Australian Government

Department of Health

Secretary

Committee Secretary
Senate Foreign Affairs, Defence and Trade References Committee
PO Box 6100
Parliament House
CANBERRA ACT 2600

Dear Committee Secretary

Inquiry into the "Use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force"

Thank you for the invitation to make a submission from the Department of Health to this Senate inquiry.

The Health Department's submission focusses on the role of the national medicines regulator, the Therapeutic Goods Administration (TGA). The TGA is responsible for administering the national system of controls over the supply, import, export, manufacturing and advertising of therapeutic goods, including medicines, vaccines, and medical devices.

Our submission to the inquiry does not specifically reflect on issues of prescription to, and adverse events from these medicines within Australian Defence Force personnel, but rather provides information on the use and regulatory status of these medicines in Australia and information on adverse event reports received.

Mefloquine

Mefloquine is registered in Australia under the brand name Lariam. Lariam received regulatory approval over 25 years ago, being entered on to the Australian Register of Therapeutic Goods on 27 January 1993.

Lariam is indicated for:

Malaria treatment
Lariam is indicated for the treatment of acute attacks of malaria due to P. falciparum infection resistant to conventional antimalarial drugs.

Following therapy of mixed P. falciparum and P. vivax malaria with Lariam, relapse chemoprophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered in order to eliminate hepatic forms of P. vivax.

Malaria chemoprophylaxis (i.e. prevention)
For travellers to countries with documented chloroquine and antifolate combination ([sulfadoxine/pyrimethamine] / [dapsone/pyrimethamine]) resistant P. falciparum malaria, who are considered to be at high risk for malaria in view of their residence or travel (of up to 3 months duration) through rural areas (between the dusk to dawn period).

For travellers hypersensitive to sulphonamides and sulphones, who are considered to be at high risk for malaria in view of their residence or travel (of up to 3 months duration) through rural areas, (between the dusk to dawn period) in countries with high level chloroquine-resistant P. falciparum malaria.

All medicines present a balance of benefits and risks for the populations in which they are intended for use, and regulatory approval by TGA is based on an assessment that at a population level the benefits of the medicine exceed risks. One way of managing risks is to advise on situations in which a particular medicine is not recommended for use. It is up to the prescribing doctor to be aware of such contraindications and to decide whether the medicine should be prescribed or an alternative selected. Discussing potential adverse effects with the patient who is to be prescribed the medicine is part of the process of informed consent in medical practice.

The use of mefloquine is contraindicated (i.e. not recommended for use) as follows:

Patients with a past history of active depression, a recent history of depression, generalised anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders or convulsions should not be prescribed Lariam prophylactically.

The Australian Product Information (PI) for Lariam, which is the main source of information on the medicine for prescribing doctors, has been continuously updated since its initial registration in 1993, in order to convey to prescribers and consumers the current state of knowledge about the safety of this medicine.

The PI was last updated on 10 January 2018. It contains the following warning about neuropsychiatric adverse effects:

Lariam may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behaviour. On occasions, these symptoms have been reported to continue long after Lariam has been stopped. Lariam should not be prescribed in patients with a history of psychiatric symptoms (see CONTRAINDICATIONS) and should be used with caution in patients with a previous history of depression.

In chemoprophylaxis the safety profile of mefloquine is characterised by a predominance of neuropsychiatric adverse reactions. During prophylactic use, if signs of unexplained acute anxiety, depression, restlessness or confusion are noticed, these may be considered

prodromal to a more serious event. In these cases, the drug must be discontinued. Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist after discontinuation of the drug. In a small number of patients it has been reported that some neuropsychiatric events (including depression, dizziness or vertigo and loss of balance) may continue for months or longer after discontinuation of the drug. Therapy should be initiated one week before travel commences (see DOSAGE AND ADMINISTRATION), as acute psychiatric effects are more likely to manifest at the start of treatment.

The Adverse Effects Section of the Lariam PI notes:

At the doses given for acute malaria, adverse reactions to Lariam may not be distinguishable from symptoms of the disease itself.

Among subjects who received Lariam for treatment, the most frequently observed adverse experiences included: dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhoea, skin rash, abdominal pain, fatigue, loss of appetite and tinnitus. Those side effects occurring less frequently included bradycardia, hair loss, emotional problems, pruritus, asthenia, transient emotional disturbances and telogen effluvium (loss of resting hair). Seizures have also been reported.

The rate of adverse events associated with Lariam is published to be similar to that with other antimalarial prophylactic medications. In chemoprophylaxis the safety profile of Lariam adverse events is characterised by a predominance of neuropsychiatric adverse reactions (see PRECAUTIONS).

Due to the long half-life of Lariam, adverse reactions to Lariam may occur or persist up to several weeks after the last dose. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine. There have been rare reports of suicidal ideations. No relationship to drug administration has been established.

The TGA collects reports of suspected adverse reactions to medicines being used in Australia. These reports contain suspected (but not confirmed) associations that reflect the observations of an individual reporting the adverse event.

It is important to keep in mind that there might be no relationship between the adverse event and the medicine; the adverse event may be due to other medicines, to the illness under treatment or any concomitant illness, or may be coincidental. Consequently, adverse event reports submitted to the TGA cannot be used to prove that a patient has had an adverse experience due to a medicine.

Rather, the purpose of reporting adverse events to the TGA is to allow the TGA to monitor the safety of medicines used in Australia to contribute to a better understanding of their possible adverse effects when they are used in routine practice and outside of the controlled conditions of clinical trials.

The TGA receives adverse event reports associated with medicines and medical devices. These reports come from a wide range of sources, including members of the public, general practitioners, nurses, other health professionals and the therapeutic goods industry. TGA maintains a public database of suspected adverse events, which can be searched by product name: www.tga.gov.au/database-adverse-event-notifications-daen.

It is important to emphasise that the search results cannot be used to determine the incidence of an adverse event (that is, how often the adverse event has occurred in patients taking a particular medicine), or the likelihood of a patient experiencing that reaction, as they do not include information on the total number of patients who have taken the medication or the total number of adverse events occurring (because reporting of adverse events is not mandatory, other than for industry sponsors). As a result the search results cannot be used to make accurate numerical comparisons between adverse events associated with different medicines.

As of 25 June 2018, the TGA's database of suspected adverse reactions to medicines contains 242 reports for mefloquine, submitted in the 25 years from 1993 to 2018 – this is an average of under 10 per annum. The most commonly-reported events are neuropsychiatric (depression 55 reports, dizziness 53, anxiety 51, headache 29, nightmare 28, insomnia 24, agitation 22) and gastrointestinal (nausea 52 reports, abdominal pain 19, diarrhoea 17). This is in keeping with the known adverse effect profile of the drug.

In that 25 year period there were 11 reports of suicidal ideation, and 4 reports of completed suicide, with no other reports of fatalities. The database does not contain any reports describing adverse events arising from the use of mefloquine in a clinical trial. The four cases of suicide reported in the database contained insufficient information to determine cause-and-effect.

The International regulatory status of mefloquine is as follows. In the UK, mefloquine is indicated for treatment of Plasmodium falciparum malaria resistant to other antimalarials, and for chemoprophylaxis for travellers to areas with multiply resistant strains of P. falciparum malaria. In Canada and the US, mefloquine is indicated for treatment of malaria caused by mefloquine-susceptible strains of P. falciparum or by P. vivax, and for prophylaxis of both P. falciparum and P. vivax.

On 1 June 2017, Health Canada published a Summary Safety Review titled "Mefloquine – assessing the potential risk of rare long-lasting and permanent adverse events related to the brain and nervous system (neurological) and mental health (psychiatric). [www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-mefloquine-assessing-potential-risk-rare-long-lasting-permanent-adverse-events-related-brain-nervous-system-neurological-mental.html]. This review found limited evidence supporting that long-lasting and permanent neurological and psychiatric adverse events are caused by the use of mefloquine. It also concluded that the current product information for mefloquine describes the potential for long-lasting neurological and psychiatric adverse events which aligns with the review findings.

In 2013, the US Food and Drug Administration strengthened warnings in the mefloquine labelling, including the possibility that the neurologic side effects (dizziness, loss of balance, or ringing in the ears) may persist or become permanent, and that the psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations [www.fda.gov/Drugs/DrugSafety/ucm362227.htm].

In 2013, the UK Medicines and Healthcare products Regulatory Agency strengthened warnings regarding neuropsychiatric side effects of mefloquine [www.gov.uk/drug-safety-update/mefloquine-strengthened-warnings-on-neuropsychiatric-side-effects]. The updated warnings stated that:

- *Psychiatric symptoms associated with use of mefloquine such as nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodromal for a more serious event.*
- *Cases of suicide, suicidal thoughts, and self-endangering behaviour such as attempted suicide have been reported in association with use of mefloquine.*
- *Adverse reactions may occur and persist up to several months after discontinuation of mefloquine because of its long half-life. In a small number of patients, dizziness or vertigo and loss of balance have been reported to continue for months after discontinuation of the drug.*
- *To minimise the risk of these adverse reactions, mefloquine must not be used for chemoprophylaxis in patients with active or a history of psychiatric disturbances such as depression, anxiety disorders, schizophrenia, or other psychiatric disorders.*
- *If neuropsychiatric reactions or changes to mental state occur during mefloquine chemoprophylaxis, the patient should be advised to stop taking mefloquine and seek medical advice as soon as possible so that it can be replaced by another medicine for malaria prevention.*

Tafenoquine

Although **tafenoquine** was developed over 20 years ago, and clinically trialled more than a decade ago, tafenoquine is not currently registered in Australia (or the US, UK or Canada).

There are presently two applications under evaluation by the TGA. One is for a single dose radical cure (prevention of relapse) of malaria submitted by GlaxoSmithKline Australia Pty Ltd (GSK). The second application, sought by Biocelect Pty Ltd, is proposed for malaria prophylaxis in adults for up to 6 months of continuous dosing. Tafenoquine is also under regulatory evaluation by the US Food and Drug Administration. While neither TGA nor FDA routinely publish the names of medicines under review, in the case of tafenoquine this information is in the public domain.

If approved it would be the first new medicine to provide a cure of relapsing malaria in over 60 years. It is being developed as single dose to prevent relapse and is to be administered along with a 3 day course of an artemisinin combination therapy. The particular potential of tafenoquine is that through a single dose it can eliminate the reservoir of P. vivax malaria parasites in the liver. The potential for elimination of vivax malaria by using a single dose means that there is tremendous interest in its use in developing countries in Australia's region, such as those in the Greater Mekong Subregion, Eastern Indonesia and Papua New Guinea. The alternative, primaquine requires daily dosing for 14 days and patient compliance with this dose regimen is a particular issue. Both tafenoquine and primaquine are associated with a risk of haemolytic side effects in patients lacking, or low in a particular enzyme glucose-6-phospahate dehydrogenase. Testing for this enzyme in patients is therefore important prior to use of these medicines.

Regulatory decisions on both applications to TGA are currently expected in September 2018.

In July 2018, the Antimicrobial Drugs Advisory Committee (AMDAC) of the United States Food and Drug Administration (FDA) voted that there is substantial evidence of the effectiveness (13 for; 0 against) and adequate evidence of the safety (12 for; 1 against) of single-dose tafenoquine for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older. The AMDAC is convened to provide the FDA with independent expert advice on a broad range of issues related to infectious diseases and disorders. The committee provides non-binding recommendations for consideration by the FDA, with the final decision on regulatory approval made by the FDA. The US FDA is expected to make an announcement in relation to the use of tafenoquine for prophylaxis in August.

TGA's assessment processes for new drugs, such as tafenoquine, are aligned internationally with major regulators such as the US FDA and the European medicines Agency. However, the TGA undertakes an independent assessment of data to support the safety, quality and efficacy of medicines using international standard and benchmarks to assist with the assessment. Where needed, TGA medical officers raise questions with applicants to clarify scientific, technical and clinical issues. The TGA assessment has a legislated timeframe of 255 working days but most medicines are approved within a shorter timeframe, particular where the medicine is seen to be a priority for patients.

Both tafenoquine applications are being assessed as a priority. An approval by TGA allows supply in Australia and also export from Australia. Subsidy for medicines is a matter for the government, based on a recommendation from the Pharmaceutical Benefits Advisory Committee, not the TGA.

Access to tafenoquine in clinical trials

Clinical trials in Australia involving unapproved medicines must be notified to the TGA before the trial commences. The TGA does not usually evaluate data relating to most clinical trials at the time of submission, rather a Human Research Ethics Committee (HREC) reviews the scientific validity of the trial design, the balance of risk versus harm of the medicine, the ethical acceptability of the trial process, and approves the trial protocol. The HREC is also responsible for monitoring the conduct of the trial. The institution or organisation at which the trial will be conducted gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC. However, sponsors of clinical trials of unapproved medicines are responsible for reporting all suspected unexpected serious adverse reactions to the medicine to the TGA within 15 days of becoming aware of the event.

During 2000-2002, the Australian Army Malaria Institute conducted two clinical trials using mefloquine and tafenoquine in Australian battalion groups deployed to East Timor [www.defence.gov.au/Publications/COI/Docs/COI-AntiMalarialTrials.pdf]. These trials were reviewed and approved by the then Australian Defence Medical Ethics Committee.

The TGA's database contains 36 reports for tafenoquine, all reported following use of tafenoquine in a clinical trial. Six reports were submitted to the TGA in 2001, and the remaining 30 reports were received during 2016-2018, although in nearly all reports the use of tafenoquine had been some time earlier, namely during the year 2000. There are 13 reports each of anxiety and depression, 7 reports of post-traumatic stress disorder, 6 reports of suicidal ideation, and 2 reports of completed suicide (with no other reports of fatalities). The database entries on the two cases of suicide contain insufficient information to determine causality.

Our staff would be happy to provide further information to the Inquiry if required.

Yours sincerely

Glenys Beauchamp

25 July 2018