

Chloroquine Information Paper

A licensed antimalarial drug developed by DoD & its partners

UNITED STATES ARMY MEDICAL RESEARCH
AND MATERIEL COMMAND



Product name: Chloroquine

Commercial name: Aralen

Application: Antimalarial drug for treatment and prevention of malaria

Date of U.S. licensure: October 1949

Type of product: 4-aminoquinoline

Company of manufacture: Multiple pharmaceutical companies were involved in the development of this drug, including Winthrop, Abbott, E.R. Squibb and Sons, Eli Lilly and Company, Sharp and Dohmne, Inc. The drug is currently manufactured by Sanofi Synthelabo.

Quinine, derived from the bark of the cinchona tree, has been a mainstay of malaria treatment for hundreds of years. The drug is very effective for some types of malaria -- especially when combined with other antimalarial drugs -- but adverse effects (referred to as "cinchonism" and a short duration of action render it an imperfect prophylactic agents. The World Wars prompted an effort to develop synthetic drugs to prevent and treat malaria because of quinine supply problems and the need for long-acting prophylactic drugs to prevent malaria in troops. During World War I, countries producing quinine were controlled by Allied forces, which led to initial efforts by German companies to synthesize antimalarial compounds. But because pharmaceutical development requires many years, such drugs were not developed until after World War I. The earliest work in synthesizing antimalarial drugs was based on the work of a German scientist named Paul Ehrlich. While studying the newly discovered aniline dyes to develop methods for staining human tissues in 1891, he observed that the dye methylene blue stained malaria parasites, and that malaria organisms did not survive after ingesting large amounts of this dye. Dr. Ehrlich cured two patients of malaria using methylene blue -- the first time a synthetic drug was used to treat humans.

Bayer, one of the leading German dye companies, soon became a leading pharmaceutical company. A team of chemists and biologists was assembled by Bayer to develop new synthetic antimalarials using methylene blue as a prototype. In 1930 German scientists synthesized another antimalarial compound based on a known dye (9-amino acridine, later known as atabrine). Although U.S. service members in Panama were involved in some clinical trials to test the efficacy of this drug, Germany controlled atabrine manufacturing until U.S. scientists succeeded in initiating the manufacture of atabrine in 1941.

The Allied push to synthesize antimalarial agents during World War II -- spearheaded by the U.S. military-- was prompted by the Japanese seizure of Java (which then supplied 90% of the world's supply of quinine). Concerns about adverse effects of atabrine (yellowing of the skin, and Japanese propaganda suggesting the drug caused



"Doctor, this will be a long war if for every division I have facing the enemy I must count on a second division in the hospital with malaria and a third division convalescing from this debilitating disease!"
GEN Douglas MacArthur - May 1943"

impotence) led to noncompliance. After dosing studies were undertaken with U.S. soldiers at Fort Knox, and Neil Fairly (an Australian military physician) showed that placing volunteer Australian troops on a daily atabrine regime was effective in preventing malaria, atabrine prophylaxis was rigidly imposed on Allied forces operating in malarious areas. Control of malaria was an important factor in Allied success in World War II.

Allied interest in chloroquine followed the capture of German supplies of a structural analog called sontoquine in Tunis in 1943. Both chloroquine and sontoquine had been patented in the U.S in 1941 by the Winthrop Company, which had a cartel agreement with IG Farbenindustrie, the original manufacturer of these compounds, but drug development had stalled. Chloroquine rapidly controlled clinical symptoms of susceptible *P. falciparum* and *P. vivax* malaria with minimal toxicity, and was also useful as a once-weekly prophylactic drug.

In the 1950's Mario Pinotti in Brazil introduced the strategy of putting chloroquine into common cooking salt as a way of distributing the drug as a prophylactic on a wide scale. This medicated salt program became known as "Pinotti's method" and was employed in South America as well as parts of Africa and Asia. Chloroquine, along with widespread use of the residual insecticide DDT, was a major component of the WHO Global Eradication Programme of the 1950's and 1960's. Chloroquine has been safely used in pregnant women and children. However, the emergence of chloroquine-resistant *P. falciparum* and *P. vivax* have rendered this drug less useful. Chloroquine has also proved useful as a treatment for connective tissue disorders.

Chloroquine References:

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www.CDC.gov/malaria/history