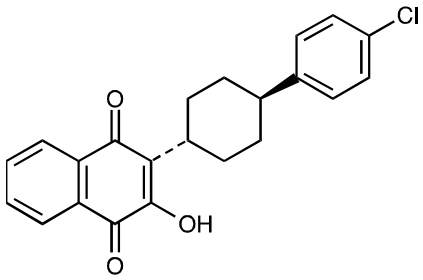
PRESCRIBING INFORMATION

MEPRON®
(atovaquone)
Suspension

DESCRIPTION

MEPRON (atovaquone) is an antiprotozoal agent. The chemical name of atovaquone is *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione. Atovaquone is a yellow crystalline solid that is practically insoluble in water. It has a molecular weight of 366.84 and the molecular formula $C_{22}H_{19}ClO_3$. The compound has the following structural formula:



MEPRON Suspension is a formulation of micro-fine particles of atovaquone. The atovaquone particles, reduced in size to facilitate absorption, are significantly smaller than those in the previously marketed tablet formulation. MEPRON Suspension is for oral administration and is bright yellow with a citrus flavor. Each teaspoonful (5 mL) contains 750 mg of atovaquone and the inactive ingredients benzyl alcohol, flavor, poloxamer 188, purified water, saccharin sodium, and xanthan gum.

MICROBIOLOGY

Mechanism of Action: Atovaquone is a hydroxy-1,4-naphthoquinone, an analog of ubiquinone, with antipneumocystis activity. The mechanism of action against *Pneumocystis carinii* has not been fully elucidated. In *Plasmodium* species, the site of action appears to be the cytochrome bc_1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain via ubiquinone. Inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis.

Activity In Vitro: Several laboratories, using different in vitro methodologies, have shown the IC_{50} (50% inhibitory concentration) of atovaquone against rat *P. carinii* to be in the range of 0.1 to 3.0 mcg/mL.

Drug Resistance: Phenotypic resistance to atovaquone in vitro has not been demonstrated for *P. carinii*. However, in 2 patients who developed *P. carinii* pneumonia (PCP) after prophylaxis with atovaquone, DNA sequence analysis identified mutations in the predicted amino acid sequence of *P. carinii* cytochrome b (a likely target site for atovaquone). The clinical significance of this is unknown.

CLINICAL PHARMACOLOGY

Pharmacokinetics: *Absorption:* Atovaquone is a highly lipophilic compound with low aqueous solubility. The bioavailability of atovaquone is highly dependent on formulation and diet. The suspension formulation provides an approximately 2-fold increase in atovaquone bioavailability in the fasting or fed state compared to the previously marketed tablet formulation. The absolute bioavailability of a 750-mg dose of MEPRON Suspension administered under fed conditions in

9 HIV-infected (CD4 >100 cells/mm^3) volunteers was 47% ± 15%. In the same study, the bioavailability of a 750-mg dose of the previously marketed tablet formulation was 23% ± 11%.

Administering atovaquone with food enhances its absorption by approximately 2 fold. In one study, 16 healthy volunteers received a single dose of 750 mg MEPRON Suspension after an overnight fast and following a standard breakfast (23 g fat: 610 kCal). The mean (±SD) area under the concentration-time curve (AUC) values were 324 ± 115 and 801 ± 320 hr●mcg/mL under fasting and fed conditions, respectively, representing a 2.6 ± 1.0-fold increase. The effect of food (23 g fat: 400 kCal) on plasma atovaquone concentrations was also evaluated in a multiple-dose, randomized, crossover study in 19 HIV-infected volunteers (CD4 <200 cells/mm^3) receiving daily doses of 500 mg MEPRON Suspension. AUC was 280 ± 114 hr●mcg/mL when atovaquone was administered with food as compared to 169 ± 77 hr●mcg/mL under fasting conditions. Maximum plasma atovaquone concentration (C_{max}) was 15.1 ± 6.1 and 8.8 ± 3.7 mcg/mL when atovaquone was administered with food and under fasting conditions, respectively.

Dose Proportionality: Plasma atovaquone concentrations do not increase proportionally with dose. When MEPRON Suspension was administered with food at dosage regimens of 500 mg once daily, 750 mg once daily, and 1,000 mg once daily, average steady-state plasma atovaquone concentrations were 11.7 ± 4.8, 12.5 ± 5.8, and 13.5 ± 5.1 mcg/mL, respectively. The corresponding C_{max} concentrations were 15.1 ± 6.1, 15.3 ± 7.6, and 16.8 ± 6.4 mcg/mL. When MEPRON Suspension was administered to 5 HIV-infected volunteers at a dose of 750 mg twice daily, the average steady-state plasma atovaquone concentration was 21.0 ± 4.9 mcg/mL and C_{max} was 24.0 ± 5.7 mcg/mL. The minimum plasma atovaquone concentration (C_{min}) associated with the 750-mg twice-daily regimen was 16.7 ± 4.6 mcg/mL.

Distribution: Following the intravenous administration of atovaquone, the volume of distribution at steady state (Vd_{ss}) was 0.60 ± 0.17 L/kg (n = 9). Atovaquone is extensively bound to plasma proteins (99.9%) over the concentration range of 1 to 90 mcg/mL. In 3 HIV-infected children who received 750 mg atovaquone as the tablet formulation 4 times daily for 2 weeks, the cerebrospinal fluid concentrations of atovaquone were 0.04, 0.14, and 0.26 mcg/mL, representing less than 1% of the plasma concentration.

Elimination: The plasma clearance of atovaquone following intravenous (IV) administration in 9 HIV-infected volunteers was 10.4 ± 5.5 mL/min (0.15 ± 0.09 mL/min/kg). The half-life of atovaquone was 62.5 ± 35.3 hours after IV administration and ranged from 67.0 ± 33.4 to 77.6 ± 23.1 hours across studies following administration of MEPRON Suspension. The half-life of atovaquone is long due to presumed enterohepatic cycling and eventual fecal elimination. In a study where ^{14}C-labelled atovaquone was administered to healthy volunteers, greater than 94% of the dose was recovered as unchanged atovaquone in the feces over 21 days. There was little or no excretion of atovaquone in the urine (less than 0.6%). There is indirect evidence that atovaquone may undergo limited metabolism; however, a specific metabolite has not been identified.

Special Populations: ***Pediatrics:*** In a study of MEPRON Suspension in 27 HIV-infected, asymptomatic infants and children between 1 month and 13 years of age, the pharmacokinetics of atovaquone were age dependent. These patients were dosed once daily with food for 12 days. The average steady-state plasma atovaquone concentrations in the 24 patients with available concentration data are shown in Table 1.

Table 1. Average Steady-State Plasma Atovaquone Concentrations in Pediatric Patients

	Dose of MEPRON Suspension		
	10 mg/kg	30 mg/kg	45 mg/kg
Age	Average C_{ss} in mcg/mL (mean ± SD)		
1-3 months	5.9 (n = 1)	27.8 ± 5.8 (n = 4)	_____
>3-24 months	5.7 ± 5.1 (n = 4)	9.8 ± 3.2 (n = 4)	15.4 ± 6.6 (n = 4)
>2-13 years	16.8 ± 6.4 (n = 4)	37.1 ± 10.9 (n = 3)	_____

Hepatic/Renal Impairment: The pharmacokinetics of atovaquone have not been studied in patients with hepatic or renal impairment.

Drug Interactions: ***Rifampin:*** In a study with 13 HIV-infected volunteers, the oral administration of rifampin 600 mg every 24 hours with MEPRON Suspension 750 mg every 12 hours resulted in a 52% ± 13% decrease in the average steady-state plasma atovaquone concentration and a 37% ± 42% increase in the average steady-state plasma rifampin concentration. The half-life of atovaquone decreased from 82 ± 36 hours when administered without rifampin to 50 ± 16 hours with rifampin.

Rifabutin, another rifamycin, is structurally similar to rifampin and may possibly have some of the same drug interactions as rifampin. No interaction trials have been conducted with MEPRON and rifabutin.

Trimethoprim/Sulfamethoxazole (TMP-SMX): The possible interaction between atovaquone and TMP-SMX was evaluated in 6 HIV-infected adult volunteers as part of a larger multiple-dose, dose-escalation, and chronic dosing study of MEPRON Suspension. In this crossover study, MEPRON Suspension 500 mg once daily, or TMP-SMX tablets (160 mg trimethoprim and 800 mg sulfamethoxazole) twice daily, or the combination were administered with food to achieve steady state. No difference was observed in the average steady-state plasma atovaquone concentration after coadministration with TMP-SMX. Coadministration of MEPRON with TMP-SMX resulted in a 17% and 8% decrease in average steady-state concentrations of trimethoprim and sulfamethoxazole in plasma, respectively. This effect is minor and would not be expected to produce clinically significant events.

Zidovudine: Data from 14 HIV-infected volunteers who were given atovaquone tablets 750 mg every 12 hours with zidovudine 200 mg every 8 hours showed a 24% ± 12% decrease in zidovudine apparent oral clearance, leading to a 35% ± 23% increase in plasma zidovudine AUC. The glucuronide metabolite:parent ratio decreased from a mean of 4.5 when zidovudine was administered alone to 3.1 when zidovudine was administered with atovaquone tablets. This effect is minor and would not be expected to produce clinically significant events. Zidovudine had no effect on atovaquone pharmacokinetics.

Relationship Between Plasma Atovaquone Concentration and Clinical Outcome: In a comparative study of atovaquone tablets with TMP-SMX for oral treatment of mild-to-moderate *Pneumocystis carinii* pneumonia (PCP) (see INDICATIONS AND USAGE), where AIDS patients received 750 mg atovaquone tablets 3 times daily for 21 days, the mean steady-state atovaquone concentration was 13.9 ± 6.9 mcg/mL (n = 133). Analysis of these data established a relationship between plasma atovaquone concentration and successful treatment. This is shown in Table 2.

Table 2. Relationship Between Plasma Atovaquone Concentration and Successful Treatment

Steady-State Plasma Atovaquone Concentrations (mcg/mL)	Successful Treatment* (No. Successes/No. in Group) (%)			
	Observed		Predicted†	
0 to <5	0/6	(0%)	1.5/6	(25%)
5 to <10	18/26	(69%)	14.7/26	(57%)
10 to <15	30/38	(79%)	31.9/38	(84%)
15 to <20	18/19	(95%)	18.1/19	(95%)
20 to <25	18/18	(100%)	17.8/18	(99%)
25+	6/6	(100%)	6/6	(100%)

* Successful treatment was defined as improvement in clinical and respiratory measures persisting at least 4 weeks after cessation of therapy. This was based on data from patients for which both outcome and steady-state plasma atovaquone concentration data are available.

† Based on logistic regression analysis.

A dosing regimen of MEPRON Suspension for the treatment of mild-to-moderate PCP has been selected to achieve average plasma atovaquone concentrations of approximately 20 mcg/mL, because this plasma concentration was previously shown to be well tolerated and associated with the highest treatment success rates (Table 2). In an open-label PCP treatment study with MEPRON Suspension, dosing regimens of 1,000 mg once daily, 750 mg twice daily, 1,500 mg once daily, and 1,000 mg twice daily were explored. The average steady-state plasma atovaquone concentration achieved at the 750-mg twice-daily dose given with meals was 22.0 ± 10.1 mcg/mL (n = 18).

INDICATIONS AND USAGE

MEPRON Suspension is indicated for the prevention of *Pneumocystis carinii* pneumonia in patients who are intolerant to trimethoprim-sulfamethoxazole (TMP-SMX).

MEPRON Suspension is also indicated for the acute oral treatment of mild-to-moderate PCP in patients who are intolerant to TMP-SMX.

Prevention of PCP: The indication for prevention of PCP is based on the results of 2 clinical trials comparing MEPRON Suspension to dapsone or aerosolized pentamidine in HIV-infected adult and adolescent patients at risk of PCP (CD4 count <200 cells/mm^3 or a prior episode of PCP) and intolerant to TMP-SMX.

Dapsone Comparative Study: This randomized, open-label trial enrolled a total of 1,057 patients at 48 study centers. Patients were randomized to receive 1,500 mg MEPRON Suspension once daily (n = 536) or 100 mg dapsone once daily (n = 521). Median follow-up was 24 months. Patients randomized to the dapsone arm who were seropositive for *Toxoplasma gondii* and had a CD4 count <100 cells/mm^3 also received pyrimethamine and folinic acid. PCP event rates are shown in Table 3. There was no significant difference in mortality rates between the groups.

Aerosolized Pentamidine Comparative Study: This randomized, open-label trial enrolled a total of 549 patients at 35 study centers. Patients were randomized to receive 1,500 mg MEPRON Suspension once daily (n = 175), 750 mg MEPRON Suspension once daily (n = 188), or 300 mg aerosolized pentamidine once monthly (n = 186). Median follow-up was 11.3 months. The results of the PCP event rates appear in Table 3. There were no significant differences in mortality rates among the groups.

Table 3. Confirmed or Presumed/Probable PCP Events (As-Treated Analysis)[*]

	Study 115-211		Study 115-213		
Assessment	Atovaquone 1,500 mg/day (n = 527)	Dapsone 100 mg/day (n = 510)	Atovaquone 750 mg/day (n = 188)	Atovaquone 1,500 mg/day (n = 172)	Aerosolized Pentamidine 300 mg/month (n = 169)
%	15%	19%	23%	18%	17%
Relative Risk[†] (CI)[‡]	0.77 (0.57, 1.04)		1.47 (0.86, 2.50)	1.14 (0.63, 2.06)	

[*] Those events occurring during or within 30 days of stopping assigned treatment.

[†] Relative risk <1 favors atovaquone and values >1 favor comparator. These trials were designed to show superiority of atovaquone to the comparator. This was not shown.

[‡] The confidence level of the interval for the dapsone comparative study was 95% and for the pentamidine comparative study was 97.5%.

An analysis of all PCP events (intent-to-treat analysis) showed results similar to those above.

Treatment of PCP: The indication for treatment of mild-to-moderate PCP is based on the results of comparative pharmacokinetic studies of the suspension and tablet formulations (see CLINICAL PHARMACOLOGY) and clinical efficacy studies of the tablet formulation which established a relationship between plasma atovaquone concentration and successful treatment. The results of a randomized, double-blind trial comparing MEPRON to TMP-SMX in AIDS patients with mild-to-moderate PCP (defined in the study protocol as an alveolar-arterial oxygen diffusion gradient $[(A\text{-}a)DO_2]$[1] ≤45 mm Hg and PaO_2 ≥60 mm Hg on room air) and a randomized trial comparing MEPRON to IV pentamidine isethionate in patients with mild-to-moderate PCP intolerant to trimethoprim or sulfa-antimicrobials are summarized below:

TMP-SMX Comparative Study: This double-blind, randomized trial initiated in 1990 was designed to compare the safety and efficacy of MEPRON to that of TMP-SMX for the treatment of AIDS patients with histologically confirmed PCP. Only patients with mild-to-moderate PCP were eligible for enrollment.

A total of 408 patients were enrolled into the trial at 37 study centers. Eighty-six patients without histologic confirmation of PCP were excluded from the efficacy analyses. Of the 322 patients with histologically confirmed PCP, 160 were randomized to receive MEPRON and 162 to TMP-SMX.

Study participants randomized to treatment with MEPRON were to receive 750 mg MEPRON (three 250-mg tablets) 3 times daily for 21 days and those randomized to TMP-SMX were to receive 320 mg TMP plus 1,600 mg SMX 3 times daily for 21 days.

Therapy success was defined as improvement in clinical and respiratory measures persisting at least 4 weeks after cessation of therapy. Therapy failures included lack of response, treatment discontinuation due to an adverse experience, and unevaluable.

There was a significant difference ($P = 0.03$) in mortality rates between the treatment groups. Among the 322 patients with confirmed PCP, 13 of 160 (8%) patients treated with MEPRON and 4 of 162 (2.5%) patients receiving TMP-SMX died during the 21-day treatment course or 8-week follow-up period. In the intent-to-treat analysis for all 408 randomized patients, there were 16 (8%) deaths in the arm treated with MEPRON and 7 (3.4%) deaths in the TMP-SMX arm ($P = 0.051$). Of the 13 patients treated with MEPRON who died, 4 died of PCP and 5 died with a combination of bacterial infections and PCP; bacterial infections did not appear to be a factor in any of the 4 deaths among TMP-SMX-treated patients.

A correlation between plasma atovaquone concentrations and death was demonstrated; in general, patients with lower plasma concentrations were more likely to die. For those patients for

whom day 4 plasma atovaquone concentration data are available, 5 (63%) of the 8 patients with concentrations <5 mcg/mL died during participation in the study. However, only 1 (2.0%) of the 49 patients with day 4 plasma atovaquone concentrations ≥5 mcg/mL died.

Sixty-two percent of patients on MEPRON and 64% of patients on TMP-SMX were classified as protocol-defined therapy successes (Table 4).

Table 4. Outcome of Treatment for PCP-Positive Patients Enrolled in the TMP-SMX Comparative Study

Outcome of Therapy*	Number of Patients (% of Total)				*P* Value
	MEPRON (n = 160)		TMP-SMX (n = 162)		
Therapy success	99	(62%)	103	(64%)	0.75
Therapy failure					
-Lack of response	28	(17%)	10	(6%)	<0.01
-Adverse experience	11	(7%)	33	(20%)	<0.01
-Unevaluable	22	(14%)	16	(10%)	0.28
Required alternate PCP therapy during study	55	(34%)	55	(34%)	0.95

* As defined by the protocol and described in study description above.

The failure rate due to lack of response was significantly larger for patients receiving MEPRON while the failure rate due to adverse experiences was significantly larger for patients receiving TMP-SMX.

There were no significant differences in the effect of either treatment on additional indicators of response (i.e., arterial blood gas measurements, vital signs, serum LDH levels, clinical symptoms, and chest radiographs).

Pentamidine Comparative Study: This unblinded, randomized trial initiated in 1991 was designed to compare the safety and efficacy of MEPRON to that of pentamidine for the treatment of histologically confirmed mild or moderate PCP in AIDS patients. Approximately 80% of the patients either had a history of intolerance to trimethoprim or sulfa-antimicrobials (the primary therapy group) or were experiencing intolerance to TMP-SMX with treatment of an episode of PCP at the time of enrollment in the study (the salvage treatment group).

Patients randomized to MEPRON were to receive 750 mg atovaquone (three 250-mg tablets) 3 times daily for 21 days and those randomized to pentamidine isethionate were to receive a 3- to 4-mg/kg single IV infusion daily for 21 days.

A total of 174 patients were enrolled into the trial at 22 study centers. Thirty-nine patients without histologic confirmation of PCP were excluded from the efficacy analyses. Of the 135 patients with histologically confirmed PCP, 70 were randomized to receive MEPRON and 65 to pentamidine. One hundred and ten (110) of these were in the primary therapy group and 25 were in the salvage therapy group. One patient in the primary therapy group randomized to receive pentamidine did not receive study medication.

There was no difference in mortality rates between the treatment groups. Among the 135 patients with confirmed PCP, 10 of 70 (14%) patients randomized to MEPRON and 9 of 65 (14%) patients randomized to pentamidine died during the 21-day treatment course or 8-week follow-up period. In the intent-to-treat analysis for all randomized patients, there were 11 (12.5%) deaths in the arm treated with MEPRON and 12 (14%) deaths in the pentamidine arm. For those patients for whom day 4 plasma atovaquone concentrations are available, 3 of 5 (60%) patients with concentrations

<5 mcg/mL died during participation in the study. However, only 2 of 21 (9%) patients with day 4 plasma concentrations ≥5 mcg/mL died.

The therapeutic outcomes for the 134 patients who received study medication in this trial are presented in Table 5.

Table 5. Outcome of Treatment for PCP-Positive Patients Enrolled in the Pentamidine Comparative Study

	Primary Treatment					Salvage Treatment				
Outcome of Therapy	MEPRON (n = 56)		Pentamidine (n = 53)		*P* Value	MEPRON (n = 14)		Pentamidine (n = 11)		*P* Value
Therapy success	32	(57%)	21	(40%)	0.09	13	(93%)	7	(64%)	0.14
Therapy failure										
-Lack of response	16	(29%)	9	(17%)	0.18	0		0		—
-Adverse experience	2	(3.6%)	19	(36%)	<0.01	0		3	(27%)	0.07
-Unevaluable	6	(11%)	4	(8%)	0.75	1	(7%)	1	(9%)	1.00
Required alternate PCP therapy during study	19	(34%)	29	(55%)	0.04	0		4	(36%)	0.03

CONTRAINDICATIONS

MEPRON Suspension is contraindicated for patients who develop or have a history of potentially life-threatening allergic reactions to any of the components of the formulation.

WARNINGS

Clinical experience with MEPRON for the treatment of PCP has been limited to patients with mild-to-moderate PCP [$(A\text{-}a)DO_2 \leq 45$ mm Hg]. Treatment of more severe episodes of PCP has not been systematically studied with this agent. Also, the efficacy of MEPRON in patients who are failing therapy with TMP-SMX has not been systematically studied.

PRECAUTIONS

General: Absorption of orally administered MEPRON is limited but can be significantly increased when the drug is taken with food. Plasma atovaquone concentrations have been shown to correlate with the likelihood of successful treatment and survival. Therefore, parenteral therapy with other agents should be considered for patients who have difficulty taking MEPRON with food (see CLINICAL PHARMACOLOGY). Gastrointestinal disorders may limit absorption of orally administered drugs. Patients with these disorders also may not achieve plasma concentrations of atovaquone associated with response to therapy in controlled trials.

Based upon the spectrum of in vitro antimicrobial activity, atovaquone is not effective therapy for concurrent pulmonary conditions such as bacterial, viral, or fungal pneumonia or mycobacterial diseases. Clinical deterioration in patients may be due to infections with other pathogens, as well as progressive PCP. All patients with acute PCP should be carefully evaluated for other possible causes of pulmonary disease and treated with additional agents as appropriate.

Rare cases of hepatitis, elevated liver function tests and one case of fatal liver failure have been reported in patients treated with atovaquone. A causal relationship between atovaquone use and these events could not be established because of numerous confounding medical conditions and concomitant drug therapies. (See ADVERSE REACTIONS.)

If it is necessary to treat patients with severe hepatic impairment, caution is advised and administration should be closely monitored.

Information for Patients: The importance of taking the prescribed dose of MEPRON should be stressed. Patients should be instructed to take their daily doses of MEPRON with meals, as the presence of food will significantly improve the absorption of the drug.

Drug Interactions: Atovaquone is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering MEPRON concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur. The extent of plasma protein binding of atovaquone in human plasma is not affected by the presence of therapeutic concentrations of phenytoin (15 mcg/mL), nor is the binding of phenytoin affected by the presence of atovaquone.

Rifampin: Coadministration of rifampin and MEPRON Suspension results in a significant decrease in average steady-state plasma atovaquone concentrations (see CLINICAL PHARMACOLOGY: Drug Interactions). Alternatives to rifampin should be considered during the course of PCP treatment with MEPRON.

Rifabutin, another rifamycin, is structurally similar to rifampin and may possibly have some of the same drug interactions as rifampin. No interaction trials have been conducted with MEPRON and rifabutin.

Drug/Laboratory Test Interactions: It is not known if MEPRON interferes with clinical laboratory test or assay results.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies in rats were negative; 24-month studies in mice showed treatment-related increases in incidence of hepatocellular adenoma and hepatocellular carcinoma at all doses tested which ranged from 1.4 to 3.6 times the average steady-state plasma concentrations in humans during acute treatment of *Pneumocystis carinii* pneumonia. Atovaquone was negative with or without metabolic activation in the Ames *Salmonella* mutagenicity assay, the Mouse Lymphoma mutagenesis assay, and the Cultured Human Lymphocyte cytogenetic assay. No evidence of genotoxicity was observed in the in vivo Mouse Micronucleus assay.

Pregnancy: Pregnancy Category C. Atovaquone was not teratogenic and did not cause reproductive toxicity in rats at plasma concentrations up to 2 to 3 times the estimated human exposure. Atovaquone caused maternal toxicity in rabbits at plasma concentrations that were approximately one half the estimated human exposure. Mean fetal body lengths and weights were decreased and there were higher numbers of early resorption and post-implantation loss per dam. It is not clear whether these effects were caused by atovaquone directly or were secondary to maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of the concurrent maternal plasma concentrations. In a separate study in rats given a single ^{14}C-radiolabelled dose, concentrations of radiocarbon in rat fetuses were 18% (middle gestation) and 60% (late gestation) of concurrent maternal plasma concentrations. There are no adequate and well-controlled studies in pregnant women. MEPRON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether atovaquone is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when MEPRON is administered to a nursing woman. In a rat study, atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma.

Pediatric Use: Evidence of safety and effectiveness in pediatric patients has not been established. A relationship between plasma atovaquone concentrations and successful treatment of PCP has been established in adults (see Table 2). In a study of MEPRON Suspension in 27 HIV-infected, asymptomatic infants and children between 1 month and 13 years of age, the pharmacokinetics of atovaquone were age-dependent (see CLINICAL PHARMACOLOGY: Special Populations). No drug-related treatment-limiting adverse events were observed in the pharmacokinetic study.

Geriatric Use: Clinical studies of MEPRON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Because many patients who participated in clinical trials with MEPRON had complications of advanced HIV disease, it was often difficult to distinguish adverse events caused by MEPRON from those caused by underlying medical conditions. There were no life-threatening or fatal adverse experiences caused by MEPRON.

PCP Prevention Studies: In the dapsone comparative study of MEPRON Suspension, adverse experience data were collected only for treatment-limiting events. Among the entire population (n = 1,057), treatment-limiting events occurred at similar frequencies in patients treated with MEPRON Suspension or dapsone (Table 6). Among patients who were taking neither dapsone nor atovaquone at enrollment (n = 487), treatment-limiting events occurred in 43% of patients treated with dapsone and 20% of patients treated with MEPRON Suspension (P <0.001). In both populations, the type of treatment-limiting events differed between the 2 treatment arms. Hypersensitivity reactions (rash, fever, allergic reaction) and anemia were more common in patients treated with dapsone, while gastrointestinal events (nausea, diarrhea, and vomiting) were more common in patients treated with MEPRON Suspension.

Table 6. Treatment-Limiting Adverse Experiences in the Dapsone Comparative PCP Prevention Study

	Percentage of Patients with Treatment-Limiting Adverse Experience			
	All Patients		Patients Not Taking Either Drug at Enrollment	
Treatment-Limiting Adverse Experience	MEPRON 1,500 mg/day (n = 536)	Dapsone 100 mg/day (n = 521)	MEPRON 1,500 mg/day (n = 238)	Dapsone 100 mg/day (n = 249)
Any event	24.4%	25.9%	20.2%	43.4%
Rash	6.3%	8.8%	7.6%	16.1%
Nausea	4.1%	0.6%	2.5%	0.8%
Diarrhea	3.2%	0.2%	2.1%	0.4%
Vomiting	2.2%	0.6%	1.3%	0.8%
Allergic reaction	1.1%	2.9%	0.8%	4.8%
Fever	0.6%	2.9%	0%	5.6%
Anemia	0%	1.5%	0%	2.0%

Table 7 summarizes the clinical adverse experiences reported by ≥20% of patients in any group in the aerosolized pentamidine comparative study of MEPRON Suspension (n = 549), regardless of attribution. The incidence of adverse experiences at the recommended dose was similar to that seen with aerosolized pentamidine. Rash was the only individual adverse experience that occurred significantly more commonly in patients treated with both dosages of MEPRON Suspension (39% to 46%) than in patients treated with aerosolized pentamidine (28%). Among patients treated with MEPRON Suspension, there was no evidence of a dose-related increase in the incidence of adverse experiences. Treatment-limiting adverse experiences occurred less often in patients treated with aerosolized pentamidine (7%) than in patients treated with 1,500 mg MEPRON Suspension once daily

(25%, $P \leq 0.001$) or 750 mg MEPRON Suspension once daily (16%, $P = 0.004$). The most common adverse experiences requiring discontinuation of dosing in the group receiving 1,500 mg MEPRON Suspension once daily were rash (6%), diarrhea (4%), and nausea (3%). The most common adverse experience requiring discontinuation of dosing in the group receiving aerosolized pentamidine was bronchospasm (2%).

Table 7. Treatment-Emergent Adverse Experiences in the Aerosolized Pentamidine Comparative PCP Prevention Study

Treatment-Emergent Adverse Experience	Percentage of Patients with Treatment-Emergent Adverse Experience		
	MEPRON 1,500 mg/day (n = 175)	MEPRON 750 mg/day (n = 188)	Aerosolized Pentamidine (n = 186)
Diarrhea	42%	42%	35%
Rash	39%	46%	28%
Headache	28%	31%	22%
Nausea	26%	32%	23%
Cough increased	25%	25%	31%
Fever	25%	31%	18%
Rhinitis	24%	18%	17%
Asthenia	22%	31%	31%
Infection	22%	18%	19%
Abdominal pain	20%	21%	20%
Dyspnea	15%	21%	16%
Vomiting	15%	22%	11%
Patients discontinuing therapy due to an adverse experience	25%	16%	7%
Patients reporting at least 1 adverse experience	98%	96%	89%

Other events occurring in ≥10% of the patients receiving the recommended dose of MEPRON included sweating, flu syndrome, pain, sinusitis, pruritus, insomnia, depression, and myalgia. Bronchospasm occurred more frequently in patients receiving aerosolized pentamidine (11%) than in patients receiving MEPRON 1,500 mg/day (4%) and MEPRON 750 mg/day (2%).

Neither MEPRON nor aerosolized pentamidine was associated with a substantial change from baseline values in any measured laboratory parameter, nor were there any significant differences in any measured laboratory parameter between MEPRON and aerosolized pentamidine. Some patients had laboratory abnormalities considered serious by the investigator or that contributed to discontinuation of therapy.

PCP Treatment Studies: Table 8 summarizes all the clinical adverse experiences reported by ≥5% of the study population during the TMP-SMX comparative study of MEPRON (n = 408), regardless of attribution. The incidence of adverse experiences with MEPRON Suspension at the recommended dose was similar to that seen with the tablet formulation of atovaquone.

Table 8. Treatment-Emergent Adverse Experiences in the TMP-SMX Comparative PCP Treatment Study

Treatment-Emergent Adverse Experience	Percentage of Patients with Treatment-Emergent Adverse Experience	
	MEPRON (n = 203)	TMP-SMX (n = 205)
Rash (including maculopapular)	23%	34%
Nausea	21%	44%
Diarrhea	19%	7%
Headache	16%	22%
Vomiting	14%	35%
Fever	14%	25%
Insomnia	10%	9%
Asthenia	8%	8%
Pruritus	5%	9%
Monilia, oral	5%	10%
Abdominal pain	4%	7%
Constipation	3%	17%
Dizziness	3%	8%
Patients discontinuing therapy due to an adverse experience	9%	24%
Patients reporting at least 1 adverse experience	63%	65%

Although an equal percentage of patients receiving MEPRON and TMP-SMX reported at least 1 adverse experience, more patients receiving TMP-SMX required discontinuation of therapy due to an adverse event. Twenty-four percent of patients receiving TMP-SMX were prematurely discontinued from therapy due to an adverse experience versus 9% of patients receiving MEPRON. Four percent of patients receiving MEPRON had therapy discontinued due to development of rash. The majority of cases of rash among patients receiving MEPRON were mild and did not require the discontinuation of dosing. The only other clinical adverse experience that led to premature discontinuation of dosing of MEPRON by more than 1 patient was vomiting (<1%). The most common adverse experience requiring discontinuation of dosing in the TMP-SMX group was rash (8%).

Laboratory test abnormalities reported for ≥5% of the study population during the treatment period are summarized in Table 9. Two percent of patients treated with MEPRON and 7% of patients treated with TMP-SMX had therapy prematurely discontinued due to elevations in ALT/AST. In general, patients treated with MEPRON developed fewer abnormalities in measures of hepatocellular function (ALT, AST, alkaline phosphatase) or amylase values than patients treated with TMP-SMX.

Table 9. Treatment-Emergent Laboratory Test Abnormalities in the TMP-SMX Comparative PCP Treatment Study

Laboratory Test Abnormality	Percentage of Patients Developing a Laboratory Test Abnormality	
	MEPRON	TMP-SMX
Anemia (Hgb<8.0 g/dL)	6%	7%
Neutropenia (ANC<750 cells/mm^3)	3%	9%
Elevated ALT (>5 x ULN)	6%	16%
Elevated AST (>5 x ULN)	4%	14%
Elevated alkaline phosphatase (>2.5 x ULN)	8%	6%
Elevated amylase (>1.5 x ULN)	7%	12%
Hyponatremia (<0.96 x LLN)	7%	26%

ULN = upper limit of normal range. LLN = lower limit of normal range.

Table 10 summarizes the clinical adverse experiences reported by ≥5% of the primary therapy study population (n = 144) during the comparative trial of MEPRON and intravenous pentamidine, regardless of attribution. A slightly lower percentage of patients who received MEPRON reported occurrence of adverse events than did those who received pentamidine (63% vs 72%). However, only 7% of patients discontinued treatment with MEPRON due to adverse events, while 41% of patients who received pentamidine discontinued treatment for this reason (P<0.001). Of the 5 patients who discontinued therapy with MEPRON, 3 reported rash (4%). Rash was not severe in any patient. No other reason for discontinuation of MEPRON was cited more than once. The most frequently cited reasons for discontinuation of pentamidine therapy were hypoglycemia (11%) and vomiting (9%).

Table 10. Treatment-Emergent Adverse Experiences in the Pentamidine Comparative PCP Treatment Study (Primary Therapy Group)

Treatment-Emergent Adverse Experience	Percentage of Patients with Treatment-Emergent Adverse Experience	
	MEPRON (n = 73)	Pentamidine (n = 71)
Fever	40%	25%
Nausea	22%	37%
Rash	22%	13%
Diarrhea	21%	31%
Insomnia	19%	14%
Headache	18%	28%
Vomiting	14%	17%
Cough	14%	1%
Abdominal pain	10%	11%
Pain	10%	10%
Sweat	10%	3%
Monilia, oral	10%	3%
Asthenia	8%	14%
Dizziness	8%	14%
Anxiety	7%	10%
Anorexia	7%	10%
Sinusitis	7%	6%
Dyspepsia	5%	10%
Rhinitis	5%	7%
Taste perversion	3%	13%
Hypoglycemia	1%	15%
Hypotension	1%	10%
Patients discontinuing therapy due to an adverse experience	7%	41%
Patients reporting at least 1 adverse experience	63%	72%

Laboratory test abnormalities reported in ≥5% of patients in the pentamidine comparative study are presented in Table 11. Laboratory abnormality was reported as the reason for discontinuation of treatment in 2 of 73 patients who received MEPRON. One patient (1%) had elevated creatinine and BUN levels and 1 patient (1%) had elevated amylase levels. Laboratory abnormalities were the sole or contributing factor in 14 patients who prematurely discontinued pentamidine therapy. In the 71 patients who received pentamidine, laboratory parameters most frequently reported as reasons for discontinuation were hypoglycemia (11%), elevated creatinine levels (6%), and leukopenia (4%).

Table 11. Treatment-Emergent Laboratory Test Abnormalities in the Pentamidine Comparative PCP Treatment Study

Laboratory Test Abnormality	Percentage of Patients Developing a Laboratory Test Abnormality	
	MEPRON	Pentamidine
Anemia (Hgb<8.0 g/dL)	4%	9%
Neutropenia (ANC<750 cells/mm^3)	5%	9%
Hyponatremia (<0.96 x LLN)	10%	10%
Hyperkalemia (>1.18 x ULN)	0%	5%
Alkaline phosphatase (>2.5 x ULN)	5%	2%
Hyperglycemia (>1.8 x ULN)	9%	13%
Elevated AST (>5 x ULN)	0%	5%
Elevated amylase (>1.5 x ULN)	8%	4%
Elevated creatinine (>1.5 x ULN)	0%	7%

ULN = upper limit of normal range.

LLN = lower limit of normal range.

Postmarketing Experience: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of MEPRON. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to MEPRON.

Blood and Lymphatic System Disorders: Methemoglobinemia, thrombocytopenia.

Immune System Disorders: Hypersensitivity reactions including angioedema, bronchospasm, throat tightness, and urticaria.

Eye Disorders: Vortex keratopathy.

Gastrointestinal Disorders: Pancreatitis.

Hepatobiliary Disorders: Rare cases of hepatitis and one case of fatal liver failure have been reported with atovaquone usage.

Skin and Subcutaneous Tissue Disorders: Erythema multiforme, Stevens-Johnson syndrome, and skin desquamation have been reported in patients receiving multiple drug therapy including atovaquone.

Renal and Urinary Disorders: Acute renal impairment.

OVERDOSAGE

There is no known antidote for atovaquone, and it is currently unknown if atovaquone is dialyzable. The median lethal dose is higher than the maximum oral dose tested in mice and rats (1,825 mg/kg/day). Overdoses up to 31,500 mg of atovaquone have been reported. In 1 such patient who also took an unspecified dose of dapsone, methemoglobinemia occurred. Rash has also been reported after overdose.

DOSAGE AND ADMINISTRATION

Dosage: Prevention of PCP: Adults and Adolescents (13 to 16 Years): The recommended oral dose is 1,500 mg (10 mL) once daily administered with a meal.

Treatment of Mild-to-Moderate PCP: Adults and Adolescents (13 to 16 Years): The recommended oral dose is 750 mg (5 mL) administered with meals twice daily for 21 days (total daily dose 1,500 mg).

Note: Failure to administer MEPRON Suspension with meals may result in lower plasma atovaquone concentrations and may limit response to therapy (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Administration: Foil Pouch: Open pouch by removing tab at perforation and tear at notch. Take entire contents by mouth. Can be discharged into a dosing spoon or cup or directly into the mouth.

Bottle: SHAKE BOTTLE GENTLY BEFORE USING.

HOW SUPPLIED

MEPRON Suspension (bright yellow, citrus flavored) containing 750 mg atovaquone in each teaspoonful (5 mL).

Bottle of 210 mL with child-resistant cap (NDC 0173-0665-18).

Store at 15° to 25°C (59° to 77°F). DO NOT FREEZE. Dispense in tight container as defined in USP.

5-mL child-resistant foil pouch - unit dose pack of 42 (NDC 0173-0547-00).

Store at 15° to 25°C (59° to 77°F). DO NOT FREEZE.

[1](A-a)DO_2 = [(713 x FiO_2) – ($PaCO_2$/0.8)] – PaO_2 (mm Hg)

GlaxoSmithKline
Research Triangle Park, NC 27709

Month Year MPR:XPI

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/s/

Renata Albrecht
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