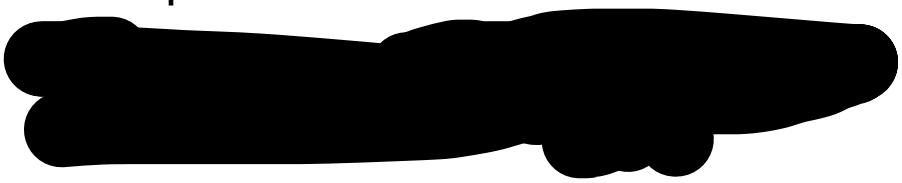
Brief for Lieutenant General (ret.) John Caligari AO, DSC

Safety and Efficacy Concerns Regarding the Experimental Antimalarial Drug Tafenoquine



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Purpose

1. This brief requests your assistance for Australian veterans who have been adversely affected by drugs given to them as part of the Army Malaria Institute (AMI) drug trials conducted in Bougainville and East Timor during the period 1998-2001. Your help is now urgently needed as recent developments internationally have brought one of these drugs, the antimalarial drug 'tafenoquine', a step closer to registration.

Importance

2. Why is this so important? Tafenoquine has caused serious long-term adverse health effects in a proportion of veterans who were exposed to this drug as part of military and pharmaceutical industry-funded clinical trials in the United States and Australia. These veterans have not been properly compensated or had their health conditions accepted by the Commonwealth, yet senior Defence officials have already stated that they will adopt tafenoquine as a key antimalarial drug for ADF personnel once the drug is registered in Australia. This is despite poor evidence of safety and appears only due to the involvement of the ADF in bringing this drug to market.

The Present Danger

3. The developers of tafenoquine have recently applied to United States and Australian health authorities for regulatory approval. The results of the AMI tafenoquine trials, particularly the East Timor 1 RAR trial in 2001 ("Study 033"), are being cited in support of these applications to justify tafenoquine as a safe and effective antimalarial drug, **despite strong evidence to the contrary**. Evidence of ill-effects that have been presented to the drug manufacturer GlaxoSmithKline (GSK) by our group have been submitted to the FDA as part of the GSK registration package, acknowledging that long-term health effects have been caused by exposure to tafenoquine for those involved in the AMI trials. **Despite this acknowledgement by the drug manufacturer, the Departments of Defence and Veterans Affairs continue to deny a causal relationship.**

Institutional Denials

4. Both Defence and DVA leaders have been informed of the serious health issues experienced by the Bougainville and East Timor drug trial veterans. They have failed to fund any investigation into these cases, despite proposals being submitted

to them on a number of occasions, and after their requests for us to make those proposals. Worse, in late 2016, senior Defence leaders prevented *any* retrospective investigation occurring into the health outcomes for these veterans by placing restrictions on data access which deny researchers access to any past trial data for these and other ADF trial cohorts. The ethical and intellectual ramifications of this action are still in dispute with senior Defence officials by the key Defence and DVA research providers, with no acceptable outcome to date despite Ministerial intervention. **Senior Defence officials have 'shut down' research into this question. This is simply unethical.**

The Risk

5. Should tafenoquine be approved by drug regulators, **there is a likelihood this drug will cause extensive harm to ADF members, including loss of life**. This has already occurred with its counterpart mefloquine over the past three decades. We do not want to see the same situation repeated. A clear statement of support is needed now, to prevent further harm to ADF members and their families in future.

Detailed Background

6. Tafenoquine is an experimental quinoline drug which was initially developed by the US Walter Reed Army Institute of Research (WRAIR) and is manufactured by GSK. The AMI trials were conducted in close cooperation with WRAIR and GSK, involving a total of 1,540 ADF tafenoquine subjects (including 492 personnel from the 1 RAR BG in Study 033), to investigate the safety and efficacy of tafenoquine for prevention and treatment of malaria. A large proportion of those subjects have since suffered serious, chronic symptoms consistent with adverse neurotoxic effects common to a number of similar quinoline antimalarial drugs.

7. Despite continued development of tafenoquine since the AMI trials, and despite our repeated requests, there have been **no follow up studies** on this large cohort (comprising more than a third of the total number of individuals administered tafenoquine worldwide to date) to assess the long term health risks of exposure to this drug.

8. In 2009, laboratory studies co-authored by WRAIR scientists found that tafenoquine was "the only [antimalarial] drug more neurotoxic than mefloquine". Mefloquine is known to be able to cause "lasting or permanent" brain damage at standard malaria prevention dosages comparable to the tafenoquine dosages used in Study 033. The symptoms of this brain damage are commonly mistaken for PTSD and other neuropsychiatric disorders.

9. Few if any of the AMI trial subjects adversely affected by tafenoquine (or mefloquine) have been provided with appropriate or effective specialist health care. Typically, those seeking help have been diagnosed and treated for PTSD or other psychiatric disorders, then subjected to ineffective and/or harmful treatments including antipsychotic drugs and electro-convulsive therapy (ECT). Unemployment, self-harm and family breakdown have been common, as well as cases of homelessness and suicide.

10. In 2014, WRAIR found that tafenoquine needs to be metabolised by the CYP2D6 enzyme in order for it to work against the malaria parasite, i.e. it does not work against malaria for individuals who have reduced CYP2D6 function, which is very common (e.g. in the range of 12-23% of Caucasians). A number of the AMI tafenoquine trial subjects who contracted vivax malaria despite supervised, documented compliance have since paid for their own CYP2D6 tests to find that they have reduced CYP2D6 function. Individual variation in CYP2D6 metabolism is also one of the possible explanations as to why only a certain proportion of individuals are susceptible to quinoline neurotoxicity.

11. Our own research has found that **ALL individuals who report significant long-term health issues that can be causally linked to being administered tafenoquine during the AMI trials are of a CYP2D6 metabolism type which makes this drug both ineffective as an antimalarial and potentially toxic at normal treatment levels.** This information has been passed to both the ADF and GSK. The ADF has ignored the potential ramifications of these findings. GSK acknowledged that they are aware of the risks for CYP2D6 poor metabolisers and were 'surprised' we had come to the same conclusion.

12. Since the AMI trials at the turn of the century, the development of tafenoquine has continued as follows:

a. GSK has continued to develop tafenoquine for the single dose treatment (aka "radical cure") of vivax malaria, in collaboration with the Medicines for Malaria Venture (MMV). The current AMI Director, Professor Dennis Shanks, is a member of the MMV scientific advisory committee. GSK recently announced that it has applied to both the US Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) for regulatory approval.

b. 60 Degrees Pharmaceuticals (60P), a company established by former US Army employee Dr Geoff Dow in 2010, has continued to develop tafenoquine for malaria prevention in collaboration with the US Army and individuals from AMI (specifically, Professor Shanks). 60P recently announced that it has applied to the FDA for regulatory approval and we anticipate that it will soon (if not already) make a similar application to the TGA.

13. 60P is attempting to downplay the importance of CYP450 phenotyping for tafenoquine use as this would make an application for prophylaxis commercially unviable.

14. While we are concerned about the development of tafenoquine in general, we are particularly concerned about the activities of 60P:

a. 60P was founded by Dr Dow while he was a contracted employee of the US Army. Dow had previously been employed at WRAIR on antimalarial drug research, then founded 60P while working on the development of tafenoquine as a contractor for the US Army Medical Materiel Development Activity (USAMMDA). Dow's supervisor at USAMMDA was Colonel Bryan Smith, who has since retired from the US Army and is now employed by Dow as the 60P Chief Medical Officer. During this period, Dow/60P was awarded the US Army

license for tafenoquine.

b. In 2014, 60P was awarded a US Army contract to "assist in the development of tafenoquine as a malaria prophylactic drug for FDA-TGA (Food and Drug Administration-Therapeutic Goods Administration) approval first in Australia and then in the United States." Dow's most recent tafenoquine paper indicates that 60P continues to receive funding from the US Army for this purpose.

c. In 2014, Smith was requested in writing to undertake follow up research on the AMI tafenoquine subjects, involving a senior US military specialist doctor, to investigate the drug's long term adverse effects. Smith acknowledged this request but declined to undertake the follow up research.

d. In 2015, Dow stated in an interview that his motivation in registering tafenoquine was to obtain a US FDA "priority review voucher" (PRV), valued at up to **several hundred million dollars**. In a 60P media release of 18 December 2017, Dow states "It is our belief our dossier will receive priority review, expediting the review of tafenoquine, and 60P may qualify for a priority review voucher."

e. Having previously declined to undertake follow up investigation of the long term adverse health effects of tafenoquine on the AMI trial subjects when they were employed by the US Army, 60P employees continue to cite the original AMI Study 033 findings in a 2017 "integrated safety analysis" paper which provides the basis of their regulatory applications.

f. The above situation reflects these comments by Professor Aaron Kesselheim (of Harvard University) when he said of the FDA PRV system last year: “I think it’s **problematic and potentially dangerous** to use this crucial process as **a lever to try to artificially create value for a for-profit company**, even for an area like neglected diseases that desperately needs more attention.”

15. Since 2015 we have made repeated efforts to raise our concerns about the safety and efficacy of tafenoquine in Australia and internationally, including but not limited to:

a. A Townsville health forum attended by senior ADF health officials, medical experts and a number of the original AMI tafenoquine trial subjects.

b. Numerous meetings with Ministers and senior officials from the Departments of Defence and Veterans Affairs.

c. A written proposal to the Minister for Veterans Affairs to fund a dedicated program of outreach, rehabilitation and research for ADF veterans adversely affected by tafenoquine and mefloquine.

d. Meetings with GSK representatives in Australia and the UK.

e. Written complaints to the TGA and the Minister for Health.

f. Written complaints to the Australian Federal Police.

16. Despite these efforts, there has been no follow up investigation into the long term adverse health impacts of tafenoquine among the 1,540 AMI trial subjects and our requests for a dedicated outreach and research program have been repeatedly rejected. During this period, senior ADF medical officials have repeatedly misled Ministers, Parliamentary committees, the media and the ex service community. We believe that this misinformation has been intended in part **to facilitate the successful registration of tafenoquine for the financial gain of 60P**.

17. In the event that tafenoquine is granted regulatory approval, we are also deeply concerned about the serious distress among the AMI tafenoquine trial subjects when they learn of the substantial financial gain to 60P after our requests for follow up research and medical have been repeatedly declined. In essence, many of these veterans and their families are begging to charity for health care while 60P stands to profit up to several hundred million dollars from the tafenoquine trials which caused so much harm.

Conclusion

18. Given that the above concerns about the safety and efficacy of tafenoquine have thus far been ignored, and health authorities are now considering applications for registration, we are now requesting you to publicly support our calls for a dedicated outreach, research and rehabilitation program those affected. This would ensure not only that the Commonwealth fulfils it's duty of care to the drug trial veterans and their families, but would also **reduce the risk of unnecessary harm to ADF personnel who may be given tafenoquine in future**.

19. We would be pleased to discuss this matter with you at your convenience on ( ) and thank you in anticipation for your support.