 2018:

- (a) the current and past policies and practices for:
 - (i) prescribing Quinoline anti-malarial drugs to ADF personnel, and
 - (ii) identifying and reporting adverse drug reactions from Quinoline anti-malarial drugs among ADF personnel;
- (b) the nature and extent of any adverse health effects of those who have taken Mefloquine/Tafenoquine on serving and former ADF personnel;
- (c) the support available for partners, carers and families of personnel who experience any adverse health effects of Quinoline anti-malarial drugs;
- (d) a comparison of international evidence/literature available on the impact of Quinoline anti-malarials;
- (e) how other governments have responded to claims regarding Quinoline anti-malarials; and
- (f) any other related matters.¹

1.2 On 20 August 2018, the Senate agreed a reporting extension until 29 November 2018.² On 29 November 2018 the Senate agreed to a further extension until 6 December 2018.³ The committee decided to table on 4 December 2018.

Conduct of the inquiry

1.3 Details of the inquiry were placed on the committee's website at http://www.aph.gov.au/senate_fadt. The committee also contacted a number of relevant individuals and organisations to notify them of the inquiry and invite submissions by 31 July 2018. The committee continued to receive submissions after the closing date. Submissions received are listed at Appendix 1.

1.4 The committee held six public hearings: Brisbane on 30 August; Townsville on 31 August; Melbourne on 5 November and Canberra on 11 October, 15 October and 8 November 2018. A list of witnesses who gave evidence is available at Appendix 3. Following the hearing on 30 August in Brisbane, the committee conducted a site

1 *Journals of the Senate*, No. 99 —19 June 2018, p. 3187.

2 *Journals of the Senate*, No. 110 —20 August 2018, p. 3534.

3 *Journals of the Senate*, No. 133 —29 November 2018, p. 4325.

visit to the Australian Defence Force Malaria and Infectious Disease Institute (ADFMIDI) at Enoggera Barracks.

Acknowledgement

1.5 The committee thanks the organisations and individuals who made submissions and those who participated in the public hearings for the inquiry.

1.6 The committee recognises the difficulties faced by individuals who are unwell in participating in the inquiry processes and thanks those who were able to make submissions and provide evidence. The committee appreciates that many individuals made submissions with their mates and families in mind and that they told their story also for those who, for whatever reason, are unable to at this time. The committee sincerely appreciates their efforts.

1.7 The committee wishes to particularly acknowledge the partners and families of veterans who also provided evidence to the committee.

Assistance provided

1.8 Realising the challenges for potential submitters, the committee provided assistance to those who wished to make submissions and thanks the Department of Veterans' Affairs (DVA) who also made assistance available. DVA also made staff available at hearings to facilitate access to support and services if required.

Structure of the report

- Chapter 1 includes key terminology, concepts and medications and summarises some other relevant inquiries (ToR e);
- Chapter 2 details the disagreement evident during the inquiry between individuals and advocates and the medical community over the cause of their symptoms (ToR a(ii), b and d);
- Chapter 3 covers Australian Defence Force (ADF) antimalarial policies and details about the trials, including the issue of informed consent (ToR a, a(i), a(ii) and b);
- Chapter 4 covers the actions taken by the Department of Defence (Defence) and DVA to date, assistance available, witnesses' experience of seeking assistance and what assistance needs to be provided moving forward; (ToR c) and
- Chapter 5 details the committee's conclusions and recommendations.

Key terminology, concepts and medications

Atovaquone and proguanil	Listed on the Australian Register of Therapeutic Goods for malaria treatment since 1998 and prevention since late 2001. ⁴ It
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4 TGA Product and Consumer Medicine Information, Malarone; Defence, *Submission 1*, p. 11.

hydrochloride (brand name Malarone)	is a combination of two drugs: atovaquone and proguanil. ⁵ It has been the second line preventative antimalarial for the ADF since 2006, used when doxycycline is not suitable. It needs to be taken daily. ⁶
Doxycycline	An antibiotic. There are a number of brands listed on the Australian Register of Therapeutic Goods. It is listed on the World Health Organization (WHO) Model List of Essential Medicines for treating bacterial infections as well as for malaria treatment and prevention. ⁷
Malaria chemoprophylaxis or malaria prophylaxis	Taking one or more drugs to prevent malaria.
Mefloquine (brand name Lariam)	An antimalarial for prevention and treatment which was put on the Australian Register of Therapeutic Goods on 27 January 1993. ⁸ Roche Products Pty Ltd advised that mefloquine emerged from 'An extensive research program undertaken independently by the United States Army [the Walter Reed Army Institute of Research] in 1963, in which over 100,000 separate compounds were evaluated prior to mefloquine being selected'. ⁹ As at 19 February 2018, mefloquine was approved in 27 countries and more than 40 million patients have been treated since it was first made available. ¹⁰ It is listed on the WHO Model List of Essential Medicines for both malaria prevention and treatment. ¹¹ It is also listed by the US Centers

5 Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health, *Committee Hansard*, 11 October 2018, p. 42.

6 Defence, *Submission 1*, p. 11.

7 WHO Model List of Essential Medicines, 20th edition, March 2017.

8 Department of Health, *Submission 3*, pp. 1–2. Note: Roche Products Pty Ltd advised that mefloquine was approved in Australia on 3 September 1986. See additional information from Roche Products Pty Ltd, received 19 November 2018.

9 *Submission 12*, p. 2.

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

11 WHO Model List of Essential Medicines, 20th edition, March 2017. The RMA notes that the WHO Model List of Essential Medicines is an expert assessment of the minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. RMA, *Submission 4*, p. 9; Mr Svend Peterson, Managing Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 1.

	for Disease Control and Prevention for malaria prevention and treatment. ¹² It is still a recommended preventative antimalarial for travellers to Timor-Leste. ¹³
Primaquine	An antimalarial used to prevent and treat relapses of malaria. It is given to people as they leave a malarious area as eradication, to kill any malaria parasites that may still be present in the body. It is taken twice daily for 14 days. ¹⁴
Prophylaxis	Medication given to prevent disease.
Radical cure	Prevention of relapse.
Tafenoquine	Recently approved by the US FDA for prevention ¹⁵ and radical cure of malaria. ¹⁶ In September 2018 it was approved by the Australian Therapeutic Goods Administration (TGA) for prevention ¹⁷ and radical cure ¹⁸ of malaria. At the time of the trials it was not yet approved in Australia for use as an anti-malarial medication. It is chemically related to primaquine ¹⁹ and is structurally different to mefloquine. ²⁰ Like primaquine, tafenoquine shares a key safety concern which is the potential to cause hemolysis (destruction of red blood cells) in individuals with a hereditary disorder, deficiency of Glucose-6-Phosphate-Dehydrogenase (G6PD) enzyme. Hence individuals

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- 12 CDC, Yellow Book, Chapter 3, Infectious Diseases Related to Travel, Malaria: <https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria>, accessed 15 October 2018.
- 13 Defence, *Submission 1*, p. 2.
- 14 Defence, *Submission 1*, p. 15.
- 15 On 26 July 2018 Sixty Degrees Pharmaceuticals announced that the Antimicrobial Drugs Advisory Committee of the US Food and Drug Administration voted to support tafenoquine for the prevention of malaria in adults which will be marketed under the brand name Arakoda. See Sixty Degrees Pharma, 'US FDA Advisory Committee votes in favour of Tafenoquine for the prevention of malaria', *Media release*, 26 July 2018.
- 16 GlaxoSmithKline (GSK) R&D in partnership with Medicines for Malaria Venture announced that on 20 July 2018 the FDA approved single dose tafenoquine (tradename Krintafel) for the radical cure (prevention of relapse) of *P. vivax* malaria in patients aged 16 years and older. See GSK, *Submission 8*, p. 2.
- 17 To be marketed as Kodatef, sponsor Bioclect Pty Ltd.
- 18 To be marketed as Kozenis, sponsor GlaxoSmithKline Australia Pty Ltd.
- 19 See Professor Geoffrey Quail, President, Australian College of Tropical Medicine, *Committee Hansard*, 30 August 2018, p. 44; Adjunct Professor Skerritt, *Committee Hansard*, 11 October 2018, p. 40.
- 20 GSK, *Submission 8*, p. 2.

	must be tested for G6PD deficiency before receiving either of these drugs. ²¹ More than 4,000 people, both military and civilian, have taken tafenoquine in clinical studies around the world. ²²
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The difference between mefloquine and tafenoquine

1.9 The differences between mefloquine and tafenoquine were discussed with GlaxoSmithKline Australia Pty Ltd. Dr Alison Webster, Head, Global Health Clinical Research and Development, GSK advised:

They're members broadly of a class of drugs that are called quinolines, but within that class there are very different chemicals, or medicines. Tafenoquine is an analogue of primaquine. Primaquine and tafenoquine are 8-aminoquinolines. They uniquely have an activity against the dormant liver stage of vivax malaria and so uniquely have the ability to prevent relapse of vivax malaria. They also share a particular safety issue, which is that they can cause anaemia in patients who lack a certain enzyme called G6PD. All patients who take either primaquine or tafenoquine must be tested for G6PD deficiency before they receive the drug. Mefloquine is a different kind of quinoline, but there are many others. Chloroquine is a member of that group, as well...All of these are unique chemicals with their own specific safety profile and their own specific activity against malaria.²³

1.10 Mr Svend Peterson, Managing Director, Roche Products Pty Ltd explained to the committee it is important that there are a range of malaria prevention and treatment options available to reduce the risk of infection and death from malaria as not all patients can tolerate the medications and certain parasites have become resistant to some antimalarials.²⁴

Malaria

1.11 Malaria is a life threatening disease caused by parasites which are transmitted to people by mosquitoes. There are five parasite species that cause malaria in humans with *P. falciparum*²⁵ and *P. vivax* causing most of the disease burden.²⁶

1.12 According to the latest WHO World Malaria Report released in November 2018 there were an estimated 219 million cases of malaria in 2017, up from 216 million cases in 2016. In 2017 there were an estimated 435,000 malaria-related

21 GSK, *Submission 8*, p. 2.

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

23 *Proof Committee Hansard*, 8 November 2018, pp. 11–12. See also Adjunct Professor Skerritt, *Committee Hansard*, 11 October 2018, p. 40.

24 *Proof Committee Hansard*, 8 November 2018, p. 1.

25 In the African region most cases are due to *P. falciparum*. See WHO World Malaria Report 2018, p. 15.

26 Australian Government, Indo-Pacific Centre for Health Security, *Submission 57*, p.1.

deaths, compared to 451,000 in 2016 and 607,000 in 2010.²⁷ The WHO has noted that resistance to antimalarial medicines is a recurring problem.²⁸ The UN Secretary-General's 2018 progress report on the UN Sustainable Development Goals states:

The world is not on a trajectory towards ending malaria by 2030 — in fact, the trends are worrisome. In 2016, there were 216 million cases of malaria, compared with 210 million cases in 2013.²⁹

1.13 Australian travellers to malaria endemic areas are at risk of contracting malaria and approximately 400 cases of imported malaria occur each year.³⁰

1.14 The Medicines for Malaria Venture (MMV) reported that *P.vivax* malaria is responsible for a significant burden of illness.³¹ The WHO estimated that 3.4 per cent of all malaria cases were caused by *P. vivax*, with 56 per cent of the vivax cases in the South-East Asia Region.³²

1.15 In 2016 WHO estimated 8.5 million cases of *P.vivax* malaria of which around 5 million were in South-East Asia with 27,000 deaths.³³

Malaria and the ADF

1.16 South East Asia is an area of operations for the military which puts ADF members at risk of malaria. In the ADF, 64 ADF members became infected with malaria during the INTERFET deployment and over 200 more developed malaria on return to Australia. These numbers were the catalyst for the approved clinical studies which were 'deemed necessary to help determine if Defence should review its policy of prescribing doxycycline as the preferred antimalarial...'.³⁴ Details about the trials are provided in Chapter 3.

1.17 In the ADF, between 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.³⁵ Over these years the Australian Defence Force Malaria and Infectious Disease Institute (ADFMIDI) formerly known as the Australian Army Malaria Institute (AMI)³⁶, 'a world-renowned,

27 WHO, World Malaria Report 2018, p. xiii.

28 WHO, Malaria Fact Sheet, 11 June 2018.

29 UN Report of the Secretary-General, Progress towards the Sustainable Development Goals, 10 May 2018, p. 5.

30 Australasian Society for Infectious Diseases, *Submission 6*, p. 1.

31 *Submission 10*, [p. 2].

32 WHO, World Malaria Report 2018, p. 36.

33 WHO, World Malaria Report 2017, pp. 33, 34, 41.

34 Defence, *Submission 1*, p. 3. Defence, *Supplementary submission 1.1*, pp. 6–7.

35 Defence, *Submission 1*, p. 1.

36 Located at Gallipoli Barracks in Brisbane.

industry leader of malarial studies' has been responsible for developing solutions to the problem of malaria on operations.³⁷

Other relevant Australian committee inquiries

1.18 On 17 March 2016, the Senate Foreign Affairs, Defence and Trade References Committee tabled a report on the mental health of ADF serving personnel. The report included two recommendations in relation to mefloquine.³⁸ Dated 15 September 2016, the government response sets out its response to the committee's recommendations.³⁹

Other relevant inquiries

1.19 The use of mefloquine by defence forces overseas has been the subject of parliamentary and other inquiries or reviews in other jurisdictions.⁴⁰

Canada

1.20 In June 2017, the House of Commons Standing Committee on Veterans Affairs undertook a study on 'mental health focused on improving the transitional support between Canadian Armed Forces and Veterans Affairs' which included the claims around the effect of mefloquine. There were two recommendations regarding mefloquine: that Veterans Affairs Canada reach out to members of the Canadian Armed Forces who served in Somalia, Rwanda or other deployment in that time period to ensure each is receiving the mental and physical health services, support, benefits and programs to which they are entitled; and that Veterans Affairs Canada cooperate with any institution concerned in any research program that would study the effects of mefloquine.⁴¹

1.21 In June 2017 Canada released a report from a military taskforce on mefloquine. Health Canada simultaneously made public its own findings about the safety of the drug. Both concluded there is no evidence that the drug causes long-lasting and permanent neurological and psychiatric problems. The military report recommended that mefloquine be considered as a drug of last resort. The findings of the reports have angered some Canadian veterans who claim they are experiencing symptoms as a result of 'mefloquine toxicity'.⁴²

37 Defence, *Submission 1*, p. 8.

38 Senate Foreign Affairs, Defence and Trade References Committee, *Mental health of ADF serving personnel*, 17 March 2016. See recommendations 5 and 6.

39 Available:
https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Foreign_Affairs_Defence_and_Trade/ADF_Mental_Health/Government_Response

40 See Defence, *Submission 1*, pp. 49–53 for more detail.

41 Defence, *Submission 1*, pp. 50–51.

42 Gloria Galloway, 'Canadian Forces curb use of mefloquine, but study findings anger vets', *The Globe and Mail*, 2 June 2017.

1.22 In 2017 the Canadian Surgeon General noted in the Canadian Standing Committee on Veterans Affairs Review, *Mental Health of Canadian Veterans: A Family Purpose* that:

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.⁴³

UK

1.23 In May 2016 the House of Commons Defence Committee published its report: *An acceptable risk? The use of Lariam for military personnel*. The committee concluded that the Ministry of Defence should designate Lariam (Mefloquine) as a drug of last resort and that prescribing it should be restricted: only to those who are unable to tolerate the available alternatives; only after a face to face individual risk assessment has been conducted; and only after the patient has been made aware of the alternatives and have been given the choice between Lariam and another suitable antimalarial drug.⁴⁴

1.24 Following this inquiry on 12 September 2016, the Ministry of Defence introduced a new policy on prescribing antimalarial drugs.⁴⁵ The revised policy directs that all antimalarial drugs are only supplied after a face to face travel health risk assessment performed by an appropriately trained and regulated health care professional. A hotline was also set up for anyone who had concerns. However, the new policy did not designate Lariam as a drug of last resort.⁴⁶

1.25 In relation to the UK inquiry the then Vice Chief of the Defence Force, VADM Ray Griggs noted in 2016 that:

The point I would make about the key difference between the UK and Australia is that, as I said at the outset, we have a tiered approach to the prescription of antimalarials, that mefloquine is our third in line and that it is being used quite rarely. In the UK, there is no tiering and mefloquine has been used much more extensively. The UK inquiry centred on whether people were given the appropriate amount of information and the

43 Defence, *Submission 1*, p. 13.

44 House of Commons, Defence Committee, *An acceptable risk? The use of Lariam for military personnel*, Fourth Report of Session 2015-16, 24 May 2016, p. 29.

45 Ministry of Defence, *Mefloquine Prescribing in the UK Armed Forces*, 12 September 2016 to 31 March 2018, published 17 May 2018.

46 Lydia Williams, 'Ministry of Defence will only hand out Lariam after face-to-face risk assessment', *The Telegraph*, 13 September 2016.

counselling part prior to being prescribed the drug. So it was a slightly different emphasis.⁴⁷

1.26 On 25 July 2018 the House of Commons Defence Committee presented a report on *Mental Health and the Armed forces, Part One: The Scale of mental health issues*. The report notes there is a lack of research into the mental health effects of physical exposure to factors such as neurotoxicity or mild traumatic brain injury:

An example is the antimalarial drug Lariam, or Mefloquine, where our predecessor Committee found that a minority of those who used it suffered serious mental health issues. Such side effects were known to occur, yet the Ministry of Defence did not take the appropriate steps to minimise the risks to those whom it prescribed the drug. A number of witnesses have suggested that other drugs being prescribed by the Armed Forces may be having similar effects but that the current lack of research and data over neurotoxicity and its potential mental health effects may be resulting in cases being missed or being misdiagnosed, for example as PTSD.⁴⁸

Other governments and organisations

US

1.27 Although there have been no specific inquiries, current US policy is that mefloquine 'should be reserved for individuals with intolerance or contraindications to both first-line medications [doxycycline and atovaquone-proguanil]'.⁴⁹ Defence advised:

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, 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.⁵⁰

1.28 It was reported in the media that mefloquine was investigated as a contributing factor in a series of murder-suicides at Fort Bragg, North Carolina in 2002 but the military panel concluded it was an unlikely factor.⁵¹

1.29 More recently, the media has reported calls by individuals and organisations for Congressional hearings into the use of mefloquine in the US military.⁵²

47 VADM Ray Griggs, VCDF, Senate Foreign Affairs, Defence and Trade Legislation Committee, *Estimates Hansard*, 10 February 2016, p. 173.

48 House of Commons Defence Committee, *Mental Health and the Armed Forces, Part One: The Scale of mental health issues*, 25 July 2018, p. 8.

49 *Submission 1*, p. 51.

50 *Submission 1*, p. 51.

51 Greg Miller, 'A gruesome war crime renews concerns about a malaria drug's psychiatric side effects', *Wired*, 15 August 2013.

Germany

1.30 In December 2016 the German defence ministry took mefloquine off the list of medications prescribed for soldiers.⁵³ Defence advised that similar to Ireland, in late 2017 Roche withdrew Lariam from the German market which became the catalyst for the German Ministry of Defence to order the cessation of use of mefloquine. Prior to that mefloquine had become a third-line antimalarial in 2013 when a new manufacturer's 'black box'⁵⁴ warning was added.⁵⁵

Ireland

1.31 Defence advised that mefloquine remains the first line antimalarial of the Irish Defence Force. Local advocates have campaigned for it to be a drug of last resort. Lariam was, however, withdrawn from sale in Ireland in July 2016 which the company said followed a review of the products and was not related to legal actions as it was still on the market in 16 other European countries. A number of current and serving members of the Irish Defence Force have submitted claims against the Defence Force and as at 27 June 2017 55 claims⁵⁶ had been received. One claim was settled on 30 November 2017 without admission of liability and the other cases are still pending.⁵⁷

NATO

1.32 Defence advised that in response to concerns raised in countries about the use of mefloquine, the Force Health Protection Working Group of the Committee of the Chiefs of Military Medical Services in NATO 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.⁵⁸

1.33 Further detail is available in the submission from Defence.⁵⁹

52 See <https://www.wusa9.com/article/news/investigations/investigation-vets-say-anti-malaria-drugs-they-were-ordered-to-take-caused-devastating-side-effects/65-560790227>, accessed 25 July 2018.

53 Sheila Pratt, 'Germany bans drug linked to brain damage, ramps up pressure on Canada', *iPolitics*, 9 December 2016.

54 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. See Defence, *Submission 1*, p. 53.

55 Defence, *Submission 1*, pp. 52–53.

56 Media in January 2018 reports 58 claims. Caroline O'Doherty, 'More soldiers to sue over malaria drug', *Irish Examiner*, 1 January 2018.

57 Defence, *Submission 1*, p. 52.

58 Defence, *Submission 1*, p. 53.

59 *Submission 1*, pp. 49–53.