QUINOLINE VETERANS AND FAMILIES ASSOCIATION

SUPPLEMENTARY SUBMISSION TO THE FOREIGN AFFAIRS, DEFENCE AND TRADE REFERENCES COMMITTEE INQUIRY INTO THE USE OF THE QUINOLINE ANTI-MALARIAL DRUGS MEFLOQUINE AND TAFENOQUINE IN THE AUSTRALIAN DEFENCE FORCE

Mr Stuart McCarthy, 10 September 2018

Introduction

QVFA thanks the Committee for their continued efforts with this inquiry. The purpose of this supplementary submission is to draw the Committee's attention to false and misleading testimony provided by Professor Geoffrey Quail and Professor Graham Brown of the Australian College of Tropical Medicine at the Committee's hearing in Brisbane on 30 August 2018. The false and misleading testimony related to malaria mortality in the Australian Defence Force (ADF), purported "drug resistance" as a justification for introducing tafenoquine, the efficacy of primaquine and tafenoquine against *P. vivax* malaria, evidence of mefloquine causing long term neurological damage and tafenoquine neuropsychiatric adverse effects observed during clinical trials.

Testimony by Professor Quail and Professor Brown on 30 August 2018

The false and misleading testimony provided by Professor Brown and Professor Quail is recorded in the following Hansard excerpts:

> ***Prof. Quail :*** *As we're all aware, malaria is one of the most serious and common infectious disease in the world. The Australian Defence Force operates predominantly in areas where malaria is endemic, so soldiers are frequently vulnerable to infection. As is the case in bacteria, where we all know about antibiotic resistance, the Plasmodium parasite causing malaria* ***has a great ability to develop resistance to drugs****. This has been the case since it was first discovered in about 1945. Even with the common drugs used today, like doxycycline, mefloquine and malarone,* ***there are areas in the world where there is drug resistance****. This is a great worry. We have to keep at the edge of research to get ahead of the parasites. We do need to have clinical trials to test new drugs that* ***act effectively and prevent recurrence****.*
>
> *The advantage of taking* ***tafenoquine over primaquine****, which was used to prevent the recurrence of malaria—all of you would be aware of the number of perhaps your uncles or grandfathers or someone who* ***came back from the Second World War or the First World War*** *and they got recurrent malaria. That was because of the parasite sitting in the liver. Tafenoquine can be given once a week, whereas primaquine was given daily.* ***Both of them can eradicate that parasite in the liver****. Tafenoquine has been proved—I can't say proved, but* ***there has been no evidence that it has caused any neuropsychiatric problems****. It can cause what we call him haemolysis in the blood—that's a thinning of the blood—but you can test for that before you use it. So* ***tafenoquine is a very good alternative to primaquine****, because troops don't like taking their drug when they come back and they feel well. If you take tafenoquine, it has a longer action and it has to be taken much less frequently.*
>
> ---
>
> ***Prof. Brown :*** *With respect to prevention of malaria, it's really important to note that our troops need to be protected from disease that can progress extremely rapidly from mild illness to death. Geoff mentioned World War 2, but* ***we still see it today****. Unfortunately, some people listen to certain unwise opinions—'I don't need antimalarials; antimalarials are poison et cetera'—****and then they die of malaria****.*
>
> *The other issue that's been raised briefly is that* ***there's increasing resistance of these parasites to the available drugs****. Each time a new drug comes in, we know that resistance*

> *will eventually occur. As you may know, we're particularly worried at the moment about our region.*
>
> *We support the views of others making submissions that there can be side effects from mefloquine, particularly in the short term, and of course the drug should be avoided for people with certain underlying conditions. I would say that* ***the available evidence does not support the view that mefloquine has a major role in long-term neurological consequences****.*
>
> ---
>
> ***Prof. Brown :*** *For example, I don't see—amongst my literature and reading or in the submissions—anything that you could specifically attribute to it.* ***And when people do the same with tafenoquine and mefloquine, they are really quite different side effects. Certainly, under observation in clinical trials you don't see these things with tafenoquine****. So when they're all rolled together, they're actually quite different drugs.*

Malaria Mortality in the ADF

Professor Brown's statement that "we still see it today … some people listen to certain unwise opinions —'I don't need antimalarials; antimalarials are poison et cetera'—and then they die of malaria" is false. In a 2017 paper on malaria mortality in the ADF, Professor G. Dennis Shanks (current Director of the Army Malaria Institute) states:

> *… no Australian soldier has died in nearly 50 years from malaria …*[1]

Purported "Drug Resistance" as a Justification for Introducing Tafenoquine

Numerous drugs are available for the prevention and treatment of *P. falciparum* and other species of malaria and more are under development. Although it is definitely true that some of these species have developed resistance to chloroquine, mefloquine and other drugs, this is not true of primaquine in relation to *P. vivax*. The testimony from Professor Quail and Professor Brown to the effect that tafenoquine is needed to address *P. vivax* resistance to primaquine is totally unsubstantiated. There is no scientific evidence to support this claim, indeed during the U.S. FDA's recent hearings to consider the GlaxoSmithKlien (GSK) application for tafenoquine, the GSK representative stated categorically that *there is no evidence of primaquine resistance after 60 years of use*.

Efficacy of Primaquine and Tafenoquine Against *P. vivax* Malaria

Professor Quail's statement that primaquine "was used to prevent the recurrence of malaria" in WWII is false. The development of primaquine commenced in 1944 and large scale clinical safety and efficacy studies began in the early 1950s, when the U.S. Army became concerned with the number of relapsing *P. vivax* malaria cases among veterans returning from the Korean War.[2] The specific reason that primaquine was adopted as an alternative to the previously used 8-aminoquinoline *P. vivax* prevention and treatment drugs is that the malaria research community accepted the *clinical evidence of neurotoxicity in the 8-aminoquinoline drugs* which were widely used by Allied forces during WWII. Primaquine became the standard *P. vivax* prevention and treatment drug for the next six decades specifically because the previously used 8-aminoquinolines are *known to be neurotoxic*.[3,4]

Although Professor Quail correctly stated that primaquine and tafenoquine are used to eradicate liver stage *P. vivax*, both he and Professor Brown misled the Committee about the efficacy of these drugs by omitting key scientific facts, specifically that the efficacy of both drugs is limited by CYP2D6 drug metabolism. As I have emphasised in my previous submissions, the most plausible explanation for the high rate of *P. vivax* malaria infections among ADF personnel is 8-aminoquinoline drug failures due to reduced CYP2D6 function, which affects around 12-23% of Caucasians. This is supported by a 2014 paper co-authored by Dr Bryan Smith (former USAMMDA tafenoquine product manager, now 60P Chief Medical Officer), which concludes in part:

> *… it is reasonable to conclude several things about ... tafenoquine. 1). The anti-hypnozoite activity of ... tafenoquine is dependent on CYP 2D6 activation. 2). ...* ***tafenoquine will likely fail for either causal prophylaxis and/or treatment indications in patients with CYP 2D6 genotypes resulting in the PM phenotype*** *and may require dose modification in some patients with an IM phenotype ...*

> *There have been numerous reports in the literature of **primaquine failures** that are associated with primaquine resistance. This **"resistance"** refers to the inability of primaquine to clear the hypnozoite form of the Plasmodium parasite. There has been **confusion around the idea of primaquine resistance** as there are many confounding factors associated with the various reports, such as patient population, patient adherence, dosing regimen, and concurrent blood schizonticidal therapy. The requirement of **CYP 2D6 activation for primaquine activity** is another factor that needs to be taken into consideration when reporting primaquine resistance. Interestingly, the **reported primaquine failure rates seem to align with CYP 2D6 polymorphic allelic frequencies for the PM genotype as individuals with this genotype will likely fail primaquine therapy**. This is not a likely coincidence and **calls into question the existence of primaquine resistance and/or Plasmodium resistance to the 8AQ class in general, particularly since the results reported herein suggest that 8AQs likely have a similar mechanism(s) of anti-malarial activity which is mediated through CYP 2D6 activation**. ... Because tafenoquine ... requires CYP 2D6 activation for activity, **rates of treatment/prophylactic failures would likely be in line with those noted for primaquine use for both compounds when administered to humans**. If insurmountable, **this would present a major pharmacogenomic liability for the 8AQ class of anti-malarial compounds**. New drugs with anti-hypnozoite activity are desperately needed to combat relapsing strains of malaria and **future research and development efforts should ensure the complete dissociation between CYP 2D6 metabolism and anti-hypnozoite activity** of new potential anti-malarial agents.*[5]

There is also clinical evidence of *tafenoquine failures among the AMI tafenoquine clinical trial subjects*, attributable to reduced CYP2D6 function. One example of this is shown at Attachment 1 (Confidential). This individual was administered 1,200 mg of tafenoquine during the Nasveld et al. AMI tafenoquine PEP trial in Bougainville and was subsequently diagnosed with *P. vivax* malaria. His CYP2D6 test results show that he is an intermediate metaboliser.

As I have highlighted in previous submissions, this issue has moved beyond an arcane academic argument. Doctors are now proactively using this scientific discovery, in clinical settings, to ensure the 8-aminoquinolines are being used safely and effectively, for example in this recent case report of relapsing *P. vivax* malaria previously misattributed to "drug resistance" or "poor compliance":

> *Primaquine (an 8-aminoquinoline malarial therapy) is the only FDA-approved therapy to treat the hypnozoite stage of P. vivax. We think of relapse occurring because of parasitic resistance or poor compliance secondary to drug toxicities. However, in patients with repeated treatment failure, we must consider CYP-450 mutations affecting drug metabolism as an important cause of relapse. A 47-year-old man who travelled to a jungle in Venezuela was diagnosed with P. falciparum and P. vivax in July 2015. He was treated with seven rounds of primaquine-based therapy in the following year, all resulted in relapse without further exposure to endemic areas. On his eighth presentation, he was found to have CYP-4502D6 mutation that affected the metabolism and activation of primaquine. Thereafter, he was treated without relapse. Primaquine efficacy depends on many factors. Understanding the mechanism responsible for malaria relapse is paramount for successful treatment and reduction in morbidity and mortality. This case illustrates the importance of considering cytochrome mutations that affect drug efficacy in cases of relapsing malaria.*[6]

Professor Quail's testimony in relation to primaquine and tafenoquine is historically false and ignores both published research and current clinical practice. I again emphasise the need for the Committee to challenge the unsubstantiated assertions by various "expert witnesses" regarding "drug resistance." There is clear, published, scientific evidence that the 8-aminoquinolines are ineffective and potentially dangerous for a significant proportion of the population, not because of "drug resistance" but because of reduced CYP2D6 function. *CYP2D6 screening is readily available*, indeed the similar G6PD screen has been a standard test for all ADF personnel for many decades, *specifically to prevent serious adverse reactions to the 8-aminoquinoline drugs primaquine and tafenoquine.*

Evidence of Mefloquine Causing Long Term Neurological Damage

Professor Brown's assertion that the available evidence does not support the view that mefloquine has a role in long-term neurological symptoms contradicts decades of published research,[4,7,8] the findings

of drug regulators including the U.S. FDA and the findings of statutory bodies such as the Repatriation Medical Authority (RMA).

Since 2013, mefloquine has been subjected to a mandatory U.S. FDA "black box" warning (Attachment 2), the most serious drug safety warning in the U.S. This warning states in part:

> ***Neurologic side effects*** *can occur at any time during drug use, and* ***can last for months to years after the drug is stopped or can be permanent****.*[9]

Research institutes accepting that mefloquine is able to cause long-term neurological symptoms include the U.S. Army's Walter Reed Army Institute of Research (WRAIR), i.e. *the organisation which originally developed mefloquine*. For example, a 2016 case report written by Dr Jeffrey Livezey from the WRAIR Department of Clinical Pharmacology states:

> *Melfoquine-induced neuropsychiatric symptoms can be* ***severely life debilitating****.*
>
> *Given the overlapping symptoms of post-traumatic stress disorder and mefloquine toxicity, it can be challenging to distinguish between the two diagnoses.*
>
> *Melfoquine toxicity can persist for several years after exposure has been discontinued, with* ***little to no abatement in symptoms over time****.*[10]

Veterans disability claims for chronic neuropsychiatric illness attributed to mefloquine use are being accepted by veterans affairs departments in the U.S. and elsewhere. For example, a case report describing the experiences of a U.S. Marine who was subjected to mefloquine (at the same doses used by the ADF) during a 1991 clinical trial states:

> *During the study [the subject] experienced insomnia, abnormal dreams, and nightmares. He also developed symptoms of anxiety, depression, cognitive dysfunction, and changes in personality—including anger and irritability—that were severe enough to be noted by his family members. The patient had not been advised of the significance of these symptoms and therefore did not report them during the clinical trial, nor did he report their intermittent presence after the study's conclusion through his retirement in 1996, fearing adverse career consequences. Subsequent exacerbations of these chronic symptoms later contributed to the patient's loss of civilian employment in 2010.*
>
> *After becoming aware of the 2013 boxed warning that these chronic symptoms could be due to his earlier exposure to mefloquine, the veteran sought evaluation by a VA clinician. On evaluation, the clinician noted no history of deployment, and no history of post-traumatic stress disorder (PTSD) criteria A stressors, and posited that the veteran's chronic neuropsychiatric symptoms were most likely a consequence of his earlier use of mefloquine. The VA subsequently awarded the veteran 50% disability for an anxiety disorder characterized by chronic sleep impairment and frequent panic attacks, attributing these to his service-connected use of the drug.*[11]

The RMA has determined mefloquine use to be a causal factor in no less than 11 chronic neuropsychiatric diseases including: depressive disorder, anxiety disorder, bipolar disorder, epileptic seizure, schizophrenia, sensorineural hearing loss, tinnitus, neuropathies, suicide and attempted suicide (RMA Submission 4). The statutory definition of "disease" used by the RMA is:

> *any physical or mental ailment, disorder, defect or morbid condition (whether of sudden onset or gradual development)*

This definition specifically excludes:

> *a temporary departure from:*
>
> > *(i) the normal physiological state; or*
> >
> > *(ii) the accepted ranges of physiological or biochemical measures.*[12]

The 11 neuropsychiatric diseases which the RMA has recognised can be caused by mefloquine are, by statutory definition, *long-term*.

Tafenoquine Neuropsychiatric Adverse Effects Observed During Clinical Trials

Professor Brown's claims that tafenoquine and mefloquine side effects "are really quite different" and "under observation in clinical trials you don't see these things with tafenoquine" are both false. During the Brisbane hearing, Mr Mark Reid testified that the AMI tafenoquine prophylaxis study involving 1 RAR personnel in East Timor ("Study 033") was "the most comprehensive randomised control study of preventive antimalarial drugs conducted in living memory." One of the key findings of this study, which directly compared the nature and incidence of neuropsychiatric side effects between a group of 492 tafenoquine subjects and 162 mefloquine subjects, was:

> *In total, 64 (13.0%) tafenoquine subjects and 23 (14.2%) mefloquine subjects reported neuropsychiatric adverse events, the most common being vertigo, dizziness and various sleep disorders. There was* ***no significant difference between the treatment groups in the incidence and type of neuropsychiatric events*** *...*[13]

Conclusion

Much of the testimony provided by Professor Quail and Professor Brown during the Committee's hearing in Brisbane was demonstrably false and misleading. This is a sad indictment on the purported expertise of the Australian College of Tropical Medicine, which appears to be either ignorant of key historical facts, relevant published scientific research and current clinical practice, or willing to deliberately mislead a Parliamentary inquiry into a serious matter of public health and safety. I trust that this will assist the Committee with its ongoing inquiry.

Attachments

1. Documentary evidence of 1,200 mg tafenoquine post exposure prophylaxis failure to prevent *P. vivax* malaria in an Army Malaria Institute clinical trial subject found to be a CYP2D6 intermediate metaboliser (confidential)

2. U.S. Food and Drug Administration, *FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects*, 29 July 2013

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Monitoring Listings for AMI001

Compliance Data for patient 13:08 Friday, March 15, 2002

Drug	Dose	Frequency	Dose1 Date	Dose2 Date	Dose3 Date	Dose1 Time	Dose2 Time	Dose3 Time
T1	400mg	OD	29/05/1999	30/05/1999	31/05/1999	12:45	12:45	7:45

Drug Levels Data for patient 13:08 Friday, March 15, 2002

Drug	Dose	Frequency
T1	400mg	OD

Laboratory Data for patient 13:08 Friday, March 15, 2002

SEX	Beta-human Chorionic Gonadotropin	Visit	Creatinine	Alanine aminotransferase	Total Bilirubin	Alkaline Phosphatase	Albumin	Aspartate aminotransferase
M	ND	Post	0.11	33	17	70	47	22
M	ND	Pre	0.09	35	16	58	47	25

Glutamyltranferase	Total Protein	Urea	White Blood Cell	Lymphocytes	MID	Granulocytes	Red Blood Cell	Hemoglobin	Hematocrit
13	77	5.2	8.1	2.6	ND	5.5	ND	135	0.39
15	73	5.3	5.9	2.2	ND	3.7	ND	131	0.37

Mean Corpuscular Volume	Mean Corpuscular Hemoglobin Concentration	Platelets	Drug Dose Levels	Bleed Date	Date of Last Dose	Bleed Time	Time of Last Dose
ND	346	252	521	01/06/1999	01/06/1999	19:02	7:30
ND	351	296	ND	22/05/1999	.	.	.

Adverse Event Data for patient 13:08 Friday, March 15, 2002

Episode	AE Diagnosis	Onset Time	End Time	Experience Course	Intensity	Outcome	Relationship to Investigational Drug
3	SWEATS	NA	NA	~~Intermittent~~ CONSTANT	Mild	Resolved	Suspected
4	URTI	NA	NA	Constant	Modarate	Resolved	~~Not related~~ UNLIKELY

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MEDICAL IN CONFIDENCE
PATHOLOGY DEPARTMENT
1st FIELD HOSPITAL HOLSWORTHY

NATA/RCPA Accredited Laboratory No. 2837.

This laboratory is registered under the registration scheme of the National Association of Testing Authorities, Australia and The Royal College of Pathologists of Australasia.

[redacted]

Collected Date : 07/10/99 Report Date : 11/10/99

Clinical History :
FEBRILE

MALARIAL PARASITES

MALARIAL FILMS Plasmodium vivax

FULL BLOOD EXAMINATION

				REFERENCE INTERVAL
*L	WHITE CELL COUNT	3.6	10^9/L	(4.0 - 11.0)
*L	RED CELL COUNT	3.4	10^12/L	(4.5 - 6.5)
*L	HAEMOGLOBIN	101	g/L	(130 - 180)
*L	HAEMATOCRIT	0.29		(0.40 - 0.54)
	MCV	88	fL	(76 - 100)
	MCH	30	pg	(27 - 32)
	MCHC	339	g/L	(300 - 350)
*L	PLATELETS	120	10^9/L	(150 - 400)
	DIFFERENTIAL LEUCOCYTE COUNT			
*L	NEUTROPHILS	1.1	10^9/L	(2.0 - 7.5)
	BANDS	0.0	10^9/L	
	LYMPHOCYTES	2.4	10^9/L	(1.5 - 4.0)
*L	MONOCYTES	0.0	10^9/L	(0.2 - 0.8)
*L	EOSINOPHILS	0.0	10^9/L	(0.0 - 0.4)
*L	BASOPHILS	0.0	10^9/L	(0.0 - 0.1)
	ATYPICAL REACTIVE CELLS	0.0	%	
*H	ESR	79	mm/h	(2 - 10)

file 19/10/99

Blood Film Comment:

Plasmodium vivax malaria parasites seen.
There is a mild thrombocytopenia.
The ESR is moderately elevated.
Red cells show mild rouleaux formation.
There is a moderate neutropenia.

[redacted]

ou
11/10/99

*** FINAL REPORT. Please File ***

Page : 2

Report Sighted

(Medical Officers Signature) (Date)

Medical-in-Confidence

[redacted]

Clinical notes available on imaged request form.

Clinical Notes : Clinical notes available on imaged request form.

Pharmacogenetic Results

Specimen type: EDTA blood
Method: Analysis performed with Autogenomics assay.

Enzyme	Genotype	Metaboliser
CYP2D6	*4/*9	Intermediate

Comments on Lab Id: 631455779

Individual Patient Specific Comment
Previous mefloquine and tafenaquine history noted.
Intermediate metaboliser status for CYP2D6 may be exacerbated by concurrent medications with further inhibit CYP2D6 function. Poor activation of Tafenaquine by CYP2D6 may inhibit clinical effectiveness. No implications for Mefloquine dosing on the basis of this test. kbaumgart@dhm.com.au
Alleles identified by Autogenomics assay are:

CYP2D6: Normal: *1, *2
Reduced function: *9, *10, *17, *29, *41
Non-functional: *3, *4, *5 (deletion), *6, *7, *8, *12, *14
Increased function: gene duplication

Note: Untested variants and clinical factors affecting drug metabolism cannot be excluded by this analysis. Clinical factors, including concurrent medications, should be considered when using this result to determine drug dosage.

[redacted]

SS

Sullivan Nicolaides Pty Ltd. ABN 38 078 202 196. NATA/RCPA Accreditation No 1964

Tests Completed: 2D6 Genotype
Tests Pending :
Sample Pending :

FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects

[7-29-2013] The U.S. Food and Drug Administration (FDA) is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride. A boxed warning, the most serious kind of warning about these potential problems, has been added to the drug label. FDA has revised the patient Medication Guide dispensed with each prescription and wallet card to include this information and the possibility that the neurologic side effects may persist or become permanent. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations (For a more complete list of potential side effects, see Additional Information for Patients).

Neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent. Patients, caregivers, and health care professionals should watch for these side effects. When using the drug to prevent malaria, if a patient develops neurologic or psychiatric symptoms, mefloquine should be stopped, and an alternate medicine should be used. If a patient develops neurologic or psychiatric symptoms while on mefloquine, the patient should contact the prescribing health care professional. The patient should not stop taking mefloquine before discussing symptoms with the health care professional.

Malaria is a serious disease caused by a parasite that commonly infects mosquitoes, which then bite humans. It is a major cause of death worldwide but is less common in the United States. The disease is a problem primarily in developing countries with warm climates. Persons who travel to these countries may be at risk of malaria infection and should take drugs to prevent or reduce that risk. People with malaria often experience fever, chills, and flu-like symptoms. Drugs must be taken to treat the disease if you have been infected, but may, themselves, have side effects.

FDA will continue to evaluate the safety of mefloquine and will communicate with the public again if additional information becomes available.

FACTS about mefloquine tablets

- Antimalarial drug indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible *P. falciparum* and *P. vivax.*
- Also indicated for the prevention of malaria infections by *P. falciparum* (including chloroquine-resistant *P. falciparum*) and *P. viva*x.

- Previously marketed under the brand name Lariam; however, the Lariam product is not currently marketed. Generic mefloquine products are available in the US.

Additional Information for Patients

- Mefloquine may cause dizziness, balance problems, and ringing in the ears. These symptoms can occur at any time during use and can last for months to years after the drug is stopped or can be permanent.
- Contact your health care professional right away if you take mefloquine and experience any of the following signs and symptoms; it may be necessary to stop mefloquine and take another medication to prevent malaria, but do not do so without first talking with your health care professional:
    - Dizziness
    - Balance problems such as a feeling that you or things around you are moving or spinning (vertigo)
    - Ringing in your ears (tinnitus)
    - Convulsions or seizures
    - Inability to sleep (insomnia)
- If you already have or develop any mental problems, you should contact your health care professional right away. These mental problems include:
    - Anxiety
    - Feelings of mistrust towards others (paranoia)
    - Seeing or hearing things that are not there (hallucinations)
    - Depression
    - Restlessness
    - Confusion
    - Behavior that is unusual
- Carefully read the Medication Guide and the wallet card that come with your mefloquine prescription.
- Discuss any questions or concerns about mefloquine with your health care professional.

- Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the Contact FDA box at the bottom of the page.

Additional Information for Health Care Professionals

- Encourage your patients to contact you if they develop neurologic or psychiatric symptoms.
- Make sure your patients receive the Medication Guide with every prescription.
- Be alert to the potential for the development of neurologic and psychiatric adverse reactions in patients using the drug. If the patient develops psychiatric or neurologic symptoms during preventive use, mefloquine should be stopped and an alternate antimalarial medicine should be used.
- Neurologic and psychiatric symptoms can be difficult to identify in children.
- Report adverse reactions involving mefloquine to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of the page.

Data Summary

The mefloquine drug label already states that mefloquine should not be prescribed to prevent malaria in patients with major psychiatric disorders or with a history of seizures. The changes to the mefloquine drug label better describe the possibility of persistent neurologic (vestibular) adverse effects after mefloquine is discontinued and the possibility of permanent vestibular damage.

In conducting its assessment of vestibular adverse reactions associated with mefloquine use, FDA reviewed adverse event reports from the FDA Adverse Event Reporting System (FAERS) and the published literature, identifying patients that reported one or more vestibular symptoms such as dizziness, loss of balance, tinnitus, and vertigo. Patients who reported vestibular adverse reactions were healthy with no known major medical problems prior to taking mefloquine for malaria prophylaxis. Some patients did not suspect their symptoms were due to mefloquine and continued to take the drug after the symptoms started.

In many cases, these symptoms developed early in the course of treatment, sometimes after one or two doses of mefloquine. Dizziness, loss of balance, tinnitus, or vertigo persisted for months to years after mefloquine was discontinued, and permanent vestibular damage was diagnosed in some cases. These symptoms interfered with patients' daily activities and ability to work. Some cases described abnormal vestibular function tests and a diagnosis of vestibular damage. In some cases, the vestibular damage was thought to be caused by mefloquine use. Some patients reported recurrence of psychiatric and vestibular symptoms when they took mefloquine for the second time. Patients who experienced vestibular symptoms usually had concomitant psychiatric symptoms such as anxiety, confusion, paranoia, and depression. Some of the psychiatric symptoms persisted for months to years after mefloquine was discontinued.

FDA will continue to evaluate the safety of mefloquine and will communicate again if additional information becomes available.