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

Submission by GlaxoSmithKline Australia Pty Ltd

GSK Australia welcomes the opportunity to respond to submissions to the above Senate Inquiry which include direct reference to GSK, and, to the extent possible, provide clarification for the Committee around some of the queries raised in respect of tafenoquine.

GSK would also like to update the Committee that on 13 September 2018, tafenoquine 300 mg single dose was approved by the Australian Therapeutic Goods Administration (TGA) for the radical cure (prevention of relapse) of P. vivax malaria in patients aged 16 years and older.

1. How does the toxicology profile of tafenoquine compare to mefloquine and other anti-malarials?

Tafenoquine and mefloquine are both quinolines but they are chemically distinct. Tafenoquine was developed as a primaquine analogue. Established anti-malarials include atovaquone/proguanil, doxycycline, mefloquine, primaquine and chloroquine. If one were to compare tafenoquine to established anti-malarials based on chemical structure, then primaquine would be the closest analogue.

Clinical studies in radical cure of P. vivax malaria show that tafenoquine and primaquine have a broadly similar safety and efficacy profile. Tafenoquine has been approved this year by both the TGA and FDA for use in the radical cure (prevention of relapse) of P. vivax malaria in patients aged 16 years and older. Prior to 2018, primaquine was the only registered medicine for the radical cure (prevention of relapse) of P. vivax malaria. Tafenoquine provides an alternative treatment option for radical cure of P. vivax malaria that can be effective in a single dose, rather than a 14-day dosage as required with primaquine.

In the 1999 – 2001 period, studies including Study 033 and Study 049, which were in collaboration with the ADF, assessed the use of tafenoquine for malaria prophylaxis.

In Submission 94, the Committee was advised – by reference to a Walter Reed Army Institute of Research (WRAIR) study – that tafenoquine is more neurotoxic than mefloquine. To clarify, the quoted reference is an in vitro cytotoxicity study in rat cell lines that was presented as a poster at a scientific meeting. This in vitro activity does not translate in vivo as no functional or histopathological neurological effects are seen in single/repeat dose studies in rats.

2. What is the neurotoxicity profile of tafenoquine?

GSK holds itself to the highest standards in striving to comply with all relevant ethical, regulatory and legal requirements when conducting clinical trials. The preclinical toxicology package for tafenoquine has been reviewed by both the TGA and FDA. Details of the definitive toxicology studies are in the public domain: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210795Orig1s000MultidisciplineR.pdf

The full report of safety data for tafenoquine has been submitted to the TGA and FDA for their review and approval, which approval has been received. GSK has no additional safety data for tafenoquine other than as already disclosed to the TGA and FDA, and ongoing studies have not revealed any new safety signal. Contrary to a suggestion made in Submission 94, there is no evidence that tafenoquine concentrates at toxic levels in the brain causing permanent brain injury.

None of the neuropsychiatric adverse events experienced in trials undertaken with the ADF and reported during the conduct of the studies fulfilled the requirements for immediate reporting to regulators. However, given the high standards that GSK holds itself to, GSK did submit the limited neuropsychiatric adverse event information available for tafenoquine to the FDA for their consideration when we became aware of these reports by veterans, many years after the completion of the studies, from 2016 onwards. In contrast to a suggestion made in Submission 16, this was not based on any conclusion of a causal relationship between the reports of ongoing ill-health from ADF veterans and tafenoquine.

With regards to vortex keratopathy, immediate reporting (15 day INDSR) was undertaken for the initial cases; further cases did not fulfil the requirements for immediate reporting to regulators, however, later safety updates were provided. Data concerning vortex keratopathy (which is benign and reversible and does not affect vision) is accurately presented in the Nasveld publication.

It is correctly noted in other submissions received by the Committee that tafenoquine did not undergo neurotoxicity testing in primates prior to the clinical trials with the ADF. This is because the rat is the standard species for the assessment of neurobehavioral effects due to the extensive historical background data available in this species and well-characterised responses to a wide-variety of drugs known to cause neurobehavioural effects. The mouse, rat, and dog are recognised by international regulatory agencies for use in safety evaluation studies (which would include the assessment of neurotoxicity) and extensive historical control histopathology background data are available in these species that would further justify their use. Studies in mice, rats and dogs indicate that tafenoquine does not represent a neurotoxicity risk at exposures that are comparable or in excess to those seen at the recommended human dose.

It should be noted that the preclinical toxicology package has been reviewed and approved by both the TGA and FDA.

3. What are the contraindicators for tafenoquine?

Tafenoquine is contraindicated in the following.

- G6PD deficiency.
- Pregnancy.
- Breastfeeding an infant who is G6PD-deficient or if the G6PD status of the infant is unknown.
- Patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of the formulation.

These contraindications are similar to those for primaquine. Given the differing chemical make-up of tafenoquine and mefloquine, the contraindications for tafenoquine differ to those for mefloquine, and have been fully reviewed by the TGA and FDA. Appropriate labelling that specifically describes the contraindications, warnings and precautions for tafenoquine has been agreed with the FDA and TGA.

4. What are the metabolization requirements for tafenoquine?

The Committee has been advised in other submissions to this Senate Inquiry that tafenoquine requires activation by the CYP 2D6 enzyme to be effective (as is the case for primaquine), and two studies in mice are referenced in support of this. Clinical trials of tafenoquine for radical cure of P. vivax malaria show no difference in efficacy resulting from CYP 2D6 metabolizer status (extensive, intermediate or poor) [St Jean 2016]. The results of the mice studies are likely accounted for by differences in substrate metabolism and tissue expression between the CYP2D orthologues (mouse and human) [Miksys 2005, Scheer 2012]. The Committee has also been advised in Submission 16 that CYP alleles have been linked to treatment failure for antimalarials, which is documented in the case of primaquine, however, GSK has found no evidence that this is the case for tafenoquine.

5. What has been reported during recent regulatory developments?

Tafenoquine 300 mg single dose was approved on July 20, 2018 by the FDA and on 13 September 2018 by the TGA 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 was held on 03 August 2018 to review the overall registerability of tafenoquine. The ACM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the TGA Delegate and considered tafenoquine to have an overall positive benefit-risk profile for the indication of radical cure of P. vivax malaria.

The FDA Advisory Committee were asked to give their opinion on the safety and efficacy of the 300mg single dose for the radical cure of P. vivax malaria, hence GSK's FDA briefing book focusses on the data relevant to this dose and indication. However, all serious or medically significant neuropsychiatric adverse events from all dosing regimens in all studies were also submitted for review. The FDA have concluded that the benefit:risk profile for tafenoquine for P. vivax malaria radical cure is appropriate for registration. The FDA and the Advisory Committee were aware of the concerns raised by ADF veterans. The same data were submitted to the TGA. The TGA Delegate concluded that the adverse effects profile with the single 300mg tafenoquine dose was considered acceptable and the overall risk-benefit was favourable.

References

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