Roche

Committee Secretary
Senate Foreign Affairs, Defence and Trade References Committee
PO Box 6100
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Canberra ACT 2600

30 July 2018

Australian Defence Force (ADF) use of mefloquine and tafenoquine

Dear Secretary,

Roche welcomes the opportunity to contribute to the Senate Foreign Affairs, Defence and Trade References Committee (the Committee) inquiry into Australian Defence Force (ADF) use of mefloquine and tafenoquine. As the sponsor of Lariam® (mefloquine), Roche hopes to be able to provide context to the Committee on how Roche seeks to ensure the quality use of its medicines.

This submission primarily focuses on Term of Reference (d) a comparison of international evidence/literature available on the impact of Quinoline anti-malarials. The submission may also be relevant 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; and (b) the nature and extent of any adverse health effects of those who have taken Mefloquine/Tafenoquine on serving and former ADF personnel.

This submission provides a brief overview of malaria and the medicines used to treat it, specifically the Roche medicine mefloquine. It outlines how the data which inform our understanding of mefloquine are generated and collected by Roche, and how the medicine is approved by the Australian Government and made available to clinicians and patients. It also notes worldwide usage of mefloquine, and its place amongst other malaria treatment options as recommended by various organisations such as the World Health Organisation (WHO) and Centres for Disease Control and Prevention (CDC).

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Executive Summary

Malaria is a life-threatening, infectious disease transmitted by mosquitoes. It has a devastating impact on a person's health and livelihood. The most serious form of malaria affects the brain and can cause death within a few days. In 2016 there were 216 million cases of malaria reported globally, and an estimated 445 thousand malaria deaths[1].

Despite the availability of several treatments for malaria, it remains a significant public health challenge. Not all patients respond to treatments equally, or are able to tolerate all treatments. In addition, some treatments may become less effective over time (resistance). As such it is important for clinicians to have a broad range of treatment options available to choose from.

Resistance to anti-malarial medicines such as chloroquine and sulfadoxine-pyrimethamine, became widespread in the 1950s and 1960s, undermining efforts to control malaria and reversing gains which had been made in child survival. Mefloquine emerged from an extensive research program undertaken independently by the United States Army [the Walter Reed Army Institute of Research] in 1963, in which over 100,000 separate compounds were evaluated prior to mefloquine being selected[2]. To secure the medicine's commercial manufacture and widespread availability, both intellectual property rights and research related to mefloquine were transferred to F. Hoffman-La Roche Ltd. (Roche).

Mefloquine was first granted marketing approval in Switzerland on 20 February 1984, and it was first included on the Australian Register of Therapeutic Goods on 3 September 1986[3]. As of 19 February 2018, mefloquine was approved in approximately 27 countries worldwide. It is estimated that more than forty million patients around the world have been treated with mefloquine since the medicine was first made available[4].

Melfloquine is currently listed as a malaria treatment option by the World Health Organisation (WHO)[5] and Centres for Disease Control and Prevention (CDC)[6]. Mefloquine is listed as a WHO Essential Medicine and continues to be recommended in other authoritative guidelines for the prophylaxis (prevention) of malaria[7-9].

All medicines in Australia must be evaluated by the Therapeutic Goods Administration (TGA). The TGA approves and regulates products based on an assessment of risks versus benefits. A medicine's side effects will be considered in the context of the disease that is being treated and how effective the medicine is. The possibility of a particular side effect may be deemed acceptable against the background of a life-threatening disease like malaria. A sponsor of therapeutic goods such as Roche has an obligation to apply to the TGA to register therapeutic goods before they are supplied, and to notify the TGA of any changes to the information used to support the registration of the product

which affect the benefit-risk analysis for the product. After registration, sponsors such as Roche are required to collect and evaluate safety information about the product continuously, in order to report serious adverse reactions and significant safety issues to the TGA, identify any changes to the benefit–risk balance of the product and to take action when necessary. Some ways in which Roche obtains safety information post-registration include: reports directly from healthcare professionals and consumers; by screening worldwide published scientific and medical literature; from media sources; and from the TGA.

While a medicine might be approved by a regulator, it is not necessarily suitable for everyone. For that reason, companies work with regulators to develop and update Product Information (PI) and Consumer Medicine Information (CMI). These assist clinicians, pharmacists and patients in knowing what factors to consider when selecting the most appropriate medicine.

The PI is an important reference document developed by pharmaceutical sponsors of a Medicine (e.g. Roche) and approved by the TGA. The PI provides objective information about the quality, safety and effectiveness of a medicine, as supported by data provided to and evaluated by the TGA. The information in the PI is intended to assist healthcare professionals when prescribing and dispensing medicines and in their consultations with patients in Australia. A version of this document intended for patients called the CMI is also made available. Both these documents are continuously updated to reflect the most up-to-date safety data. Updates to the PI are based on updates to the Core Data Sheet (CDS). The CDS represents the Global company position and forms the basis of the Australian document. The CDS for each product includes all pivotal data, and relevant technical, clinical, and non-clinical safety and efficacy data. The CDS is updated and reviewed throughout the lifecycle of the product, when new information becomes available.

All medicines have benefits and risks. Clinicians carefully evaluate these factors when considering which medicines to prescribe and how to do so. Roche closely monitors the safety profile of each of its medicines, including mefloquine, and ensures all reports of side effects from prescribers, patients and researchers are used to update and inform safety information. Roche updates the labels (Product Information) of all its medicines on an ongoing basis to reflect the most up-to-date known safety data.

In the case of mefloquine, important safety information from patient and clinician reports have been included in PIs and CMIs since the medicine was made available in Australia[10-13]. This has included information about neuropsychiatric side effects and precautions around use by people with existing mental health conditions. The purpose of this is to allow healthcare professionals to make a considered judgement on whether mefloquine or another antimalarial is most appropriate for a given person.

Based on Roche's evaluation of all available information, including data from post-marketing experience, published literature and other safety-risk management sources, the benefit-risk profile of mefloquine use in the prevention and treatment of malaria remains positive. This is aligned with the views of regulators such as the TGA and bodies such as the WHO and CDC. As a result, it remains available as an option for clinicians and patients to consider when selecting a medicine to prevent or treat the serious condition of malaria.

1.0 Malaria

Malaria is a common and life-threatening disease which affects adults and children in many tropical and subtropical countries. It is currently endemic in over 90 countries[1].

It is an infectious disease caused by *Plasmodium* parasites. The parasites are spread to humans through the bites of infected female *Anopheles* mosquitoes. There are 5 *Plasmodium* parasite species which cause malaria in humans: *P. facliparum, P.Vivax, P.malariae, P.ovale* and *P.knowlesi.* Two species *P.falciparum* and *P.vivax* pose the greatest threat. *P.falciparum* is the most prevalent malaria parasite on the African continent. It is responsible for most malaria-related deaths globally. *P.vivax* is the dominant malaria parasite in most countries outside of sub-Saharan Africa[1].

1.1 Consequences of malarial infections

Malaria remains a significant public health challenge, and has a devastating impact on a person's health and livelihoods. According to the latest *World Malaria Report* released in November 2017, there were 216 million cases of malaria globally in 2016, and an estimated 445 thousand malaria deaths - a similar number to the previous year[1].

Malaria is an acute, feverish illness. Acute malaria generally requires hospitalisation. Symptoms usually appear 10-15 days after the infective mosquito bite and include fever, headache and chills. Initial symptoms may be mild and difficult to recognise as symptoms of malaria. If not treated within 24 hours, *P. falciparum* malaria can progress to severe illness, often leading to death[1].

In its mild form malaria causes fever, shaking chills, headache, muscle aches, and tiredness. Nausea, vomiting and diarrhoea may also occur. Malaria may cause anaemia and jaundice because of the loss of red blood cells. If not promptly treated, the infection can become severe and may cause kidney failure, seizures, mental confusion, coma, and death.

Infection of the brain is called cerebral malaria. Cerebral malaria is the most common complication and cause of death in severe *P.falciparum* infection. In falciparum malaria, 10% of all hospital admissions and 80% of deaths are due to the involvement of the central nervous system (CNS).

Patients with malaria should be treated immediately because *P.falciparum* infections can rapidly progress to severe illness or death in as little as 1 to 2 days[1].

1.2 Treatment of malaria

Medicines for the treatment of malaria can be used to help **prevent** (prophylaxis) or **treat** the *Plasmodium* infections. These include atovaquone-proguanil, artemether-lumefantrine, chloroquine, clindamycin (used in combination with quinine), doxycycline (used in combination with quinine), mefloquine, quinine and quinidine. All these medicines have different efficacy and side effect profiles, as well as varied resistance patterns.

1.3 Treatment options

Not all patients respond to treatments equally, or are able to tolerate all treatments. In addition, some treatments may become less effective over time as the infective organisms develop mechanisms which limit their susceptibility to those medicines (resistance). As such it is important for clinicians to have a broad range of treatment options available to choose from. This is particularly the case when treating life-threatening diseases such as malaria.

The medical need for chemoprophylaxis of malaria is determined according to whether the probability of harm from a malaria infection and its serious consequences, outweighs the probability of harm from chemoprophylaxis. Thus, for travel destinations with a high risk of infection, the benefit-risk balance favours chemoprophylaxis[8].

1.4 Resistance to treatment and development of mefloquine

Like many infectious organisms, *Plasmodium* parasites can develop resistance to medicines routinely used to treat them, meaning that the medicines are no longer effective against them. This is a significant and recurring problem with malaria treatments.

Resistance of *P. falciparum* to previously-used anti-malarial medicines such as chloroquine and sulfadoxine-pyrimethamine became widespread in the 1950s and 1960s, undermining malaria control efforts and reversing gains in child survival[1]. There was therefore a vital need for new anti-malarial drugs. Mefloquine emerged from an extensive research program undertaken by the United States Army [the Walter Reed Army Institute of Research] in 1963. Over 100,000 separate compounds were evaluated during the research and development program, prior to mefloquine being developed[2].

To secure the drug's commercial manufacture and widespread availability, intellectual property rights and research related to mefloquine were transferred to F. Hoffman-La Roche Ltd. (Roche). Roche launched mefloquine in the United States in the late 1980s and it was first included on the Australian Register of Therapeutic Goods on 3 September 1986[3]. At the time of first global approval, mefloquine

was the only new anti-malarial drug available for treatment and prophylaxis of multi-resistant *Plasmodium falciparum* malaria. It is now one of a range of options for malaria management[5].

2.0 Lariam (mefloquine)

Mefloquine is an antimalarial medicine available as a prescription-only product in Australia, and is primarily used by travellers to malaria endemic zones. Mefloquine acts on the asexual intra-erythrocytic (i.e. within red blood cell) forms of the human malaria parasites: *P.falciparum, P. vivax, P. malariae, P. ovale and P. knowlesi.* Mefloquine is effective against malaria parasites resistant to other antimalarials such as chloroquine, proguanil, pyrimethamine, and pyrimethamine-sulfonamide combinations[5]. It is administered once-weekly when used for prophylaxis[10].

2.1 Mefloquine worldwide approvals

Mefloquine was first granted marketing approval in Switzerland on 20 February 1984. Mefloquine was first approved in the European Union (EU) on 17 May 1985 (national approval in France). Roche launched mefloquine in the United States in the late 1980s and it was first included on the Australian Register of Therapeutic Goods on 3 September 1986. As of 19 February 2018 mefloquine was approved in approximately 27 countries worldwide[4].

Approximately forty million patients around the world are estimated to have been treated with mefloquine since the drug was first made available[4].

2.2 Mefloquine indications in Australia

Mefloquine is indicated as a treatment for those already suffering from malaria, or as a preventative medicine for those travelling to malarious areas[10].

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. *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.*

2.3 Mefloquine recommendations in global Malaria treatment guidelines

Mefloquine is listed as a malaria treatment option by the World Health Organisation (WHO)[5] and Centres for Disease Control and Prevention (CDC)[6]. Mefloquine continues to be recommended in other authoritative guidelines for the chemoprophylaxis of malaria, including those of the '*Institut Pasteur*' in France, 2017[7] and the 2017 edition of '*Guidelines for malaria prevention in travellers from the UK*' published by Public Health England in the United Kingdom[8]. The '*Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit*' updated their malaria prevention guidelines in May 2018 to advise the recent risk minimisation procedures, and added, "*With attention to the contraindications and warnings, mefloquine has as before important status in the chemoprophylaxis of malaria in pregnant women, children, migrants and long term travellers, as well as individuals who have tolerated the medication well on repeated occasions*"[9].

2.4 Roche's licence to supply mefloquine in Australia

All therapeutic goods in Australia must be evaluated by the Australian health authority – the Therapeutic Goods Administration (TGA). The TGA approves and regulates products based on an assessment of risks against benefits. A sponsor of therapeutic goods such as Roche has an obligation to apply to the TGA to register therapeutic goods before they are supplied and to notify the TGA of any changes to the information used to support the registration of the product and which affects the benefit risk analysis for the product.

The TGA-approved Product Information (PI) is an important reference document developed by pharmaceutical sponsors of a medicine (e.g. Roche) and approved by the TGA. The PI provides objective information about the quality, safety and effectiveness of a medicine, as supported by data provided to and evaluated by the TGA. The information in the PI is intended to assist healthcare professionals when prescribing and dispensing medicines and in their consultations with patients in Australia. A version of this document intended for patients is called the Consumer Medicine Information (CMI) is also available from pharmacists. Both these documents are routinely updated to reflect the most up-to-date safety data. Updates to the PI are based on updates to the Core Data Sheet (CDS). The CDS represents the company position and forms the basis of the local PI. The CDS for each product includes all pivotal data, and relevant technical, clinical, and non-clinical safety and efficacy data. The CDS is updated and reviewed throughout the lifecycle of the product, when new information becomes available.

2.5 Contraindications and precautions contained in the Roche Australia mefloquine PI and CMI of relevance to the Enquiry

All medicines have benefits and risks. Clinicians carefully evaluate these factors when considering which medicines to prescribe and how to do so.

The current version of the PI[10] includes the following relevant contraindications and precautions:
CONTRAINDICATIONS - "*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* [mefloquine] *prophylactically.*"

PRECAUTIONS - *"Neuropsychiatric 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* [mefloquine]*has been stopped. Lariam* [mefloquine] s*hould 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 …"*

The current version of the CMI[11] includes the following relevant information: *"Do not take Lariam* [mefloquine]*as a preventative medicine if you have depression or have a history of psychiatric disorders, such as depression or anxiety. Some people who take Lariam may have sudden serious mental problems. Symptoms of serious mental problems may include- severe anxiety, hallucinations, depression, feeling restless, unusual behaviour, feeling confused."*

Before you start to take Lariam [mefloquine] *tell your doctor if you have or have had any health problems, especially the following: psychiatric disorders particularly mood disturbances (e.g. anxiety, depression) epilepsy (fits or seizures) or convulsions ….*

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Lariam [mefloquine]. *Lariam* [mefloquine]*helps most people but it may have unwanted side effects in a few people. All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects….. etc"*

Earlier versions of these documents reflected similar information, for example The PI (dated 11 Sept 1998)[12] contained the following contraindication:

CONTRAINDICATIONS - "*Patients with a past history of psychiatric disturbances or convulsions should not be prescribed Lariam*[mefloquine] *prophylactically.*"

PRECAUTIONS - *"…. neuropsychiatric reactions have been reported….*
ADVERSE REACTIONs: Psychiatric disorders: somnolescence, sleep disorders, anxiety, depressive mood, confusion, restlessness, forgetfulness, hallucinations, and psychotic or paranoid reactions"

The CMI dated (11 September 1998)[13] advised the patient to tell their doctor if they had "*any medical conditions, especially the following: fits or seizures (epilepsy, convulsions), psychiatric disturbances particularly mood disturbances (e.g. anxiety, depression).*"

These were the relevant reference documents at the time of the clinical trials conducted by the Army Malaria Institute (AMI) around 2000-2001.

3.0 Roche's patient safety measures

Roche closely monitors the safety profile of all its medicines, including mefloquine, and takes all reports of side effects from prescribers, patients and researchers very seriously. Roche updates the labels (prescribing information) of all its medicines on an ongoing basis to reflect the most up-to-date safety data.

Roche has a range of commitments in relation to monitoring and maintaining guidance documents for our products, stemming from the company's commitment to safety and compliance with international and local regulations. Roche maintains a global safety database which captures all adverse events, caused by or associated with mefloquine, reported to Roche or retrieved by Roche from published medical literature. Such information is continually reviewed, analysed and communicated to national health authorities, including the TGA, in accordance with local regulations.

The safety of our patients is of primary importance to us, and accordingly Roche (in Australia and globally) takes several measures to ensure that our medicines are used safely. For mefloquine, this includes:

i. Collecting and monitoring information on reported 'adverse events' – where negative side-effects are experienced by patients taking our medicine. These can be reported directly to Roche, or the Health Authorities in various countries (i.e. the TGA in Australia) by members of the public, patients or healthcare professionals.
ii. Monitoring published scientific and medical literature for new and significant safety information relevant to mefloquine, in order to keep risk assessments current and up to date.
iii. Undertaking regular reviews of the product safety database to update the understanding of the benefit: risk profile of the medicine.
iv. On the basis of that, updated risk assessment and monitoring of safety signals: - Updating the Core data sheet, Product Information and Consumer Medicine Information documents, which are publicly available for all to consult online.

4.0 Use by the ADF

Mefloquine is available as a prescription-only product in Australia and is primarily used by travellers to malaria endemic zones. This has included Australian defence personnel. Roche estimates that around 8,810 mefloquine scripts were issued in Australia in 2017. According to the ADF, during that same year two defence personnel were issued with scripts for mefloquine. Roche does not actively promote mefloquine to the ADF. Roche provides it to a wholesaler, who supplies the medicine to customers, which may include the ADF, pharmacies and other providers.

5.0 Commercial arrangements for Lariam (mefloquine) from 2018

As a Research and Development-focused company, Roche focuses its resources on bringing new and innovative medicines to patients. As a result, from time to time, Roche will divest a medicine and transition its management to another company. In February 2018, Roche globally divested mefloquine, along with a portfolio of established medicines, to Cheplapharm. In Australia, Roche will transition the management of mefloquine to Pharmaco (Australia) Ltd on 1 August 2018.

6.0 Conclusion

Based on Roche's evaluation of all available information, including data from post-marketing experience, published literature and other safety-risk management sources, the benefit-risk profile of mefloquine use in the prevention and treatment of malaria remains positive. This is aligned with the views of regulators such as the TGA and bodies such as the WHO and CDC. As a result, it remains available as an option for clinicians and patients to consider when selecting a medicine to prevent or treat the serious condition of malaria.

Sincerely,

Svend Petersen
Managing Director
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