Senate Foreign Affairs Defence and Trade References Committee Inquiry into the ADF use of Mefloquine and Tafenoquine.

Submission by GlaxoSmithKline Australia Pty Ltd

A. TERMS OF REFERENCE

*The use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force (**ADF**), with particular reference to:*

(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.

B. GLAXOSMITHKLINE AUSTRALIA SUBMISSION

1. For the purpose of assisting the Senate Foreign Affairs Defence and Trade References Committee (**Committee**) inquiry into the ADF's use of Mefloquine and Tafenoquine according to the terms of reference above, GlaxoSmithKline Australia Pty Ltd (**GSKA**) submits the following information for the Committee's consideration.

2. Ensuring the safety of any person that participates in a GlaxoSmithKline (**GSK**) clinical study is GSK's number one priority. All of our clinical trials are governed by strict regulation and monitoring to protect the safety and wellbeing of study participants. GSK is committed to the highest level of integrity in all clinical data production and has a long-standing commitment to clinical trial transparency.

Tafenoquine

3. Tafenoquine is an 8-aminoquinoline, and an analogue of primaquine, and is structurally distinct from mefloquine. Unlike other antimalarials, tafenoquine and primaquine are effective against the dormant liver stages (hypnozoites) of the *Plasmodium Vivax* (***P.vivax***) malaria parasite and also share a key safety concern: 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 must be tested for G6PD deficiency before receiving either of these drugs. Although primaquine has been widely used for over 60 years, estimates of the risks remain imprecise.

4. However, almost all reported serious adverse events are related to hemolysis in G6PD deficient individuals; in G6PD normal people the incidence is close to zero. Primaquine CNS side effects listed in the Australian consumer medical information (CMI, Primacin (*primaquine phosphate*) tablets 7.5mg) include headache and dizziness and the risk of significant CNS toxicity appears to be low: there has been only one report of a severe adverse event of psychosis in a patient who had received chloroquine and primaquine (Recht 2014). Nonetheless, the CNS safety profile for each new molecule must be adequately evaluated; information for tafenoquine is summarised below.

Regulatory matters

5. GSKA would like to state that, at time of this submission tafenoquine is not a medicinal product registered by the Therapeutic Goods Administration (**TGA**) and is not, and has never been, marketed in Australia. However, tafenoquine is currently under evaluation by the TGA for consideration as a single dose treatment for the radical cure (prevention of relapse) of *P.Vivax* malaria.

6. Tafenoquine 300 mg single dose was approved[1] on July 20, 2018 by the US Food and Drug Administration (**FDA**) for the radical cure (prevention of relapse) of *P. vivax* malaria in patients aged 16 years and older. As part of the US FDA review process, an Anti-Microbial Drugs Advisory Committee (**AMDAC**) meeting was held on 12 July 2018 during which the committee voted positively that there was substantial evidence of effectiveness (13-0) and adequate evidence of safety (12-1) for the use of tafenoquine in the clinical indication for radical cure of *P. vivax* malaria. Similarly, as part of the standard Australian TGA review process for new medicines, a closed TGA Advisory Committee for Medicines (**ACM**) meeting will be held on 03 August 2018 to review the overall registerability of tafenoquine.

[1] GSK R&D, in partnership with Medicines for Malaria Venture (MMV), has announced that the FDA approved, on the 20th July 2018, single-dose Krintafel (Tradename) (tafenoquine) for the radical cure (prevention of relapse) of *Plasmodium vivax* (*P. vivax*) malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection.

7. Tafenoquine has been historically used in clinical trials also for prophylaxis investigation with a repeat dosing regimen. As part of the clinical development program, clinical studies were conducted including among others, patients and healthy volunteers in Australia pursuant to clinical study protocols aligned to the TGA regulations governing clinical trials in Australia at the time, as detailed below.

Tafenoquine 300mg single dose for the radical cure (prevention of relapse) of P.vivax malaria

8. Thirteen clinical studies have been submitted to US and Australian regulatory authorities that specifically support the safety and efficacy of tafenoquine 300mg for the radical cure of *P.vivax* malaria. A total of more than 800 patients have received this dose during those studies. Three primary studies in patients with *P.vivax* malaria have shown this single dose regimen to be efficacious, and to have an acceptable safety profile that is generally similar to that of primaquine (15mg daily for 14 days), the only other currently approved drug for the clinical indication for radical cure of *P.vivax* malaria.

9. Common nervous system adverse events, such as dizziness and headache, were reported at similar frequencies in the tafenoquine and primaquine recipients. Insomnia and anxiety were the only psychiatric adverse events that were reported for tafenoquine; these events were reported at low frequency (4% and <1%, respectively), and at similar rates in the tafenoquine and primaquine groups. None of these events were reported as severe or serious, and each of them resolved. In addition, in an ophthalmologic safety study, where 330 healthy volunteers received tafenoquine 300mg single dose, there was no evidence of retinal toxicity, using sensitive techniques (ocular coherence tomography and fundus autofluorescence).

10. Across the clinical studies for individuals receiving a 300mg single dose of tafenoquine (which includes 33 completed studies in healthy volunteers and patients), for individuals receiving a single dose of tafenoquine, two serious psychiatric adverse events of psychosis occurred following dosage of ≥ 350mg. These occurred in individuals with a history of psychosis and schizophrenia (not disclosed at study entry), which represent clear risk factors for these events. Two cases of depressed mood were reported following single doses of 600mg. Only one of these events occurred in an individual without a prior history of depression; the event resolved within 3 days, without intervention.

11. Safety data relating to neurologic and psychiatric adverse events from all subjects receiving tafenoquine throughout the clinical development program (across all dosing regimens and indications) were evaluated when considering the efficacy and safety of tafenoquine during the AMDAC[2] and the FDA review of the regulatory submission supporting the radical cure indication. It should also be noted that as part of the US approval, post-marketing surveillance will be conducted, and this will include follow-up on any neurologic and central nervous system (**CNS**) adverse effects.

[2] The FDA briefing document for the meeting of the Antimicrobial Drugs Advisory Committee on 12 July 2018 is available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM612874.pdf

12. Taken together, these clinical data indicate a low risk for serious or concerning CNS adverse effects in patients without a history of psychiatric disorder, as no such events have occurred in >800 individuals treated with the 300mg single dose.

Tafenoquine Studies in Australian Defence Force personnel

13. Three studies concerning tafenoquine were conducted in Australian Defence Force (**ADF**) personnel deployed to malaria-endemic areas during 1999-2001. A total of 1536 ADF personnel received tafenoquine. Treatment regimens were studied in randomised trials for (1) post-exposure prophylaxis at the end of deployment; and (2) long term prophylaxis during deployment. In addition, ADF personnel with recurrent *P.vivax* malaria received tafenoquine under a 'compassionate use' programme.

    (1) **Post exposure prophylaxis** - Following a standard prophylaxis regimen with doxycycline, tafenoquine doses of 200mg or 400mg daily for 3 days (total cumulative dose 600mg or 1200mg) were compared with a 14 day course of primaquine. This study was unblinded; 1013 individuals received tafenoquine (Elmes 2008).

    (2) **Prophylaxis** – A regimen of tafenoquine 200mg on three successive days (loading dose), and then 200mg weekly for 6 months (total cumulative dose 5200mg) was compared with mefloquine (registered in Australia 1993), an approved drug and routinely used for prophylaxis at the time of the study. This study was blinded; 492 individuals received tafenoquine (Nasveld 2010).

14. As for all of GSK's clinical trials, the protocols for both studies contained detailed guidelines on eliciting and documenting adverse experiences during the study. The results of these two randomised clinical trials have been published. The safety issues that were identified during these studies were as follows: poorer GI tolerability with the 1200mg dose administered over 3 days, and the occurrence of vortex keratopathy with the long-term prophylaxis regimen. This condition, affecting the cornea, is benign, reversible after the end of therapy, and did not affect vision.

15. In the compassionate use study, 31 individuals who had previously relapsed with *P.vivax* malaria despite treatment with chloroquine + primaquine received tafenoquine 200mg on 3 successive days, and then 200mg once weekly for 8 weeks. The treatment was reported to be well-tolerated. (Kitchener 2007).

16. GSKA is aware of safety concerns related to ongoing neurologic and/or psychiatric health issues raised in the last two years by a number of ADF veterans[3] who participated in studies investigating mefloquine and/or tafenoquine. GSK has followed up with those who have recently reported events and will continue to do so. These recent reports, which describe more CNS

[3] So far as GSKA is aware, reports of psychiatric disorders have been made by 18 subjects out of the >1500 individuals who received tafenoquine in the ADF studies.

events than were reported at the time of the studies, prompted a thorough evaluation by GSK R&D of all available clinical trial data and relevant literature.

17. That evaluation was made more challenging by the following factors:

    (1) The reports that were received provided only limited medical information, and were not medically confirmed; and

    (2) The majority of soldiers making reports were exposed to triggers for post-traumatic stress syndrome, the symptoms of which are similar to those included in their reports.

18. The evaluation found that the rate for CNS effects (reported at the time of the study) was higher in the ADF study compared to another study which studied the same tafenoquine dosing regimen (200mg x 3 loading dose, then 200mg weekly for 6months) in healthy volunteers, including non-deployed military personnel (Leary 2009). The absence of an untreated control group in the ADF study poses difficulties in the interpretation of these data compared to background rates of CNS events in a military population. Literature suggest that there is a substantial background rate of depression[4] and anxiety disorders[5] in military populations.

19. To date, it has not been possible to make a connection between mild to moderate side effects reported during the ADF study and any permanent serious long-term effects with onset after completion of the study. It is therefore possible that the deployed ADF soldiers represented a higher risk population.

Conclusion

20. GSKA encourages individuals, who participate, or who have participated, in historical, recent and ongoing studies to report any adverse events to us so that we can continue to monitor the safety profile of our medicines.

21. Data from the randomized prophylaxis studies have been submitted to regulatory authorities (FDA and TGA), as have the recent reports of ongoing mental health issues received from ADF veterans. Safety data across the various tafenoquine studies, relating to different doses and durations of therapy have been reviewed as part of the US FDA review and subsequent regulatory approval of tafenoquine 300 mg single dose for the approved clinical indication for radical cure (prevention of relapse) of *P.vivax* malaria inpatients aged 16 years and older. Additionally, this safety information is also being currently reviewed by the TGA for a regulatory submission concerning the same proposed radical cure clinical indication.

22. GSKA would be willing to provide the Committee with any such further information as is relevant to the terms of reference as the Committee may request and which is within GSKA's knowledge.

[4] ~12%, Brignone, 2017; Fanning, 2013; Ilgen, 2010; O'Toole, 2015; Ramsawh, 2014
[5] ~10%, Brignone, 2017; Fanning, 2013; Ilgen, 2010; McFarlane, 2011; O'Toole, 2015

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