Atovaquone and proguanil hydrochloride (Malarone®)

National Drug Monograph

May 2014

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

# Executive Summary1, 20

* Atovaquone/proguanil is a fixed-dose combination antimalarial agent with synergistic activity against the liver and blood stages of *Plasmodium* spp.
* Atovaquone/proguanil was FDA approved in July 2000 for prevention and treatment of uncomplicated *Plasmodium falciparum* malaria, including areas with chloroquine-resistance.
* Atovaquone/proguanil is recommended by the CDC prophylaxis of malaria in chloroquine-sensitive and -resistant areas; treatment of uncomplicated *P*. *falciparum* malaria (or species that were not identified) in chloroquine-resistant or areas with unknown resistance; and treatment of uncomplicated *P. vivax* malaria (in combination with primaquine) in chloroquine-resistant areas.
* The recommended prophylaxis dosage regimen is 1 tablet orally once daily with food or milk, start 1-2 days prior to entering malaria-endemic areas, continue throughout the stay, and for 7 days after returning. However, choosing a drug to prevent malaria differs by country of travel and information can be found at <http://wwwnc.cdc.gov/travel/destinations/list>. Medication counseling should include the following statement: “No antimalarial drug is 100% protective and must be combined with the use of personal protective measures (i.e. insect repellent, long sleeves, long pants, sleeping in mosquito-free setting or using an insecticide-treated bednet)”.
* The recommended treatment dosage regimen is 4 tablets orally once daily with food or milk for 3 consecutive days. However, treatment of malaria is multifactorial and depends on the type of *Plasmodium* parasites, the geographic area of infection and drug-resistance status, clinical status, co-morbidities, pregnancy status, drug allergies, and concomitant medications. For detail information regarding drug for malaria treatment in the United States, please refer to the following link <http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>
* Atovaquone/proguanil has been shown to be efficacious in preventing *P*. *falciparum* malaria in both non-immune travelers to malaria-endemic area and semi-immune adults. It also has demonstrated curative efficacy for the treatment of uncomplicated *P*. *falciparum* acquired in areas with chloroquine- and multidrug-resistant parasites in adults. The overall primary efficacy endpoint (i.e, 28-day cure rate) was 98-100%.
* Atovaquone/proguanil has safety considerations with warning/precautions in pregnant/lactating women, and patients with severe renal impairment. The most commonly observed adverse events in clinical trials were headache, nausea, vomiting, abdominal pain, and diarrhea.
* Overall, fixed-dose combination atovaquone/proguanil was shown to be efficacious for both prevention and treatment of uncomplicated *P*. *falciparum* malaria, including areas with chloroquine-resistance. CDC guidelines provide recommendations for the role of atovaquone/proguanil for prophylaxis and treatment of malaria. Prevention of malaria involves a balance between taking antimalarial drug as prescribed and using the appropriate prevention measures. As for treatment of malaria, clinicians should take in consideration of local information on prevalence of resistance to antimalarial drugs by referring to the CDC treatment guidelines. Dietary fat can increase absorption of atovaquone/proguanil, therefore; it is important to take the medication with food or milk. The most commonly reported adverse events associated with atovaquone/proguanil were headache, abdominal pain, nausea, vomiting, and diarrhea. Overall, atovaquone/proguanil should be avoided in travelers with history of severe renal impairment, and pregnant or breastfeeding women.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating atovaquone/proguanil hydrochloride for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics1,2

Atovaquone /proguanil hydrochloride is a-fixed dose combination antimalarial drug that is active against the liver and blood stages of *Plasmodium* spp.

Atovaquone /proguanil works in 2 different pathways to interfere with pyrimidine synthesis that is required for DNA replication. Atovaquone is a selective inhibitor of parasite mitochondrial electron transport at the level of cytochrome bc(1) complex and collapses mitochondrial membrane potential. Atovaquone selectively acts on parasite electron transport because of the 1000 fold greater sensitivity of this system to atovaquone over the mammalian electron transport chain. Proguanil HCl primarily exerts its effect by means of the metabolite cycloguanil which inhibits dihydrofolate reductase (DHFR) in the malaria parasite and disrupts deoxythymidylate synthesis.

The manufacturer has stated that the combination of 2 drugs with different mechanisms of actions is less likely to induce resistance. In addition, both in vitro and in vivo studies have revealed the synergistic antimalarial action of atovaquone and proguanil.

Table 1: Pharmacokinetic Comparison of Malaria Prophylaxis agents

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Atovaquone/proguanil** | **Chloroquine** | **Primaquine** | **Mefloquine** | **Doxycycline** |
| Metabolism | enterohepatic/CYP2C19a | Partially hepatic b  | hepatic | hepaticCYP 3A4 | not hepatic, GI chelation |
| Elimination | bile,feces/40-60%renal | >50% renal |  renal (<2%) | bile, feces, 5% renal | Feces, 23% renal  |
| Half-life | 15-17 hours/ 2-3 days | 1-3 weeks | 6-30 hours | 2-4 weeks | 14-24 hours |
| Protein Binding | 99/75%b | 55% | ---c | 98% | 90% |
| Bioavailability | 23% with dietary fatd | >75% | 96% | >85% with food | >90% |

a Proguanil is metabolized into cycloguanil and p-chlorophenylbiguanide (pCBG) primarily via CYP2C19 enzymes present in the liver.

b Chloroquine is partially metabolized by the liver to main metabolite, deesthylchloroquine

c No information available

d Dietary fat taken with atovaquone increases AUC 2-3 folds and Cmax 5 fold over fasting

# FDA Approved Indication(s)1

**Prevention of malaria:** atovaquone/proguanil hydrochloride is FDA-approved for the prophylaxis of *Plasmodium falciparum* malaria, including in areas where chloroquine-resistance has been reported.

**Treatment of malaria:** atovaquone/proguanil hydrochloride is FDA-approved for the treatment of acute, uncomplicated *Plasmodium falciparum* malaria.

**CDC Guidelines** 11

Malaria is transmitted among humans by female mosquitoes of the genus Anopheles. Anophelines are found worldwide except Antarctica. Malaria is transmitted by different Anopheles species, depending on the region and the environment. Anophelines that can transmit malaria are found not only in malaria-endemic areas, but also in areas where malaria has been eliminated. It is important for travelers to obtain a detailed itinerary including all possible destinations that may be encountered during the trip and check to see if malaria transmission occurs in these locations. Detail information on malaria information by country can be found on the CDC websites <http://www.cdc.gov/malaria/travelers/country_table/a.html> or <http://www.cdc.gov/malaria/map/index.html>.

Where malaria is found depends mainly on climatic factors such as temperature, humidity, and rainfall. Areas with highest malaria transmission rate are found in Africa South of the Sahara and in parts of Oceania such as Papua New Guinea.

Atovaquone/proguanil is recommended by the CDC for the following:

* Prophylaxis of malaria in chloroquine-sensitive and -resistant areas
* Treatment of uncomplicated *P*. *falciparum* malaria (or species that were not identified) in chloroquine-resistant or areas with unknown resistance
* Treatment of uncomplicated *P. vivax* malaria (in combination with primaquine) in chloroquine-resistant areas

Official guidelines and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration. For detail information regarding drug for malaria treatment in the United States, please refer to the following link <http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>

**Potential Off-label Uses**

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s [Guidance on “Off-label” Prescribing](http://vaww.national.cmop.va.gov/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.pdf) (available on the VA PBM Intranet site only).

According to clinicaltrials.gov, there are no on-going clinical trials evaluating atovaquone/proguanil for other indications.

# Current VA National Formulary Alternatives1, 11-12

Chloroquine, Doxycycline and Primaquine. Please note that primaquine can cause hemolytic anemia in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency; Patients must be screened for G6PD deficiency prior to starting primaquine.

Non-formulary Options: On July 29, 2013, FDA notified healthcare professionals of a new box warning added to the prescribing information of mefloquine. The box warning states that “mefloquine can cause neurologic and psychiatric side effects which can occur at any time during drug use, and can last for months to years after drug is stopped or can be permanent”; therefore, mefloquine drug label states that it should not be prescribed to prevent malaria in patients with major psychiatric disorders or with a history of seizure. Detail information can be found on <http://www.fda.gov/drugs/drugsafety/ucm362227.htm>. The CDC Guidelines for Treatment of Malaria state “Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used” for the treatment of uncomplicated *P*. *falciparum* malaria (or species that were not identified) in chloroquine-resistant or areas with unknown resistance.

Of note, atovaquone alone is available on formulary; however, atovaquone is FDA-approved only for prophylaxis or treatment of mild-moderate *pneumocystis jirovecii* pneumonia. The CDC does not recommend atovaquone for neither treatment nor prophylaxis of malaria in their guideline.

**Prevention Considerations**

* When choosing a drug to prevent malaria, several parameters should be taken in consideration: country of travel, drug-drug interaction, drug resistance, and medical contraindications (such as allergies).The CDC recommendation of drugs for malaria prophylaxis in the United States is available through the CDC website <http://www.cdc.gov/malaria/travelers/drugs.html>.
* Per the CDC, no antimalarial drug is 100% protective and must be combined with the use of personal protective measures (i.e., insect repellent, long sleeves, long pants, sleeping in a mosquito-free setting or using an insecticide-treated bednet).

**Treatment Considerations**

* Treatment of malaria is multifactorial and depends on the type of Plasmodium parasite, the geographic area of infection and drug-resistance status, clinical status, co-morbidities, pregnancy status, drug allergies, and concomitant medications.
* CDC treatment algorithm can be found at The CDC Guidelines for drugs for malaria treatment in the United States is available through the CDC website <http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html>. <http://www.cdc.gov/malaria/resources/pdf/algorithm.pdf>.
* CDC clinicians are on-call 24-hours to provide advice to clinicians on the diagnosis and treatment of malaria and can be reached through the Malaria Hotline 770-488-7788 or toll free 855-856-4713.

# Dosage and Administration1

|  |  |
| --- | --- |
| **Indication** | **Recommended dose** |
| **Prophylaxis** | Atovaquone/proguanil 250 mg/100 mg (1 tablet) by mouth once dailya; start 1-2 days prior to entering a malaria-endemic area, continue throughout the stay and for 7 days after returning. |
| **Treatment** | Atovaquone/proguanil 1000 mg/400 mg (4 tablets) by mouth as a single dosea, once daily for 3 consecutive days. |

aAdminister with food or milk-based drink at the same time each day. If vomiting occurs within 1 hour of administration, repeat the dose. For patients who have difficulty swallowing tablets, tablets may be crushed and mixed with condensed milk just prior to administration

**Renal adjustment:**

|  |  |
| --- | --- |
| **Creatinine Clearance**  | **Dose adjustment** |
| ≥30 mL/minute | No dosage adjustment necessary |
| <30 mL/minute | **Prevention:** Use is contraindicated.**Treatment:** No dosage adjustment necessary; however, use with extreme caution and only if the benefits outweigh the risks. |

**Hepatic adjustment:**

|  |  |
| --- | --- |
| **Liver impairment** | **Dose adjustment** |
| Mild to moderate | No dosage adjustment necessary |
| Severe | No studies have been done |

# Efficacy1, 8-20,23-24

**Prophylaxis**

For the original FDA review, the fixed dose combination of atovaquone/proguanil was evaluated for prophylaxis of malaria in 4 clinical trials in malaria–endemic areas, of these 4 trials, 1 trial was evaluated in pediatric population and is not included in this review (Table 2).

In the 3 clinical trials described below, the primary efficacy endpoint was the development of parasitemia with any species of plasmodium during chemoprophylaxis defined by negative malaria smears confirmed by at least 2 microbiologists. Primary efficacy analyses were performed using the intention-to-treat population (ITT), which was defined as the subjects who were randomized to receive either atovaquone/proguanil or comparators during chemosuppression, who received at least one dose of treatment during chemosuppression, and who had a negative baseline smear. Overall, atovaquone/proguanil was shown to be effective in preventing malaria in semi-immune adults.

**Table 2: Efficacy of atovaquone/proguanil for malaria prophylaxisa**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country (population)** | **Study design**  | **ITT population**  | **Duration of prophylaxis**  | **Protection rate (95% CI, p value)b** |
| South Africa (non-immune adult 16-65 years old) | Open-label, non-comparative | 175 | up to 10 weeks | 69% AP (61% -75%)  |
| Kenya (semi-immune adults 18-65 years old) | Randomized, double-blind, placebo-controlled, 3-arm parallelc | 198 | 10 weeks | 83% AP (2tabs/day) vs. 79% AP (1 tab/day) vs. 48% placebo (p<0.001) |
| Zambia (semi-immune adults 18-65 years old) | Randomized, double-blind, placebo-controlled | 272 | 10 weeks  | 75% AP vs. 51% placebo (p<0.001) |

a Data obtained from FDA Medical Review

b 95% CI and p values provided when available

c All subjects received 4 tablets of atovaquone/proguanil daily x 3 days. Then, patients were randomized to one of the 3 suppressive treatment regimens: atovaquone/proguanil 1 tablet or 2 tablets per day or placebo daily

AP=Atovaquone/proguanil

The FDA approval of atovaquone/proguanil in 2000 relied on clinical studies performed in malaria-endemic areas where study subjects were presumed to partially immune to malaria as described in Table 2. The prophylactic efficacy of atovaquone/proguanil in non-immune subjects was not well-studied. On this basis, two phase 4 international, multicenter, randomized, double-blind, active-controlled trials in non-immune travelers were requested by the FDA, following initial approval of atovaquone/proguanil. These studies differed primarily in comparators used (atovaquone/proguanil vs. mefloquine or chloroquine/proguanil). For both studies, the primary objective was to evaluate adverse event rates, and the secondary objective was to evaluate prophylactic efficacy. Overall, the prophylactic efficacies for these two studies were 99% for both treatment groups. The FDA reviewer indicated that the two studies were not powered to demonstrate comparative efficacy but stated that the results suggested all regimens used in the studies are effective for malaria prophylaxis.

Since FDA approval, there have been more clinical trials that assessed efficacy of atovaquone/proguanil; please refer to the review article written by Boggild A and colleagues for summary of additional trials data (reference #19).

**Treatment**

In 3 phase II clinical trials, atovaquone alone, proguanil alone, and fixed dose atovaquone/proguanil were evaluated for the treatment of acute, uncomplicated malaria caused by *P*. *falciparum*. The study evaluated 156 patients, the parasitological cure rates were 66% vs. 6% vs. 100% for atovaquone, proguanil, and fixed dose atovaquone/proguanil, respectively.

For the FDA review, the fixed dose combination of atovaquone/proguanil was evaluated for the treatment of acute, uncomplicated malaria in 8 phase III controlled clinical trials, of which, 7 trials were active-controlled trials, one trial was evaluated in pediatric population and not included in this review (Table 3). In these trials, the primary efficacy endpoint was cure rate defined as parasite clearance within 7 days without recurrence up to day 28. The recommended dose of atovaquone/proguanil in all clinical trials was 4 tablets once daily (1000mg/400mg) for 3 days. Secondary efficacy endpoints included parasite clearance time (PCT) and fever clearance time (FCT). PCT was defined as the time from treatment initiation to the time of the first of three negative films. FCT was defined as the time from treatment initiation to the time of the decrease in fever below 37.2°C that remains below this target for at least 24 hours. Overall, atovaquone/proguanil was shown to be effective in treating acute, uncomplicated *P*. *falciparum* malaria.

**Table 3: Efficacy of atovaquone/proguanil for malaria treatmenta**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country (population)** | **Study type**  | **Evaluable patients**  | **Primary efficacy** | **Secondary efficacy**  |
| **Cure rate (95% CI)b** | **Mean FCT****(hours)c**  | **Mean PCT****(hours)c** |
| Philippines (semi-immune, 12-65 years old) | Randomized, open-label, active-controlled, AP vs. chloroquine (CQ) vs. SP+CQd | 109 | 100% AP vs. 30.4% CQ vs. 87.5% CQ+SP  | 38.7 AP vs. 46.8 CQ vs. 34.7 CQ+SP  | 47.3 AP vs. 60.1 CQ vs. 42.9 CQ + SP  |
| Brazil (semi-immune men 18-65 years old) | Randomized, open-label, AP vs. quinine + tetracycline (QT) | 150 | 98.6% AP vs. 100% QT(-5.3% -2.6%) | 22.8 AP vs. 32.5 QT(p<0.021) | 55.5 AP vs. 63.6 QT(p=0.011) |
| Thailand (adults 16-65 years old) | Randomized, open-label, active -controlled , AP vs. mefloquine | 158 | 100% AP vs. 86.1% mefloquine (5% - 22.8%)  | 58.6 vs. 52.6 (p=0.270) | 65.1 vs 73.5 (p=0.025) |
| Zambia (semi-immune, 14-54 years old) | Randomized, open-label, active-controlled, AP vs. sulfadoxine / pyrimethamine (SP) | 160 | 100% AP vs. 98.8% SP (-2.4% - 4.9%) | 30.6 AP vs. 45.5 SP (p<0.001) | 63.8 vs. 51.5 (p< 0.001) |
| Gabon (semi-immune , 15-65 years old) | Randomized, open-label, active-controlled, AP vs. amodiaquine (AQ) | 126 | 98.4% AP vs. 81% AQ (5.7% - 29.2%) | 27.2 AP vs. 19.6 AQ (p=0.041) | 72.9 AP vs. 65.8 AQ (p=0.04) |
| France (non-immune, > 16 years old) | Randomized, multicenter, open-label, active-controlled, AP vs. halofrantrine (HF) | 39 | 100% AP vs. 100% HF  | 61.1 AP vs. 62.9 HF | 62.7AP vs. 50.0 HF |
| Peru(semi-immune, 12-65 years old) | Randomized, open-label, active controlled, 2 phasesPhase 1: AP vs. chloroquine (CQ)Phase 2: AP vs. sulfadoxine/pyrimethamine(SP)  | 392712 | 100% AP vs. 7.7% CQ100% AP vs. 100% SP | 42.9 AP vs. 40.6 CQ38.4 AP vs. 4.68 SP  | 55.7 AP vs. 54.1 CQ44.4 AP vs. 38.6 SP |

a Data obtained from FDA Statistical Review

b 95% CI provided when available

c p values provided when available.

d In this study, after 40 patients had been entered in to the trial, the cure rate with chloroquine was < 35%, and, for ethical reasons, the protocol was amended so that patients subsequently randomized to receive chloroquine also received a sulfadoxine-pyrimethamine (SP +CQ) combination.

# Adverse Events (Safety Data) 1, 20

The most commonly reported adverse events possibly attributed to atovaquone/proguanil were headache, nausea, vomiting, abdominal pain, and diarrhea (Refer to Table 4 and 5). Among subjects who received atovaquone/proguanil prophylaxis for malaria in comparator-controlled trials, fewer neuropsychiatric adverse experiences occurred in atovaquone/proguanil treated patients than mefloquine.

**Table 4: Adverse events occurring of adults patients in clinical trials for prophylaxis of malaria**

|  |  |  |
| --- | --- | --- |
| **Adverse eventsa**  | **Atovaquone/proguanil** **(n=206)**  | **Placebo** **(n=206)** |
| Headache | 22 (3) | 27 (7) |
| Abdominal pain | 9 (4)  | 10 (5) |
| Fever | 5 (0) | 13 (1) |
| Diarrhea | 6 (2) | 8 (3) |
| Dyspepsia | 3 (2) | 5 (4) |
| Gastritis | 3 (3) | 3 (2) |
| Cough | 6 (< 1) | 8 (<1) |

aPercent of subjects with adverse experiences (percent of subjects with adverse experiences attributable to therapy)

**Table 5: Adverse events occurring of adults patients in clinical trials for prophylaxis of malaria**

|  |  |  |
| --- | --- | --- |
| **Adverse eventa** | **Study 1** | **Study 2** |
| **Atovaquone/****proguanil****(n=493)** | **Mefloquine****(n=483)** | **Atovaquone/****proguanil****(n=511)** | **Chloroquine/****Proguanil****(n=511)** |
| Diarrhea | 38 (8) | 36 (7) | 34 (5) | 39 (7) |
| Nausea | 14 (3) | 20 (8) | 11 (2) | 18 (7) |
| Abdominal pain  | 17 (5) | 16 (5) | 14 (3) | 22 (6) |
| Headache | 12 (4) | 17 (7) | 12 (4) | 14 (4) |
| Dreams | 7 (7) | 16 (14) | 6 (4) | 7 (3) |
| Insomnia | 5 (3) | 16 (13) | 4 (2) | 5 (2) |
| Fever | 9 (<1) | 11 (1) | 8 (<1) | 8 (<1) |
| Dizziness | 5 (2) | 14 (9) | 7 (3) | 8 (4) |
| Vomiting | 8 (1) | 10 (2) | 8 (0) | 14 (2) |
| Oral ulcers | 9 (6) | 6 (4) | 5 (4) | 7 (5) |
| Pruritus | 4 (2) | 5 (2) | 3 (1) | 2 (<1) |
| Visual difficulties | 2 (2) | 5 (3) | 3 (2) | 3 (2) |

aPercent of subjects with adverse experiences (percent of subjects with adverse experiences attributable to therapy)

The higher treatment doses of atovaquone/proguanil were less well tolerated than the lower prophylactic doses. Among adults who received atovaquone/proguanil for treatment of malaria, attributable adverse experiences that occurred > 5% of patients were abdominal pain (17%), nausea (12%), vomiting (12%), diarrhea (8%), asthenia (8%), anorexia (5%), and dizziness (5%).

## Tolerability1, 10

In placebo-controlled trials for malaria prophylaxis, atovaquone/proguanil was discontinued prematurely due to a treatment-related adverse experience in 3 of 381 adults. In comparator-controlled trials for malaria prophylaxis, atovaquone/proguanil was discontinued prematurely due to a treatment-related adverse experience in 7 of 1,004 travelers.

## Deaths and Other Serious Adverse Events1, 20

One death was reported during the conduct of the clinical trials. Patient was a young Zambian man with a psychiatric history whose malaria was treated with atovaquone alone for 7 days. He was transferred to a psychiatric ward for treatment but died on day 13. While the patient’s antecedent delusions and agitation may have been attributable to atovaquone, his death was unlikely to have been related to atovaquone.

Nine patients experienced serious adverse events, of which; five were on atovaquone/proguanil. Two out of 9 events were attributable to study medication. These were anaphylactic reaction (atovaquone/proguanil) and delusions/agitation prior to sudden death (Zambian man as mentioned above who was on atovaquone alone)

# Contraindications1

* Individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation. During clinical trials, 1 case of anaphylaxis following treatment with atovaquone/proguanil was observed.
* When used for prophylaxis of *P*. *falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30 mL/min)

# Warnings and Precautions1

* Atovaquone/proguanil is contraindicated for prophylaxis of *P*. *falciparum* malaria in patients with severe renal impairment (i.e. creatinine clearance < 30 ml/min)
* Atovaquone/proguanil should not be used for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including hyperparsitemia, pulmonary edema, or renal failure.
* Absorption of atovaquone may be reduced in patients with diarrhea or vomiting. If atovaquone/proguanil is used in patients who are vomiting, parasitemia should be closely monitored and the use of an antiemetic should be considered.
* Parasite relapse occurred commonly when *P.* *vivax* malaria was treated with atovaquone/proguanil alone
* In the event of recrudescent *P*. *falciparum* infections after treatment or failure of prophylaxis with atovaquone/proguanil, patients should be treated with a different antimalarial agent.
* The concomitant administration of atovaquone/proguanil and any other medication containing proguanil hydrochloride should be avoided.
* Increased transaminase levels and hepatitis have been reported with prophylactic use; single case report of hepatic failure requiring transplantation documented. Monitor closely and use caution in patients with existing hepatic impairment. Elevations in AST/ALT may persist for up to 4 weeks following treatment

# Special Populations 1, 7-9

**Pregnancy:** Atovaquone/proguanil is categorized as pregnancy category C. Falciparum malaria carries a higher risk of morbidity and mortality in pregnant women than in the general population with maternal death and fetal loss are both known complications of falciparum malaria in pregnancy. Therefore, the manufacturer recommended that atovaquone/proguanil may be used if the potential benefit justified the potential risk to the fetus. In addition, pregnant women who must travel to malaria-endemic areas, personal protection against mosquito bites should always be employed in addition to antimalarials. However, atovaquone/proguanil is not currently recommended for use during pregnancy by the CDC.

**Lactation:** Caution should be exercised when atovaquone/proguanil is administered to a nursing woman. Proguanil is excreted in human milk in small quantities. However, it is not known whether atovaquone is excreted in human milk.

**Geriatrics:** In a single-dose study, the pharmacokinetics of atovaquone/proguanil was compared in 13 elderly subjects (65-79 years old) to 13 younger subjects (30-45 years old). In the elderly subject, the extent of systemic exposure (AUC) of cycloguanil (metabolite of proguanil) was increased by approximately 2 fold and half-life was longer in elderly subjects (mean 14.9 hours) compared with younger subjects (mean 8.3 hours). However, the manufacturer has no specific recommendation for dose adjustment in elderly patients.

**Hepatic impairment:** In a single dose study, the pharmacokinetics of atovaquone/proguanil was compared in 13 subjects with mild-moderate hepatic impairment to 13 subjects with normal hepatic function. In subjects with moderate hepatic impairment, the elimination half-life and AUC of atovaquone/proguanil increased in subjects with hepatic impairment compared to healthy volunteers. The manufacturer has no recommendation for dose adjustment in patients with mild-moderate hepatic impairment. No studies have been done in patients with severe hepatic impairment.

**Renal impairment:** In patient with severe renal impairment (creatinine clearance < 30 ml/min), atovaquone AUC and Cmax are reduced but the elimination half-lives for proguanil and cycloguail and prolonged, with correspondent increased in AUC resulting in the potential of drug accumulation with repeated dosing. Atovaquone/proguanil is contraindicated in patients with severe renal impairment for malaria prophylaxis. If atovaquone/proguanil is used for malaria treatment, benefit must outweigh the risk in patients with severe renal impairment.

# Postmarketing Safety Experience1

**Skin:** Cutaneous reactions from rash, photosensitivity, and urticarial to rare cases of erythema multiforme and Stevens-Johnson syndrome.

**Central nervous system:** Rare cases of seizure and psychotic events (e.g. hallucinations); however, a causal relationship has not been established.

**Blood and Lymphatic System Disorders:** Pancytopenia in patients with severe renal impairment.

**Hepatibiliary disorders:** elevated liver function tests and rare cases of hepatitis.

# Sentinel Events

No data.

# Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs.  Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
| Atovaquone/proguanil | None | None | None | Atovaquone, Atovastatin/ezetimibe |
| Malarone | None | None | None | Mepron, Malathion |

# Drug Interactions 1,3-4, 21-22

The metabolism of atovaquone is not well understood. Atovaquone is excreted unchanged in the feces and less than 0.6% of the drug is found in the urine. Proguanil is metabolized to cycloguanil primarily via CYP2C19 and 4-chlorophenylbiguanide with 40-60% of proguanil is excreted by the kidneys.

**Rifampin, rifabutin:** There is a lack of studies on rifabutin, rifampin and atovaquone/proguanil co-administration for malaria prophylaxis and treatment. However, studies that used atovaquone in the treatment of *Toxoplasma gondii* showed that atovaquone area under the cure (AUC) decreased remarkably (50%) when combined with rifampin and by 34% with rifabutin. Overall, the manufacturer does not recommend concomitant administration of atovaquone/proguanil with rifampin or rifabutin.

**Metoclopramide:** According to atovaquone/proguanil prescribing information, concurrent use of atovaquone with metoclopramide has been associated with reduced atovaquone bioavailability. As a result, atovaquone should only be used with metoclopramide if no other antiemetics are available. The specific mechanism for this interaction is uncertain, but increased intestinal motility due to the actions of metoclopramide leading to decreased atovaquone absorption is likely to be at least partially responsible.

**Folate supplement:** While proguanil acts by inhibiting the parasitic dihydrofolate reduction, there is no clinical data indicated that folate supplementation diminishes drug efficacy. The manufacturer recommended women of childbearing age receiving folate supplements to prevent neural tube defects should continue the supplement while taking atovaquone/proguanil.

**Warfarin:** Atovaquone/proguanil may potentiate the anticoagulant effect of warfarin. The mechanism of this potential drug interaction has not been established. The manufacturer recommended that when atovaquone/proguanil is administered with warfarin concomitantly, suitable coagulation tests should be closely monitored.

**Antiretroviral therapy:** Concomitant of atovaquone/proguanil with lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r) did result in a decrease of AUC by 74% and 46%, respectively for LPV/r and ATV/r. When atovaquone/progunail is administered with efavirenz, the AUC decreases approximately by 70% for atovaquone and 50% for proguanil. The Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretrovial Agents in HIV-1 Infected Adults and Adolescents recommended considering alternative drug for malaria prophylaxis if possible when antiretrovirals (i.e LPV/r, ATV/r, efavirenz) are administered concomitantly with atovaquone/proguanil. For more information on interaction between atovaquone/proguanil and antiretrovials, please refer to reference #21.

# Acquisition Costs

Please refer to the last page for VA drug acquisition costs.  Prices shown in this internal, draft document may include additional discounts available to VA.  This information is considered strictly confidential and must not be shared outside of VA.  All cost information will be removed from the document when posted to the PBM website.

# Pharmacoeconomic Analysis

No published pharmacoeconomic evaluations are available.

# Conclusions

Overall, fixed-dose combination atovaquone/proguanil was shown to be efficacious for both prevention and treatment of uncomplicated *P*. *falciparum* malaria, including areas with chloroquine-resistance. CDC guidelines provide recommendations for the role of atovaquone/proguanil for prophylaxis and treatment of malaria. Prevention of malaria involves a balance between taking antimalarial drug as prescribed and using the appropriate prevention measures. As for treatment of malaria, clinicians should take in consideration of local information on prevalence of resistance to antimalarial drugs by referring to the CDC treatment guidelines. Dietary fat can increase absorption of atovaquone/proguanil, therefore; it is important to take the medication with food or milk. The most commonly reported adverse events associated with atovaquone/proguanil were headache, abdominal pain, nausea, vomiting, and diarrhea. Overall, atovaquone/proguanil should be avoided in travelers with history of severe renal impairment, and pregnant or breastfeeding women.

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