Australasian Society for Infectious Diseases (ASID) Inc
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Committee Secretary
Foreign Affairs, Defence and Trade References Committee
Department of the Senate
PO Box 6100
Parliament House
CANBERRA ACT 2600

Submission for: Senate Inquiry on the Use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force

We write on behalf of the Australasian Society for Infectious Diseases, the main professional body for infectious diseases and microbiology in Australia, to offer comments on the clinical aspects related to the inquiry. Our members include infectious diseases physicians with extensive experience in antimalarial clinical trials, prescription of antimalarial drugs for the treatment and prophylaxis of malaria in travellers to endemic countries and the use of antimalarial agents for patients in endemic countries.

Our comments are summarised below:

1. Whilst mefloquine and tafenoquine are quinoline antimalarial drugs, they have very different chemical structures, pharmacokinetics and mechanisms of action. Mefloquine is a chiral quinoline methanol and tafenoquine is an 8-aminoquinoline compound. Therefore, one cannot infer the safety and efficacy of one of these agents from the other.

2. Tafenoquine has activity against different stages (asexual, sexual and liver stages) of the malaria parasites. Tafenoquine, and the closely related drug primaquine, are unique in being the only available drugs with activity against the dormant liver stages (hypnozoites) of the that occur in *P. vivax* and *P. ovale* infection. The killing of all stages of the parasite is known as “radical cure”, without which patients with malaria are at risk of relapse. Tafenoquine has advantages over primaquine as it can be given as a single dose, rather than once or twice a day for 14 days. [1].

3. The ability to provide safe and effective radical cure of malaria is crucial for preventing relapsing malaria and cumulative risk of morbidity and mortality associated with recurrent *P. vivax* malaria. In Asia and the Americas the inability to provide reliable cure has resulted in a relative rise in the proportion of malaria due to *P. vivax*. The current regimen of 14 days primaquine is poorly adhered to, since many patients stop taking antimicrobial drugs once their fever has resolved [2]. The ability of tafenoquine to provide safe and effective radical cure with a single dose treatment represents one of the most significant advances in malaria therapeutics in the last 60 years.

4. Australian travellers to malaria endemic areas are at risk of contracting malaria; approximately 400 cases of imported malaria occur each year. Military deployments to malaria endemic areas are vulnerable to illness despite the availability of effective malaria chemoprophylaxis. The primary barrier to preventing malaria is adherence to chemoprophylaxis; weekly instead of daily dosing has significant advantages. Drug

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resistance has emerged to other prophylactic drugs including Malarone®, doxycycline and mefloquine. Tafenoquine provides a safe and effective alternative for chemoprophylaxis, administered weekly in individuals who are G6PD normal [3].

5. The most important toxicity associated with both tafenoquine and primaquine is their ability to cause severe haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD6) deficiency. Primaquine is structurally very similar to tafenoquine and has been used in a huge number of patients; its safety profile has been reviewed recently in a report by the World Health Organisation [4, 5]. More than 36 million people have been treated with the primaquine, most of the reported severe adverse events relate to haemolysis. The risk of haemolysis can be mitigated by testing for G6PD deficiency prior to prescribing primaquine. None of the reports of severe haemolysis occurred in patients known to be G6PD normal. Hence the main adverse events associated with tafenoquine can be readily managed by prior testing for G6PD deficiency.

6. Mefloquine is prescribed for the treatment and prophylaxis of malaria. It is well known to cause neurotoxicity, including insomnia, seizures, depression and psychosis. At a treatment dose of 25mg/kg, the incidence of severe neuropsychosis is about 1 in 1500 patients [6]. These severe events are related to the peak blood concentrations (CMax) and total exposure (Area under the curve; AUC); symptoms start early after treatment. When used for malaria prophylaxis individuals often experience sleep disturbance and anxiety. There is no clear proof of a causal relationship between the administration of weekly mefloquine chemoprophylaxis and long term irreversible mental health outcomes in patients without a prior history. The risks of acute neurotoxicity are about 1 in 10,000, but are significantly greater in individuals with a prior neuropsychiatric history; for this reason mefloquine is contraindicated in patients with a neuropsychiatric diagnosis. In view of its neuropsychiatric safety profile mefloquine should be used with caution for antimalarial chemoprophylaxis in our Defence Forces.

7. It is important to note that neurotoxicity is a well described complication of malaria infection itself, including coma, encephalopathy, seizures and mood disturbance. While this occurs predominantly with severe falciparum malaria, it can also occur in patients with uncomplicated malaria and *P. vivax* [7]. The risk of neurotoxicity is also dependent on prior medical history. Patients with a history of neuropsychiatric disorder are approximately 150 fold more likely to have acute neurotoxicity within 30 days of malaria, irrespective of treatment (unpublished data). Hence the presence of malaria confounds the ability to attribute neurotoxic symptoms in patients to either the drug or the disease.

8. There have been claims that tafenoquine causes neurotoxic adverse events in Australian military recruited into clinical trials. These have been sporadic and vary in presentation. In a few cases symptoms begin early after treatment, however many of the reports occur long after exposure, which is not in keeping the neurotoxicity observed with other antimalarial drugs such as chloroquine or mefloquine. Whilst these warrant close examination, there is no conclusive evidence of a causal relationship between the tafenoquine and neurotoxicity. The extensive experience of the structurally similar compound primaquine is reassuring. In more than 36 million exposures, there has been only 1 report of neurotoxicity in a 55 year old man who developed depression and psychosis after the 2nd dose of primaquine which resolved

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within 24 hrs on stopping the drug [8]. There are another 1518 reports of neurological symptoms in the Uppsala WHO Monitoring Centre for adverse events; most of these are mild and self-limiting in keeping with symptoms often seen in malaria e.g. dizziness and headache. Four of the reports were associated with seizure and psychosis, however all patients had received primaquine co-administered with either chloroquine or mefloquine, both with known risks of neurotoxicty.

9. The risk of adverse events needs to be considered in the context of the adverse consequences of malaria infection, which include haemolysis, neurotoxicity and death. Clinically, the greatest priority in military personal, travellers, and individuals from or living in malarious area, is to provide rapid effective cure, prevent recurrence and the need for re-treatment. In this context the ability of tafenoquine to provide effective radical cure with a single dose, without any convincing evidence of neurotoxicity, is an extremely important contribution to the pharmacopeia.

Thank you for the opportunity to provide comment on this important inquiry. We trust that our feedback will assist the committee to identify the most positive health outcome for our Defence Forces and we remain at the committee's disposal for any additional expert advice that may be required.

Yours sincerely,

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