

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEPRON suspension safely and effectively. See full prescribing information for MEPRON suspension.

MEPRON (atovaquone) oral suspension

Initial U.S. Approval: 1992

INDICATIONS AND USAGE

MEPRON suspension is a quinone antimicrobial drug indicated for:

- Prevention of *Pneumocystis jiroveci* pneumonia (PCP) in adults and adolescents aged 13 years and older who cannot tolerate trimethoprim-sulfamethoxazole (TMP-SMX). (1.1)
- Treatment of mild-to-moderate PCP in adults and adolescents aged 13 years and older who cannot tolerate TMP-SMX. (1.2)

Limitations of Use (1.3):

- Treatment of severe PCP (alveolar arterial oxygen diffusion gradient [(A-a)DO₂] >45 mm Hg) with MEPRON has not been studied.
- The efficacy of MEPRON in subjects who are failing therapy with TMP-SMX has also not been studied.

DOSAGE AND ADMINISTRATION

- Prevention of PCP: 1,500 mg (10 mL) once daily with food (2.1)
- Treatment of PCP: 750 mg (5 mL) twice daily with food for 21 days (2.2)
- Supplied in Foil Pouches and Bottles:
 - Foil Pouch: For a 5-mL dose, take entire contents by mouth either by dispensing into a spoon or cup or directly into the mouth. For a 10-mL dose, take two pouches. (2.3)
 - Bottle: Shake bottle gently before use. (2.3)

DOSAGE FORMS AND STRENGTHS

Oral suspension: 750 mg per 5 mL. (3)

CONTRAINDICATIONS

Known serious allergic/hypersensitivity reaction (e.g., angioedema, bronchospasm, throat tightness, urticaria) to atovaquone or any of the components of MEPRON. (4)

WARNINGS AND PRECAUTIONS

- Failure to administer MEPRON suspension with food may result in lower plasma atovaquone concentrations and may limit response to therapy. Patients with gastrointestinal disorders may have limited absorption resulting in suboptimal atovaquone concentrations. (5.1)
- Hepatotoxicity: Elevated liver chemistry tests and cases of hepatitis and fatal liver failure have been reported. (5.2)

ADVERSE REACTIONS

- PCP Prevention: The most frequent adverse reactions (≥25% that required discontinuation) were diarrhea, rash, headache, nausea, and fever. (6.1)
- PCP Treatment: The most frequent adverse reactions (≥14% that required discontinuation) were rash (including maculopapular), nausea, diarrhea, headache, vomiting, and fever. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact

GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant administration of rifampin or rifabutin reduces atovaquone concentrations; concomitant use with MEPRON suspension is not recommended. (7.1)
- Concomitant administration of tetracycline reduces atovaquone concentrations; use caution when coadministering. Monitor patients for potential loss of efficacy of MEPRON if coadministration of tetracycline is necessary. (7.2)
- Concomitant administration with metoclopramide reduces atovaquone concentrations; administer concomitantly only if other antiemetics are not available. (7.3)
- Concomitant administration of indinavir reduces indinavir trough concentrations; use caution when coadministering. Monitor patients for potential loss of efficacy of indinavir if coadministration is necessary. (7.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- Prevention of *Pneumocystis jiroveci* Pneumonia
- Treatment of Mild-to-Moderate *Pneumocystis jiroveci* Pneumonia
- Limitations of Use

2 DOSAGE AND ADMINISTRATION

- Dosage for the Prevention of *P. jiroveci* Pneumonia
- Dosage for the Treatment of Mild-to-Moderate *P. jiroveci* Pneumonia
- Important Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Risk of Limited Oral Absorption
- Hepatotoxicity

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

7 DRUG INTERACTIONS

- Rifampin/Rifabutin
- Tetracycline

7.3 Metoclopramide

7.4 Indinavir

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use
- Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacokinetics
- Microbiology

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- Prevention of PCP
- Treatment of PCP

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Prevention of *Pneumocystis jiroveci* Pneumonia

MEPRON[®] suspension is indicated for the prevention of *Pneumocystis jiroveci* pneumonia (PCP) in adults and adolescents (aged 13 years and older) who cannot tolerate trimethoprim-sulfamethoxazole (TMP-SMX).

1.2 Treatment of Mild-to-Moderate *Pneumocystis jiroveci* Pneumonia

MEPRON suspension is indicated for the acute oral treatment of mild-to-moderate PCP in adults and adolescents (aged 13 years and older) who cannot tolerate TMP-SMX.

1.3 Limitations of Use

Clinical experience with MEPRON for the treatment of PCP has been limited to subjects with mild-to-moderate PCP (alveolar-arterial oxygen diffusion gradient [(A-a)DO₂] ≤45 mm Hg). Treatment of more severe episodes of PCP with MEPRON has not been studied. The efficacy of MEPRON in subjects who are failing therapy with TMP-SMX has also not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for the Prevention of *P. jiroveci* Pneumonia

The recommended oral dosage is 1,500 mg (10 mL) once daily administered with food.

2.2 Dosage for the Treatment of Mild-to-Moderate *P. jiroveci* Pneumonia

The recommended oral dosage is 750 mg (5 mL) twice daily (total daily dose = 1,500 mg) administered with food for 21 days.

2.3 Important Administration Instructions

Administer MEPRON oral suspension with food to avoid lower plasma atovaquone concentrations that may limit response to therapy [see *Warnings and Precautions (5.1), Clinical Pharmacology (12.3)*].

MEPRON Foil Pouch

- Open each 5-mL pouch by removing tab at perforation and tear at notch.
- For a 5-mL dose, take entire contents either by placing directly into the mouth or by dispensing into a dosing spoon (5 mL) or cup prior to administration by mouth.
- For a 10-mL dose, take the entire contents of two pouches.

MEPRON Bottle

Shake bottle gently before administering the recommended dosage.

3 DOSAGE FORMS AND STRENGTHS

MEPRON is a bright yellow, citrus-flavored, oral suspension containing 750 mg of atovaquone in 5 mL. MEPRON is supplied in 210-mL bottles or 5-mL foil pouches.

4 CONTRAINDICATIONS

MEPRON suspension is contraindicated in patients who develop or have a history of hypersensitivity reactions (e.g., angioedema, bronchospasm, throat tightness, urticaria) to atovaquone or any of the components of MEPRON.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Limited Oral Absorption

Absorption of orally administered MEPRON suspension is limited but can be significantly increased when the drug is taken with food. Failure to administer MEPRON suspension with food may result in lower plasma atovaquone concentrations and may limit response to therapy. Consider therapy with other agents in patients who have difficulty taking MEPRON suspension with food or in patients who have gastrointestinal disorders that may limit absorption of oral medications [*see Clinical Pharmacology (12.3)*].

5.2 Hepatotoxicity

Cases of cholestatic hepatitis, elevated liver enzymes, and fatal liver failure have been reported in patients treated with atovaquone [*see Adverse Reactions (6.2)*].

If treating patients with severe hepatic impairment, closely monitor patients following administration of MEPRON.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hepatotoxicity [*see Warnings and Precautions (5.2)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Additionally, because many subjects who participated in clinical trials with MEPRON had complications of advanced human immunodeficiency virus (HIV) disease, it was often difficult to distinguish adverse reactions caused by MEPRON from those caused by underlying medical conditions.

PCP Prevention Trials

In two clinical trials, MEPRON suspension was compared with dapsone or aerosolized pentamidine in HIV-1-infected adolescent (13 to 18 years) and adult subjects at risk of PCP (CD4 count <200 cells/mm³ or a prior episode of PCP) and unable to tolerate TMP-SMX.

Dapsone Comparative Trial: In the dapsone comparative trial (n = 1,057), the majority of subjects were white (64%), male (88%), and receiving prophylaxis for PCP at randomization (73%); the mean age was 38 years. Subjects received MEPRON suspension 1,500 mg once daily (n = 536) or dapsone 100 mg once daily (n = 521); median durations of exposure were 6.7 and 6.5 months, respectively. Adverse reaction data were collected only for adverse reactions requiring discontinuation of treatment, which occurred at similar frequencies in subjects treated with MEPRON suspension or dapsone (Table 1). Among subjects taking neither dapsone nor atovaquone at enrollment (n = 487), adverse reactions requiring discontinuation of treatment occurred in 43% of subjects treated with dapsone and 20% of subjects treated with MEPRON suspension. Gastrointestinal adverse reactions (nausea, diarrhea, and vomiting) were more frequently reported in subjects treated with MEPRON suspension (Table 1).

Table 1. Percentage (>2%) of Subjects with Selected Adverse Reactions Requiring Discontinuation of Treatment in the Dapsone Comparative PCP Prevention Trial

| Adverse Reaction | All Subjects | |
|------------------|---|---|
| | MEPRON Suspension 1,500 mg/day (n = 536) % | Dapsone 100 mg/day (n = 521) % |
| Rash | 6.3 | 8.8 |
| Nausea | 4.1 | 0.6 |
| Diarrhea | 3.2 | 0.2 |
| Vomiting | 2.2 | 0.6 |

Aerosolized Pentamidine Comparative Trial: In the aerosolized pentamidine comparative trial (n = 549), the majority of subjects were white (79%), male (92%), and were primary prophylaxis patients at enrollment (58%); the mean age was 38 years. Subjects received MEPRON suspension once daily at a dose of 750 mg (n = 188) or 1,500 mg (n = 175) or received aerosolized pentamidine 300 mg every 4 weeks (n = 186); the median durations of exposure were 6.2, 6.0, and 7.8 months, respectively. Table 2 summarizes the clinical adverse reactions reported by ≥20% of the subjects receiving either the 1,500-mg dose of MEPRON suspension or aerosolized pentamidine.

Rash occurred more often in subjects treated with MEPRON suspension (46%) than in subjects treated with aerosolized pentamidine (28%). Treatment-limiting adverse reactions occurred in 25% of subjects treated with MEPRON suspension 1,500 mg once daily and in 7% of subjects treated with aerosolized pentamidine. The most frequent adverse reactions requiring discontinuation of dosing in the group receiving MEPRON suspension 1,500 mg once daily were rash (6%), diarrhea (4%), and nausea (3%). The most frequent adverse reaction requiring discontinuation of dosing in the group receiving aerosolized pentamidine was bronchospasm (2%).

Table 2. Percentage (≥20%) of Subjects with Selected Adverse Reactions in the Aerosolized Pentamidine Comparative PCP Prevention Trial

| Adverse Reaction | MEPRON Suspension 1,500 mg/day (n = 175) % | Aerosolized Pentamidine (n = 186) % |
|-------------------------|---|--|
| Diarrhea | 42 | 35 |
| Rash | 39 | 28 |
| Headache | 28 | 22 |
| Nausea | 26 | 23 |
| Fever | 25 | 18 |
| Rhinitis | 24 | 17 |

Other reactions occurring in ≥10% of subjects receiving the recommended dose of MEPRON suspension (1,500 mg once daily) included vomiting, sweating, flu syndrome, sinusitis, pruritus, insomnia, depression, and myalgia.

PCP Treatment Trials

Safety information is presented from 2 clinical efficacy trials of the MEPRON tablet formulation: 1) a randomized, double-blind trial comparing MEPRON tablets with TMP-SMX in subjects with acquired immunodeficiency syndrome (AIDS) and mild-to-moderate PCP [(A-a)DO₂] ≤45 mm Hg and PaO₂ ≥60 mm Hg on room air; 2) a randomized, open-label trial comparing MEPRON tablets with intravenous (IV) pentamidine isethionate in subjects with mild-to-moderate PCP who could not tolerate trimethoprim or sulfa antimicrobials.

TMP-SMX Comparative Trial: In the TMP-SMX comparative trial (n = 408), the majority of subjects were white (66%) and male (95%); the mean age was 36 years. Subjects received MEPRON 750 mg (three 250-mg tablets) 3 times daily for 21 days or TMP 320 mg plus SMX 1,600 mg 3 times daily for 21 days; median durations of exposure were 21 and 15 days, respectively.

Table 3 summarizes all clinical adverse reactions reported by $\geq 10\%$ of the trial population regardless of attribution. Nine percent of subjects who received MEPRON and 24% of subjects who received TMP-SMX discontinued therapy due to an adverse reaction. Among the subjects who discontinued, 4% of subjects receiving MEPRON and 8% of subjects in the TMP-SMX group discontinued therapy due to rash.

The incidence of adverse reactions with MEPRON suspension at the recommended dose (750 mg twice daily) was similar to that seen with the tablet formulation.

Table 3. Percentage ($\geq 10\%$) of Subjects with Selected Adverse Reactions in the TMP-SMX Comparative PCP Treatment Trial

| Adverse Reaction | MEPRON Tablets (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 |

Two percent of subjects treated with MEPRON and 7% of subjects treated with TMP-SMX had therapy prematurely discontinued due to elevations in ALT/AST.

Pentamidine Comparative Trial: In the pentamidine comparative trial (n = 174), the majority of subjects in the primary therapy trial population (n = 145) were white (72%) and male (97%); the mean age was 37 years. Subjects received MEPRON 750 mg (three 250-mg tablets) 3 times daily for 21 days or a 3- to 4-mg/kg single pentamidine isethionate IV infusion daily for 21 days; the median durations of exposure were 21 and 14 days, respectively.

Table 4 summarizes the clinical adverse reactions reported by $\geq 10\%$ of the primary therapy trial population regardless of attribution. Fewer subjects who received MEPRON reported adverse reactions than subjects who received pentamidine (63% vs. 72%). However, only 7% of subjects discontinued treatment with MEPRON due to adverse reactions, while 41% of subjects who received pentamidine discontinued treatment for this reason. Of the 5 subjects who discontinued therapy with MEPRON, 3 reported rash (4%). Rash was not severe in any subject. The most frequently cited reasons for discontinuation of pentamidine therapy were hypoglycemia (11%) and vomiting (9%).

Table 4. Percentage ($\geq 10\%$) of Subjects with Selected Adverse Reactions in the Pentamidine Comparative PCP Treatment Trial (Primary Therapy Group)

| Adverse Reaction | MEPRON Tablets (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 |
| Sweat | 10 | 3 |
| Monilia, oral | 10 | 3 |

Laboratory abnormality was reported as the reason for discontinuation of treatment in 2 of 73 subjects (3%) who received MEPRON, and in 14 of 71 subjects (20%) who received pentamidine. One subject (1%) receiving MEPRON had elevated creatinine and BUN levels and 1 subject (1%) had elevated amylase levels. In this trial, elevated levels of amylase occurred in subjects (8% versus 4%) receiving MEPRON tablets or pentamidine, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of MEPRON suspension. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Hepatitis, fatal liver failure.

Skin and Subcutaneous Tissue Disorders

Erythema multiforme, Stevens-Johnson syndrome, and skin desquamation.

Renal and Urinary Disorders

Acute renal impairment.

7 DRUG INTERACTIONS

7.1 Rifampin/Rifabutin

Concomitant administration of rifampin or rifabutin and MEPRON suspension is known to reduce atovaquone concentrations [*see Clinical Pharmacology (12.3)*]. Concomitant administration of MEPRON suspension and rifampin or rifabutin is not recommended.

7.2 Tetracycline

Concomitant administration of tetracycline and MEPRON suspension has been associated with a reduction in plasma concentrations of atovaquone [*see Clinical Pharmacology (12.3)*]. Caution should be used when prescribing tetracycline concomitantly with MEPRON suspension. Monitor patients for potential loss of efficacy of MEPRON if coadministration is necessary.

7.3 Metoclopramide

Metoclopramide may reduce the bioavailability of atovaquone and should be used only if other antiemetics are not available [*see Clinical Pharmacology (12.3)*].

7.4 Indinavir

Concomitant administration of atovaquone and indinavir did not result in any change in the steady-state AUC and C_{max} of indinavir but resulted in a decrease in the C_{trough} of indinavir [*see Clinical Pharmacology (12.3)*]. Caution should be exercised when prescribing MEPRON suspension with indinavir due to the decrease in trough concentrations of indinavir. Monitor patients for potential loss of efficacy of indinavir if coadministration with MEPRON suspension is necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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. 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 (dose of 1,000 mg/kg/day in rats). 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 (dose of 1,200 mg/kg/day in rabbits). 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 ¹⁴C-radiolabelled dose (1,000 mg/kg), concentrations of radiocarbon in rat fetuses were 18% (middle gestation) and 60% (late gestation) of concurrent maternal plasma concentrations.

8.3 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 (with doses of 10 and 250 mg/kg), atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma at both doses.

8.4 Pediatric Use

Evidence of safety and effectiveness in pediatric patients (aged 12 years and younger) has not been established. In a trial of MEPRON suspension administered once daily with food for 12 days to 27 HIV-1-infected, asymptomatic infants and children aged between 1 month and 13 years, the pharmacokinetics of atovaquone were age-dependent. The average steady-state plasma atovaquone concentrations in the 24 subjects with available concentration data are shown in Table 5.

Table 5. Average Steady-state Plasma Atovaquone Concentrations in Pediatric Subjects

| Age | Dose of MEPRON Suspension | | |
|--------------|---|------------------------|-----------------------|
| | 10 mg/kg | 30 mg/kg | 45 mg/kg |
| | 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) | – |

C_{ss} = Concentration at steady state.

8.5 Geriatric Use

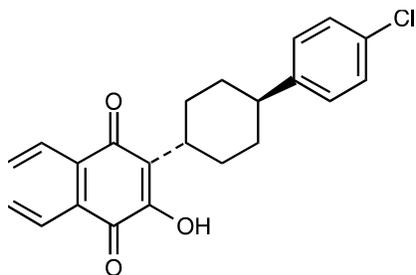
Clinical trials of MEPRON did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

In one patient who took an unspecified dose of dapsone, methemoglobinemia occurred. Rash has also been reported after overdose. There is no known antidote for atovaquone, and it is currently unknown if atovaquone is dialyzable.

11 DESCRIPTION

MEPRON (atovaquone) is a quinone antimicrobial drug for oral administration. 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 C₂₂H₁₉ClO₃. The compound has the following structural formula:



MEPRON suspension is a formulation of micro-fine particles of atovaquone.

Each 5 mL of MEPRON suspension contains 750 mg of atovaquone and the inactive ingredients benzyl alcohol, flavor, poloxamer 188, purified water, saccharin sodium, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atovaquone is a quinone antimicrobial drug [see *Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Absorption

Atovaquone is a highly lipophilic compound with low aqueous solubility. The bioavailability of atovaquone is highly dependent on formulation and diet. The absolute bioavailability of a 750-mg dose of MEPRON suspension administered under fed conditions in 9 HIV-1-infected ($CD4 >100$ cells/mm³) volunteers was $47\% \pm 15\%$.

Administering atovaquone with food enhances its absorption by approximately 2-fold. In one trial, 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 (\pm SD) area under the concentration-time curve (AUC) values under fasting and fed conditions were 324 ± 115 and 801 ± 320 h•mcg/mL, 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 trial in 19 HIV-1-infected volunteers ($CD4 <200$ cells/mm³) receiving daily doses of 500 mg MEPRON suspension. AUC values under fasting and fed conditions were 169 ± 77 and 280 ± 114 h•mcg/mL, respectively. Maximum plasma atovaquone concentration (C_{max}) values under fasting and fed conditions were 8.8 ± 3.7 and 15.1 ± 6.1 mcg/mL, 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-1-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 IV administration of atovaquone, the volume of distribution at steady state ($V_{d,ss}$) 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-1-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 IV administration in 9 HIV-1-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 trials following administration of MEPRON suspension. The half-life of atovaquone is due to presumed enterohepatic cycling and eventual fecal elimination. In a trial 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.

Hepatic/Renal Impairment

The pharmacokinetics of atovaquone have not been studied in patients with hepatic or renal impairment.

Relationship between Plasma Atovaquone Concentration and Clinical Outcome

In a comparative trial of atovaquone tablets with TMP-SMX for oral treatment of mild-to-moderate PCP [see *Clinical Studies (14.2)*], where subjects with HIV/AIDS received atovaquone tablets 750 mg 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 (Table 6).

Table 6. Relationship between Plasma Atovaquone Concentration and Successful Treatment

| Steady-state Plasma Atovaquone Concentrations (mcg/mL) | Successful Treatment ^a No. Successes/No. in Group (%) | | | |
|--|---|------|------------------------|------|
| | Observed | | Predicted ^b | |
| 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% |

^a Successful treatment was defined as improvement in clinical and respiratory measures persisting at least 4 weeks after cessation of therapy. Improvement in clinical and respiratory measures was assessed using a composite of parameters that included oral body temperature, respiratory rate, severity scores for cough, dyspnea, and chest pain/tightness. This analysis

was based on data from subjects for whom both outcome and steady-state plasma atovaquone concentration data were available.

^b Based on logistic regression analysis.

A dosing regimen of MEPRON suspension for the treatment of mild-to-moderate PCP was 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 6). In an open-label PCP treatment trial 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 ($n = 18$).

Drug Interactions

Rifampin/Rifabutin: In a trial with 13 HIV-1-infected volunteers, the oral administration of rifampin 600 mg every 24 hours with MEPRON suspension 750 mg every 12 hours resulted in a $52\% \pm 13\%$ decrease in the average steady-state plasma atovaquone concentration and a $37\% \pm 42\%$ 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. In a trial of 24 healthy volunteers, the oral administration of rifabutin 300 mg once daily with MEPRON suspension 750 mg twice daily resulted in a 34% decrease in the average steady-state plasma atovaquone concentration and a 19% decrease in the average steady-state plasma rifabutin concentration.

Tetracycline: Concomitant treatment with tetracycline has been associated with a 40% reduction in plasma concentrations of atovaquone.

Metoclopramide: Concomitant treatment with metoclopramide has been associated with decreased bioavailability of atovaquone.

Indinavir: Concomitant administration of atovaquone (750 mg twice daily with food for 14 days) and indinavir (800 mg three times daily without food for 14 days) did not result in any change in the steady-state AUC and C_{\max} of indinavir, but resulted in a decrease in the C_{trough} of indinavir (23% decrease [90% CI: 8%, 35%]).

Trimethoprim/Sulfamethoxazole: The possible interaction between atovaquone and TMP-SMX was evaluated in 6 HIV-1-infected adult volunteers as part of a larger multiple-dose, dose-escalation, and chronic dosing trial of MEPRON suspension. In this crossover trial, MEPRON suspension 500 mg once daily (not the approved dosage), or TMP-SMX tablets (trimethoprim 160 mg and sulfamethoxazole 800 mg) 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.

Zidovudine: Data from 14 HIV-1-infected volunteers who were given atovaquone tablets 750 mg every 12 hours with zidovudine 200 mg every 8 hours showed a $24\% \pm 12\%$ decrease in zidovudine apparent oral clearance, leading to a $35\% \pm 23\%$ 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.

12.4 Microbiology

Mechanism of Action

Atovaquone is a hydroxy-1,4-naphthoquinone, an analog of ubiquinone, with antipneumocystis activity. The mechanism of action against *Pneumocystis jiroveci* 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 results in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and adenosine triphosphate (ATP) synthesis.

Activity In Vitro

Several laboratories, using different in vitro methodologies, have shown the IC₅₀ (50% inhibitory concentration) of atovaquone against *P. jiroveci* to be 0.1 to 3.0 mcg/mL.

Drug Resistance

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in rats were negative; 24-month studies in mice (dosed with 50, 100, or 200 mg/kg/day), showed treatment-related increases in incidence of hepatocellular adenoma and hepatocellular carcinoma at all doses tested, which correlated with 1.4 to 3.6 times the average steady-state plasma concentrations in humans during acute treatment of PCP. 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.

14 CLINICAL STUDIES

14.1 Prevention of PCP

The indication for prevention of PCP is based on the results of 2 clinical trials comparing MEPRON suspension with dapsone or aerosolized pentamidine in HIV-1-infected adolescent (aged 13 to 18 years) and adult subjects at risk of PCP (CD4 count <200 cells/mm³ or a prior episode of PCP) and unable to tolerate TMP-SMX.

Dapsone Comparative Trial

This open-label trial enrolled 1,057 subjects, randomized to receive MEPRON suspension 1,500 mg once daily (n = 536) or dapsone 100 mg once daily (n = 521). The majority of subjects were white (64%), male (88%), and receiving prophylaxis for PCP at randomization (73%); the mean age was 38 years. Median follow-up was 24 months. Subjects randomized to the dapsone arm who were seropositive for *Toxoplasma gondii* and had a CD4 count <100 cells/mm³ also received pyrimethamine and folinic acid. PCP event rates are shown in Table 7. Mortality rates were similar.

Aerosolized Pentamidine Comparative Trial

This open-label trial enrolled 549 subjects, randomized to receive MEPRON suspension 1,500 mg once daily (n = 175), MEPRON suspension 750 mg once daily (n = 188), or aerosolized pentamidine 300 mg once monthly (n = 186). The majority of subjects were white (79%), male (92%), and were primary prophylaxis patients at enrollment (58%); the mean age was 38 years. Median follow-up was 11.3 months. The results of the PCP event rates appear in Table 7. Mortality rates were similar among the groups.

Table 7. Confirmed or Presumed/Probable PCP Events (As-Treated Analysis)^a

| Assessment | Trial 1 | | Trial 2 | | |
|--|--|------------------------------|--|--|--|
| | MEPRON Suspension 1,500 mg/day (n = 527) | Dapsone 100 mg/day (n = 510) | MEPRON Suspension 750 mg/day (n = 188) | MEPRON Suspension 1,500 mg/day (n = 172) | Aerosolized Pentamidine 300 mg/month (n = 169) |
| % | 15 | 19 | 23 | 18 | 17 |
| Relative Risk ^b (CI) ^c | 0.77 (0.57, 1.04) | | 1.47 (0.86, 2.50) | 1.14 (0.63, 2.06) | |

^a Those events occurring during or within 30 days of stopping assigned treatment.

^b Relative risk <1 favors MEPRON and values >1 favor comparator. Trial results did not show superiority of MEPRON to the comparator.

^c The confidence level of the interval for the dapsone comparative trial was 95% and for the pentamidine comparative trial was 97.5%.

An analysis of all PCP events (intent-to-treat analysis) for both trials showed results similar to those shown in Table 7.

14.2 Treatment of PCP

The indication for treatment of mild-to-moderate PCP is based on the results of two efficacy trials: a randomized, double-blind trial comparing MEPRON tablets with TMP-SMX in subjects with HIV/AIDS and mild-to-moderate PCP (defined in the protocol as $[(A-a)DO_2] \leq 45$ mm Hg and $PaO_2 \geq 60$ mm Hg on room air) and a randomized open-label trial comparing MEPRON tablets with IV pentamidine isethionate in subjects with mild-to-moderate PCP who could not tolerate trimethoprim or sulfa antimicrobials. Both trials were conducted with the tablet formulation using 750 mg three times daily. Results from these efficacy trials established a relationship between plasma atovaquone concentration and successful outcome. Successful outcome was defined as improvement in clinical and respiratory measures persisting at least 4 weeks after cessation of therapy. Comparative pharmacokinetic trials of the suspension and tablet formulations established the currently recommended suspension dose of 750 mg twice daily [see *Clinical Pharmacology* (12.3)].

TMP-SMX Comparative Trial

This double-blind, randomized trial compared the safety and efficacy of MEPRON tablets with that of TMP-SMX for the treatment of subjects with HIV/AIDS and histologically confirmed PCP. Only subjects with mild-to-moderate PCP were eligible for enrollment.

A total of 408 subjects were enrolled into the trial. The majority of subjects were white (66%) and male (95%); the mean age was 36 years. Eighty-six subjects without histologic confirmation of PCP were excluded from the efficacy analyses. Of the 322 subjects with histologically confirmed PCP, 160 were randomized to receive 750 mg MEPRON (three 250-mg tablets) 3 times daily for 21 days and 162 were randomized 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. Improvement in clinical and respiratory measures was assessed using a composite of parameters that included oral body temperature, respiratory rate, severity scores for cough, dyspnea, and chest pain/tightness. 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 favoring TMP-SMX. Among the 322 subjects with confirmed PCP, 13 of 160 (8%) subjects treated with MEPRON and 4 of 162 (2.5%) subjects 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 subjects, there were 16 (8%) deaths among subjects treated with MEPRON and 7 (3.4%) deaths among subjects treated with TMP-SMX ($P = 0.051$). Of the 13 subjects with confirmed PCP and 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 subjects.

A correlation between plasma atovaquone concentrations and death demonstrated that subjects with lower plasma concentrations were more likely to die. For those subjects for whom Day 4 plasma atovaquone concentration data are available, 5 (63%) of 8 subjects with concentrations <5 mcg/mL died during participation in the trial. However, only 1 (2.0%) of the 49 subjects with Day 4 plasma atovaquone concentrations \geq 5 mcg/mL died.

Sixty-two percent of subjects on MEPRON and 64% of subjects on TMP-SMX were classified as protocol-defined therapy successes (Table 8).

Table 8. Outcome of Treatment for PCP-positive Subjects Enrolled in the TMP-SMX Comparative Trial

| Outcome of Therapy ^a | Number of Subjects (%) | | | |
|---|-----------------------------|-----|----------------------|-----|
| | MEPRON Tablets (n = 160) | | TMP-SMX (n = 162) | |
| Therapy success | 99 | 62% | 103 | 64% |
| Therapy failure due to: | | | | |
| -Lack of response | 28 | 17% | 10 | 6% |
| -Adverse reaction | 11 | 7% | 33 | 20% |
| -Unevaluable | 22 | 14% | 16 | 10% |
| Required alternate PCP therapy during trial | 55 | 34% | 55 | 34% |

^a As defined by the protocol and described in trial description above.

The failure rate due to lack of response was significantly higher for subjects receiving MEPRON, while the failure rate due to an adverse reaction was significantly higher for subjects receiving TMP-SMX.

Pentamidine Comparative Trial

This unblinded, randomized trial was designed to compare the safety and efficacy of MEPRON with that of pentamidine for the treatment of histologically confirmed mild or moderate PCP in subjects with HIV/AIDS. Approximately 80% of the subjects 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 trial (the salvage treatment group). A total of 174 subjects were enrolled into the trial. Subjects were randomized to receive MEPRON 750 mg (three 250-mg tablets) 3 times daily for 21 days or pentamidine isethionate 3- to 4-mg/kg single IV infusion daily for 21 days. The majority of subjects were white (72%) and male (97%); the mean age was approximately 37 years. Thirty-nine subjects without histologic confirmation of PCP were excluded from the efficacy analyses. Of the 135 subjects 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 subject in the primary therapy group randomized to receive pentamidine did not receive trial medication.

There was no difference in mortality rates between the treatment groups. Among the 135 subjects with confirmed PCP, 10 of 70 (14%) subjects receiving MEPRON and 9 of 65 (14%) subjects receiving pentamidine died during the 21-day treatment course or 8-week follow-up period. In the intent-to-treat analysis for all subjects, there were 11 (12.5%) deaths among those treated with MEPRON and 12 (14%) deaths among those treated with pentamidine. Among subjects for whom Day 4 plasma atovaquone concentrations were available, 3 of 5 (60%) subjects with concentrations <5 mcg/mL died during participation in the trial. However, only 2 of 21 (9%) subjects with Day 4 plasma concentrations ≥5 mcg/mL died. The therapeutic outcomes for the 134 subjects who received trial medication in this trial are presented in Table 9.

Table 9. Outcome of Treatment for PCP-positive Subjects (%) Enrolled in the Pentamidine Comparative Trial

| Outcome of Therapy | Primary Treatment | | | | Salvage Treatment | | | |
|---|--------------------|------|-------------------------|-----|--------------------|-----|-------------------------|-----|
| | MEPRON (n = 56) | | Pentamidine (n = 53) | | MEPRON (n = 14) | | Pentamidine (n = 11) | |
| Therapy success | 32 | 57% | 21 | 40% | 13 | 93% | 7 | 64% |
| Therapy failure due to: | | | | | | | | |
| -Lack of response | 16 | 29% | 9 | 17% | 0 | | 0 | |
| -Adverse reaction | 2 | 3.6% | 19 | 36% | 0 | | 3 | 27% |
| -Unevaluable | 6 | 11% | 4 | 8% | 1 | 7% | 1 | 9% |
| Required alternate PCP therapy during trial | 19 | 34% | 29 | 55% | 0 | | 4 | 36% |

16 HOW SUPPLIED/STORAGE AND HANDLING

MEPRON suspension (bright yellow, citrus-flavored) containing 750 mg atovaquone in 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*.

17 PATIENT COUNSELING INFORMATION

Administration Instructions

Instruct patients to:

- Ensure the prescribed dose of MEPRON suspension is taken as directed.

- Take their daily doses of MEPRON suspension with food, as food will significantly improve the absorption of the drug.
- Shake MEPRON suspension gently before use each time.

MEPRON is a registered trademark of the GSK group of companies.



GlaxoSmithKline
Research Triangle Park, NC 27709

©2015, the GSK group of companies. All rights reserved.