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Subject: CEASING USE OF MEFLOQUINE IN US ARMY SPECIAL OPERATIONS COMMAND UNITS
Originator: MESSAGE CENTER(MC)
DTG: 132013Z Sep 13
Precedence: ROUTINE
DAC: General
To: USASFC MSG CENTER(MC), USAJFKSWCS MSG CTR(MC), ARSOAC MSG CENTER(MC), MISOC MSG CENTER(MC), CDR75RGRRGT(SC), 95TH CA BDE MSG CTR(MC), 528 SUST BDE MSG CTR(MC), JTF SWORD MSG CENTER(MC)

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CDR TF SWORD
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MSGID/GENADMIN/USASOC G33 OPNS//
REF/A/MEMORANDUM/OSD-HA/15APR2013//
REF/B/MEMORANDUM/OSD-HA/4FEB2009//
REF/C/DRUG SAFETY COMMUNICATION/FDA/29JUL2013// REF/D/DODI/DOD/20MAR2009//
REF/E/DOCUMENT/NCMI/23AUG2011
REF/F/ARTICLE/J AM ACAD PSYCHIATRY LAW/41:2013// NARR/REF A IS OSD-HA MEMORANDUM "GUIDANCE ON MEDICATIONS FOR PROPHYLAXIS OF MALARIA". REF B IS HA POLICY 09-017 "POLICY MEMORANDUM ON THE USE OF MEFLOQUINE (LARIUM) IN MALARIA PROPHYLAXIS". REF C IS FDA DRUG SAFETY COMMUNICATION "FDA APPROVES LABEL CHANGES FOR ANTIMALARIAL DRUG MEFLOQUINE HYDROCHLORIDE DUE TO RISK OF SERIOUS PSYCHIATRIC AND NERVE SIDE EFFECTS". REF D IS DODI 6420.01 NATIONAL CENTER FOR MEDICAL INTELLIGENCE. REF E IS DEFENSE INTELLIGENCE REFERENCE DOCUMENT DIA-16-1108-093 "USING NCMI MALARIA RISK ASSESSMENTS TO SUPPORT CHEMOPROPHYLAXIS CHOICES". REF F IS A PEER REVIEWED ARTICLE "PSYCHIATRIC SIDE EFFECTS OF MEFLOQUINE: APPLICATIONS TO FORENSIC PSYCHIATRY".// 1. (U) SITUATION. ON 29 JUL 2013 THE FDA ANNOUNCED A BLACK BOX WARNING FOR MEFLOQUINE IN A SIGNIFICANT CHANGE TO THE DRUG'S APPROVED LABELING. UPDATED FDA GUIDANCE NOW EXPANDS ON PRIOR GUIDANCE TO EMPHASIZE THE NEED TO DISCONTINUE MEFLOQUINE SHOULD ANY NEUROLOGICAL OR PSYCHIATRIC SYMPTOMS DEVELOP WHILE TAKING THE DRUG AND HIGHLIGHTS THAT CERTAIN NEUROLOGIC SYMPTOMS HAVE BEEN REPORTED TO BE PERMANENT. FURTHER, MILITARY AUTHORS WRITING FOR THE CDC HAVE NOTED THAT THE SYMPTOMS CAUSED BY MEFLOQUINE MAY "CONFOUND THE DIAGNOSIS" OF PTSD AND TBI. THE UPDATED PRODUCT DOCUMENTATION NOTES THAT PSYCHIATRIC SYMPTOMS RANGING FROM ANXIETY, FEELING RESTLESS OR CONFUSED, PARANOIA AND DEPRESSION TO

HALLUCINATIONS AND PSYCHOTIC BEHAVIOR CAN OCCUR AND CONTINUE FOR MONTHS OR YEARS AFTER MEFLOQUINE USE; CASES OF SUICIDAL IDEATION AND SUICIDE HAVE BEEN REPORTED.// 2. (U) MISSION. USASOC COMMANDERS AND MEDICAL PERSONNEL WILL DECREASE THE RISK OF NEGATIVE DRUG RELATED SIDE EFFECTS BY CEASING USE OF MEFLOQUINE AS A MEANS OF CHEMOPROPYLAXIS FOR THE PREVENTION OF MALARIA; CONCURRENTLY ADDRESS AND ASSESS THE POSSIBILITY AND IMPACT OF MEFLOQUINE TOXICITY IN THEIR POPULATIONS.// 3. (U) EXECUTION.
3.A. CONCEPT OF THE OPERATION.
3.A.1. USASOC MEDICAL PERSONNEL WILL IMMEDIATELY CEASE THE PRESCRIBING AND USE OF MEFLOQUINE FOR MALARIA PROPHYLAXIS.
3.A.2. PERSONNEL CURRENTLY TAKING MEFLOQUINE FOR PREVENTION OF MALARIA WILL TRANSITION TO ONE OF THREE ALTERNATIVE OPTIONS FOR PROPHYLAXIS DEPENDING ON THEIR LOCATION, DRUG RESISTANCE, AND THE MALARIA RISK.
3.A.3. PERSONNEL CONDUCTING MEDICAL INTELLIGENCE PREP OF THE ENVIRONMENT (MIPOE) WILL REVIEW REF E TO IDENTIFY PREVALENCE AND TYPE OF MALARIA AS WELL AS DRUG RESISTANCE TO ENSURE THE APPROPRIATE USE OF EFFECTIVE MEDICATIONS.
3.A.3.A. MEDICAL PERSONNEL WILL ENSURE THAT THE SELECTION OF ATOVAQUONE-PROGUANIL (MALARONE), DOXYCYCLINE OR CHLOROQUINE IS DRIVEN BY COMMAND POLICY, PREVALENCE AND TYPE OF MALARIA, INDIVIDUAL CONTRAINDICATIONS, AND REGIONALLY UNIQUE DRUG RESISTANCE.
3.A.3. PERSONNEL REDEPLOYING FROM P. VIVAX ENDEMIC AREAS (IAW REF E) WILL CONTINUE TO TAKE FOURTEEN DAYS OF APPROVED POST-EXPOSURE CHEMOPROPHYLAXIS (PRIMAQUINE).
3.A.4. MEDICAL PERSONNEL WILL ADDRESS AND, IF APPROPRIATE, REFER REPORTS OF SUSPECTED CASES OF "MEFLOQUINE TOXICITY" IAW COORDINATING INSTRUCTIONS.
3.B. COORDINATING INSTRUCTIONS.
3.B.1. COMMANDERS AND SUPERVISORS AT ALL LEVELS WILL:
3.B.1.A. ENSURE THAT DEPLOYED PERSONNEL CONTINUE TO BE PROTECTED FROM MALARIA THROUGH THE USE OF ATOVAQUONE-PROGUANIL, DOXYCYCLINE AND CHLOROQUINE (PRE-EXPOSURE) AND PRIMAQUINE (POST-EXPOSURE FOR P. VIVAX AND P. OVALE ENDEMIC AREAS) IAW COMMAND POLICY.
3.B.1.B. APPROVED MEDICATIONS FOR MALRIA CHEMOPROPHYLAXIS IN USASOC.
3.B.1.B.1 ATOVAQUONE-PROGUANIL IS THE FIRST LINE CHEMOPROPHYLAXIS FOR USASOC PERSONNEL BASED ON THE RESIDUAL PROTECTION AND MINIMAL SIDE-EFFECT PROFILE. DOXYCYCLINE IS AN EQUALLY EFFECTIVE MEDICATION FOR THE PREVENTION OF MALARIA AND NO KNOWN RESISTANCE EXISTS. IF EVIDENCE OF ATOVOQUONE-PROGUANIL RESISTANCE EXISTS OR EMERGES, DOXYCYCLINE IS THE DRUG OF CHOICE. PRE-DEPLOYMENT RESEARCH IS CRITICAL TO DETERMINING THE MOST APPROPRIATE AND EFFECTIVE CHEMOPROPHYLAXIS FOR ANY DEPLOYMENT.
3.B.1.B.2. THE EFFECTIVENESS OF CHLOROQUINE VARIES BY TYPE OF MALARIA AND BY REGION.
3.B.1.B.2.A. P. FALCIPARUM: HIGH LEVELS OF RESISTANCE RESULTING FROM YEARS OF HEAVY USE HAVE RENDERED CHLOROQUINE INEFFECTIVE IN THE PREVENTION OF P. FALCIPARUM MALARIA IN AFRICOM, CENTCOM, PACOM, AND A FEW AREAS OF SOUTHCOM. CHLOROQUINE REMAINS AN EFFECTIVE CHEMOPROPHYLAXIS AGAINST P. FALCIPARUM ONLY IN PARTS OF SOUTHCOM, INCLUDING BELIZE, COSTA RICA, THE DOMINICAN REPUBLIC, EL SALVADOR, HAITI, HONDURAS, NICARAGUA, AND PARAGUAY.
3.B.1.B.2.B. P. VIVAX: HIGH LEVELS OF CHLOROQUINE-RESISTANT P. VIVAX HAVE BEEN REPORTED IN TURKEY AND INDONESIA, AND RESISTANCE IS INCREASINGLY BEING DOCUMENTED THROUGHOUT MUCH OF ASIA. INCREASING RESISTANCE HAS BEEN NOTED IN PARTS OF SOUTHCOM, PARTICULARLY IN BRAZIL AND COLOMBIA. DESPITE MANY YEARS OF CHLOROQUINE

USE, EVEN AS SINGLE-DRUG THERAPY, CHLOROQUINE REMAINS LARGELY EFFECTIVE AGAINST P. VIVAX IN MUCH OF CENTCOM.
3.B.1.B.3. POST-EXPOSURE CHEMOPROPHYLAXIS WITH PRIMAQUINE IS NECESSARY TO KILL THE LIVER STAGE OF THE P. VIVAX AND P. OVALE MALARIA PARASITES. IF NOT TREATED WITH PRIMAQUINE THESE TYPES OF MALARIA WILL RELAPSE UNTIL THE LIVER STAGE OF THE PARASITE IS TREATED.
3.B.1.B.3.A. PRIMAQUINE IS NOT BE USED IN PERSONNEL WITH G6PD DEFICIENCY WITHOUT THE CONSULTATION OF AN INFECTIOUS DISEASE SPECIALIST.
3.C. MEFLOQUINE TOXICITY.
3.C.1. SEE ENCLOSURE 1 FOR DETAILS REGARDING THE SYMPTOMS OF MEFLOQUINE TOXICITY BASED ON ITS POSSIBLE EFFECTS ON THE LIMBIC SYSTEM AND BRAINSTEM.
3.C.2. CLINICAL EXPERTISE ON MEFLOQUINE TOXICITY IS CURRENTLY LIMITED; HOWEVER THERE ARE INDIVIDUAL CLINICIANS AVAILABLE FOR CONSULTATION.
3.C.2.A. CLINICAL QUERIES REGARDING MEFLOQUINE-RELATED VESTIBULAR DISORDERS MAY BE DIRECTED TO CAPT MICHAEL E. HOFFER, MC, NAVAL MEDICAL CENTER SAN DIEGO, MICHAEL.HOFFER@MED.NAVY.MIL, (619) 532-6964.
3.C.2.B. GENERAL CLINICAL INQUIRIES REGARDING SUSPECTED CASES OF MEFLOQUINE TOXICITY MAY BE SUBMITTED THROUGH THE WAR RELATED ILLNESS AND INJURY STUDY CENTER (WRIISC) WEBSITE: WWW.WARRELATEDILLNESS.VA.GOV.
3.C.3. PERSONNEL CURRENTLY IN OR TRANSITIONING TO THE VETERANS HEALTHCARE ADMINISTRATION (VHA) CAN BE REFERRED TO THE WRIISC BY A PROVIDER IN THE VHA. POC AT THE WRIISC IS DR. DREW HELMER, DREW.HELMER@VA.GOV, (908) 202-4382.
4. (U) SUSTAINMENT. N/A.//
5. (U) USASOC POCS.
5.A.1. SURGEON CHOPS IS LTC CURTIS DOUGLASS 910-432-3038 CURTIS.W.DOUGLASS@AHQB.SOC.MIL.
5.A.2. USASOC SURGEON POC IS COL JENNIFER CACI 910-432-9884 JENNIFER.CACI@AHQB.SOC.MIL.
AUTHENTICATION/BROWER, COL, COFS, OFFICIAL: DODGE, COL, G3//
AKNLDG/YES/INST: ALL CSC/U ACKNLDG UPON RECEIPT, TO DSN 236-0371, COMM (910) 396-0371.// ENCLOSURE 1. (U) INFORMATION PAPER: SIDE EFFECTS OF MEFLOQUINE.// BT UUUU

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AOMD
3 Sep 13

INFORMATION PAPER

SUBJECT: Side Effects of Mefloquine

1. Purpose. On 29 July 2013 the FDA announced a black box warning for mefloquine in a significant change to the drug's approved labeling. Updated FDA guidance now expands on prior guidance to emphasize the need to discontinue mefloquine should any neurological or psychiatric symptoms develop while taking the drug.

2. Summary. The development of any neurological or psychiatric symptoms may be an indication of a personal risk of mefloquine toxicity. These symptoms may occur at any time during use of mefloquine, even among individuals who have previously tolerated the drug. Recent changes in the product documentation warn of the potential for long lasting serious mental health problems and based on the widespread use of mefloquine within ARSOF consideration must be made for the impact of this medication on our population.

3. Background and Discussion.

a. Since 1989 mefloquine product labeling has warned that if symptoms of "anxiety, depression, restlessness or confusion" developed while taking the drug, the drug must be discontinued.

b. Some U.S. military personnel who were prescribed the drug despite a history of mental illness or TBI may have incorrectly attributed side-effects to their pre-existing condition, rather than to the drug. As a result, military personnel with persistent symptoms following use of mefloquine should be evaluated for the effects of possible drug toxicity.

d. The CDC now notes that the symptoms caused by mefloquine may "confound the diagnosis" of PTSD and TBI. Therefore lasting symptoms resembling those of PTSD or TBI without clear attribution to personal history need to be considered in the differential diagnosis.

e. Careful attention must also be paid to symptoms previously contributing to the diagnosis of malingering, conversion, somatoform, or personality disorders, as the subtle neurological and psychiatric effects of mefloquine toxicity may mimic or be mistaken for these disorders.

f. Neurologic symptoms such as dizziness or vertigo, tinnitus, and loss of balance have been reported. These adverse reactions may occur early in the course of mefloquine use and in some cases have been reported to continue for months or years after mefloquine has been stopped. Dizziness or vertigo, tinnitus and loss of balance have been reported to be permanent in some cases.

g. Psychiatric symptoms ranging from anxiety, paranoia and depression to hallucinations and psychotic behavior can occur with mefloquine use. Symptoms may occur early in the course of mefloquine use and in some cases these symptoms have been reported to continue for months or years after mefloquine has been stopped. Cases of suicidal ideation and suicide have been reported. The updated patient U.S. medication guide expands the list of psychiatric symptoms that can occur to include "feeling restless, unusual behavior or feeling confused".

h. Literature review suggests additional psychiatric symptoms may occur from the drug's toxicity, to include persistent sleep disorders and nightmares, cognitive problems, particularly deficits in short-term memory, panic attacks and agoraphobia, and changes in mood and personality, particularly irritability and decreased impulse control.

i. It is highly unlikely that individuals who have previously taken mefloquine without issue will suffer ill effects in the absence of future use.

j. There is limited support for clinical queries regarding mefloquine toxicity at this time. However, specific questions regarding mefloquine-related vestibular disorders may be directed to CAPT Michael E. Hoffer, MC, Naval Medical Center San Diego, michael.hoffer@med.navy.mil, office (619) 532-6964. General inquiries regarding suspected cases of mefloquine toxicity may be submitted through the War Related Illness and Injury Study Center (WRIISC) website: www.warrelatedillness.va.gov. The USASOC Surgeon's Office (910-432-9884) is also available to field queries and assist in finding clinical support.

COL J. CACI/910-432-9884