Atovaquone-Proguanil Information Paper

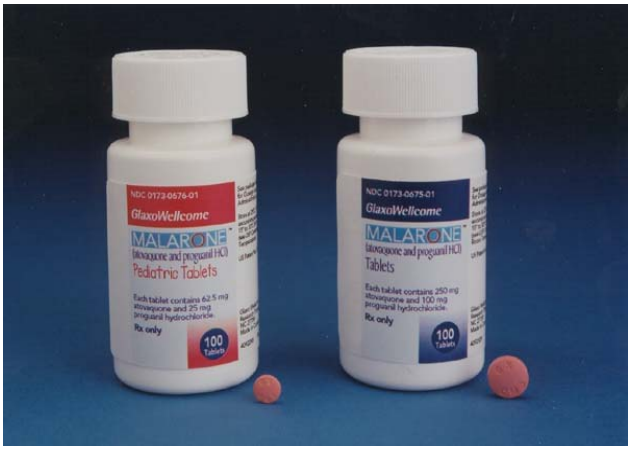
Licensed antimalarial drugs developed by DoD and its partners

Product Name: Atovaquone - Proguanil
Commercial name: Malarone
Application: Prophylaxis/treatment of falciparum malaria
Commercial manufacturer: GlaxoSmithKline
Date of U.S. licensure: July 2000

Type of product: Malarone is a combination of atovaquone (a 3-substituted-2-hydroxynaphthoquinone) and proguanil (biguanide). These drugs act against blood forms and early liver stage of malaria. Atovaquone (as a single agent) is a hydroxynaphthoquinone currently marketed in the United States under the trade name Mepron for pneumocystis carinii pneumonia, and acts on the malaria parasite by inhibiting the electron transport system at the level of cytochrome bc1 complex, thereby inhibiting pyrimidine biosynthesis, which is essential for Plasmodia (in contrast, mammalian cells are able to salvage pyrimidines). Atovaquone also causes collapse of the parasite mitochondrial membrane potential in P. falciparum. The structure of atovaquone differs from that of other antimalarial drugs. Proguanil (Paludrine) which interferes with folic acid synthesis crucial to malaria parasite survival (via binding to the enzyme dihydrofolate reductase in much the same way as pyrimethamine) was developed by the British during World War II, and approved in the U.S. in 1948 for use in malaria. Because proguanil was not widely used in this country, it ceased to be marketed as a single drug in the U.S. in the 1970s. Proguanil is still used overseas as an antimalarial, especially in combination with chloroquine. However, the primary role of proguanil in Malarone may not be as an antifolate. There is demonstrable antimalarial synergy when atovoquone and proguanil are combined, although the mechanism for this enhancement is unclear, and resistance to the antimalarial effect of proguanil alone is common.

Reasons for development: (1) Resistance to the effective action of other antimalarial drugs used to prevent malaria is an important clinical problem. (2) Adverse effects have been noted with other antimalarial drugs (photosensitivity, diarrhea with doxycycline, and neurotoxicity with mefloquine).

Role of DoD: Development of drug combination strategies, dose-ranging pre-clinical and clinical studies and pivotal efficacy trials were organized by the Walter Reed Army Institute of Research in partnership with GlaxoSmithKline. Early malaria preclinical efficacy testing of atovaquone was conducted at the Walter Reed Army Institute of Research, and subsequent dose-ranging



studies were undertaken at the Armed Forces Research Institute of Medical Science (AFRIMS) in Thailand. In the treatment of acute uncomplicated falciparum malaria, atovaquone proved to be consistently effective in clearing the initial parasitemia. However, unacceptable rates (up to 25%) or recrudesence precluded the further development of atovaquone as monotherapy. Concurrent administration with proguanil, selected for its synergistic activity with atovaquone solidified its role as an antimalarial drug in studies when evaluated at AFRIMS. Subsequent trials were conducted worldwide including WRAIR laboratories in Brazil and in Kenya which demonstrated 99% efficacy for treatment of uncomplicated multidrug-resistant malaria, and 98% efficacy for prophylaxis in placebo-controlled trials. Additional prophylaxis studies have been completed by the NAMRU-2 in Jakarta, Indonesia. Malarone was licensed for treatment of P. falciparum malaria in 30 countries, including Australia, prior to U.S. licensure.

Current status:
Malarone has few associated adverse effects other than mild gastrointestinal intolerance, but experience with this drug is relatively limited. This medication is very expensive, and out of economic reach of millions around the world who suffer from malaria. Rapid development of resistance related to spontaneously arising mutations in the parasite that confer drug resistance has been noted when the drug has been used alone as a malaria treatment.

The current status of malaria is worrisome: According to the World Health Organization, there are 300 to 500 million cases of malaria each year resulting in 1.5-2.7 million deaths. Children aged 1-4 are the most vulnerable to infection and death.

Atovaquone-Proguanil References:

Anonymous. FDA approves Malarone for the prevention and treatment of malaria. FDA talk paper. July 14, 2000.

De Alencar FEC, Cerutti C, Durlacher RR, et al. Atovaquone and proguanil for the treatment of malaria in Brazil. Journal of Infectious Diseases 1997;175:1544-7.