Primaquine Information Paper

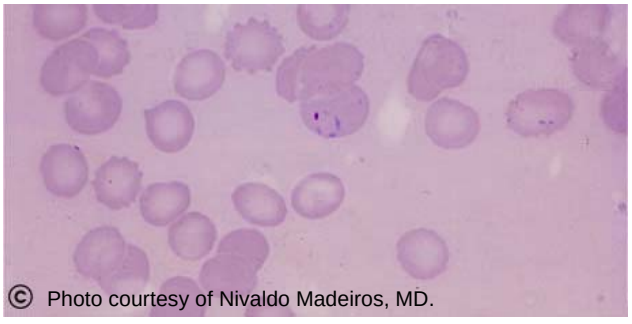
A licensed antimalarial drug developed by DoD and its partners

Product name: Primaquine
Commercial name: Primaquine
Application: Anti-malarial drug for treatment and prevention of relapsing malaria
Date of U.S. licensure: January 1952 (for military use only); August 1952 (for all persons, including civilians)
Type of product: 8 aminoquinoline oral drug
Company of manufacture: Winthrop-Stearns, Inc.

Reasons for development: Relapsing malaria due primarily to P. vivax afflicted U.S. service members during World War II and the Korean War. These relapses are associated with release of latent forms of parasites from the liver following *P. vivax* and *P. ovale* infections.

Role of DoD:
Primaquine is derived from methylene blue and is a close structural analog of pamaquine, the first synthetic antimalarial agent produced in Germany in 1926, which was too toxic for clinical use. Primaquine (synthesized by Dr. Robert C. Elderfield of Columbia University) was developed by the U.S. Army during World War II beginning in 1944, when malaria (some of it relapsing illness due to P. vivax) was a serious burden to U.S. troops in the Pacific and India-Burma theaters. The 8-aminoquinoline group of antimalarials demonstrated potent activity against the liver forms of some malaria parasites.

The U.S. Army did further large-scale safety and efficacy studies to develop primaquine beginning in the early 1950's when relapsing malaria due to *P. vivax* emerged as a major problem in returning U.S. veterans from the Korean War. Because service member compliance with chloroquine was adequate in the field, malaria did not become apparent until after cessation of chloroquine when the troops departed Korea. Dr. Alf Alving at the University of Chicago led a research team under contract to the U.S. Army which evaluated safety, toxicity, and efficacy of new antimalarial agents. Volunteers were recruited from inmates of the Illinois State Penitentiary at Stateville in Joliet, Illinois for these studies. Primaquine was found to kill liver malaria parasites caused by two types of human malaria (*P. vivax* and *P. ovale*) before these are released into the blood stream weeks to months after primary infection, and therefore the drug can cure relapsing malaria. The relatively short half-life (4-6 hours) of primaquine requires daily administration for 14 days to achieve a cure. During the Korean war, primaquine was given as directly observed therapy daily during the 14 day voyage from Korea to the United States. Fortunately, primaquine was shown not to aggravate the problem of seasickness. At the time of FDA licensure, it was known that the dose of 15 mg/day would not be sufficient to cure all strains of *P. vivax* (such as the Chesson strain), but higher doses were associated with hemolytic anemia in persons of African descent.



Malaria is a blood infection spread by a bite from a mosquito carrying the malaria parasite. Pictured are blood cells infected with P. vivax..

Subsequently, it became known that doses of primaquine above 15 mg a day can cause anemia due to break-up of blood cells in persons with a genetic defect known as glucose-6-phosphate dehydrogenase deficiency. It is therefore necessary to test for G6PD deficiency if doses larger than 15 mg of primaquine/day are used. This enzyme deficiency is most common in persons of African, Mediterranean, Middle Eastern and southeast Asian descent. The current recommendation of 30 mg/day x 14 days for treatment of *P. vivax* infections therefore is not caused by continuing emergence of primaquine-resistant *P. vivax*.

In recent years a multidisciplinary working group from the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Institute (NMRI) reviewed the existing data on primaquine to determine whether primaquine could be useful as a prophylactic drug, and the Navy laboratory in Jakarta has completed a pivotal Phase III study. The U.S. Centers for Disease Control and Prevention now recommends primaquine as a chemoprophylactic agent option to prevent malaria when other antimalarial drugs cannot be administered.

Tafenoquine (WR 238605), an 8-aminoquinoline analog of primaquine with a half-life of 2-3 weeks, is under development and is expected to be effective both for preventing and treating *P. falciparum* and *P. vivax* malaria.

Primaquine references:

Garrison PL, Hankey DD, Walter GC: Cure of Korean vivax malaria with pamaquine and primaquine. JAMA 1952; 149:1562-3.

Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia. Am J Trop Med Hyg 1995;52:479-84.

Fryauff DJ, Baird JK, Basri H: Randomized placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. Lancet 1995; 346:1190-3.

Alving A. Clinical treatment of malaria. Presented at the course "Recent Advances in Medicine & Surgery" at the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C., April 19-30, 1954, p. 209-218.

Edgcomb et al. Primaquine. SN13, 272, a new curative agent in vivax malaria: a preliminary report. Journal National Malaria Society 1950; 9:285-292

Clayman et al. Toxicity of primaquine in caucasians. JAMA 1952; 149(17):1563-1968.

Hockwald et al. Toxicity of primaquine in negroes. JAMA 1952; 149(17):1568-1570.

Marshall, IH. Malaria in Returning Veterans. Presented at the course "Recent Advances in Medicine and Surgery" Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C., April 19-30,1954.