Furthermore, WHO now recommends avoiding a mefloquine-containing ACT step-down therapy for severe malaria in patients with impaired consciousness (WHO, 2015).

In 2013 the FDA strengthened and updated warnings and made label changes regarding neurologic and psychiatric adverse effects associated with mefloquine (FDA, 2013).

NEUROPHARMACOLOGY DATA

Although there is not yet evidence of involvement of one or more specific neuronal mefloquine receptors, their existence is strongly implied in published literature. Mefloquine accumulates in the CNS, reaching concentrations as high as 100 μM (Baudry *et al.,* 1997). Because the free brain concentration and/or concentrations at the sites of putative receptors are not known, the relevance of these levels is difficult to interpret, given the lipophilicity of mefloquine and its affinity for biologic membranes. However, mefloquine is known to affect or interact with numerous targets and cellular process in the 100-μM range (el Benna *et al.,* 1992; Go *et al.,* 1995; Maertens *et al.,* 2000; Dow *et al.,* 2003; Weiss *et al.,* 2003; Cruikshank *et al.,* 2004; McArdle *et al.,* 2005, 2006; Thompson and Lummis, 2008). The most likely target is the A2A receptor, based on the nanomolar effects of mefloquine and the association of this target with anxiety and sleep disorders (Weiss *et al.,* 2003). Based on observations in neuropharmacology studies (Martin and Handforth, 2006), mefloquine is assumed to target connexins *in vivo.* Direct toxicity to neurons may also be important *in vivo,* as evidenced by mefloquine-induced neurodegeneration of important brainstem nuclei in rodent studies (Dow *et al.,* 2006). The actions of mefloquine on some of these targets show enantioselectivity, as is the case with the A2A receptor (Weiss *et al.,* 2003), although this is not universally the case (Caridha *et al.,* 2008). Gene-silencing techniques using small interfering RNA have identified downregulation of nonreceptor tyrosine kinase by mefloquine in a rat model, leading to apoptotic response and oxidative injury to neurons (Milatovic *et al.,* 2011).

Dose-related neurologic effects have been observed after mefloquine administration in rodents (Satayavivad *et al.,* 2004). Mefloquine-like neurologic effects interpreted to be analogous to anxiety, insomnia, and ataxia have been observed in rats after administration of a single treatment-equivalent dose, but not prophylactic-equivalent doses (Dow *et al.,* 2006). There have been no neurobehavioral studies reported that mimic the effects of continuous (i.e. prophylaxis) dosing. The mechanistic basis of such effects has not been determined. There have been no neurobehavioral studies reported in higher animals.

6b. Pneumonitis

In a postmarket safety review of mefloquine, 13 cases of pneumonitis or eosinophilic pneumonia were associated with both prophylactic ($n = 6$) and therapeutic use ($n = 5$) of this drug. This review was prompted by the manufacturer's request to revise the Adverse Reactions—Postmarketing section of the label to include pneumonitis as a possible allergic side effect. The product labeling was updated in May 2008 to reflect this new safety information. Of the 13 case reports, 5 have been reported in the medical literature (Drent, 1998; Udry *et al.,* 2001). An online report summarizes the FDA's analysis of these 13 cases. All patients in this case series were hospitalized with the onset of fever, chills, headache, myalgias, shortness of breath, and nonproductive cough. All had various respiratory diagnoses, including pneumonitis, diffuse interstitial pneumopathy, and dyspnea and lung infiltration. Radiographic imaging indicated bilateral lung infiltrates in 7 patients. Leukocytosis and markedly elevated C-reactive protein and lactate dehydrogenase were seen. One patient died, and 5 required systemic corticosteroid therapy.

6c. Contraindications and risk factors

Mefloquine is contraindicated for individuals who have an allergy to mefloquine, related compounds, or inactive excipients, or preexisting neurologic or psychiatric conditions (in particular depression, anxiety, psychosis, seizures, and insomnia) (Roche, 2003a; Taylor and White, 2004; Verdun, 2006). Individuals with preexisting psychiatric or neurologic conditions are much more likely to experience adverse neurologic events (Taylor and White, 2004). Among the traveling population, 10% have a preexisting medical condition that precludes the use of mefloquine (Nevin *et al.,* 2008). In individuals without a preexisting neurologic condition, risk factors for adverse events among travelers include first-time mefloquine use, gender (women are more susceptible), and BMI ≤ 20 (van Riemsdijk *et al.,* 2004). Among women, there is also an association between adverse neurologic outcomes and polymorphisms in the *MDRl* gene that encodes P-gP (Aarnoudse *et al.,* 2006). Although the product labels (Roche, 2003a; Verdun, 2006) state that particular care should be taken when driving or operating machinery owing to the possible development of vertigo or balance disorders or peripheral or CNS disorders (Verdun, 2006), and the United Kingdom Civil Aviation Authority advises that mefloquine not be administered to pilots (Civil Aviation Authority, 2015), there is no clear evidence for these relative contraindications (Chen *et al.,* 2007).

7. CLINICAL USES OF THE DRUG

Mefloquine has a narrow range of clinical uses: (1) malaria prophylaxis in people traveling to malaria-endemic areas, (2) mefloquine monotherapy for imported malaria in nonendemic countries (now rarely recommended), (3) treatment of malaria in endemic countries in combination with artesunate, and (4) standby emergency treatment (SBET) in combination with artesunate. Physicians should review current guidelines before prescribing mefloquine or other antimalarials, because the recommendations are continually reviewed and updated.