

ATOVAQUONE- atovaquone suspension
McKesson Corporation dba SKY Packaging

ATOVAQUONE ORAL SUSPENSION, USP

1 INDICATION AND USAGE

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1.1 Prevention of Pneumocystis jirovecii Pneumonia

Atovaquone oral suspension is indicated for the prevention of Pneumocystis jirovecii 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 jirovecii Pneumonia

Atovaquone oral 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 atovaquone 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 atovaquone has not been studied. The efficacy of atovaquone in subjects who are failing therapy with TMP-SMX has also not been studied.

2 DOSAGE AND ADMINISTRATION

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2.1 Dosage for the Prevention of P. jirovecii 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. jirovecii 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 atovaquone 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)*].

Atovaquone Unit Dose Cup

Shake gently before using.

3 DOSAGE FORMS AND STRENGTHS

Atovaquone oral suspension USP is a bright yellow, tutti frutti flavored, oral suspension containing 750 mg of atovaquone per 5 mL. Atovaquone is supplied in one unit dose cup

4 CONTRAINDICATIONS

Atovaquone oral 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 atovaquone oral solution.

5 WARNINGS AND PRECAUTIONS

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5.1 Risk of Limited Oral Absorption

Absorption of orally administered atovaquone oral suspension is limited but can be significantly increased when the drug is taken with food. Failure to administer atovaquone oral 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 atovaquone oral 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 atovaquone.

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 atovaquone had complications of advanced human immunodeficiency virus (HIV) disease, it was often difficult to distinguish adverse reactions caused by atovaquone from those caused by underlying medical conditions.

PCP Prevention Trials

In 2 clinical trials, atovaquone oral 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 atovaquone oral 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 atovaquone oral 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 atovaquone oral suspension. Gastrointestinal adverse reactions (nausea, diarrhea, and vomiting) were more frequently reported in subjects treated with atovaquone oral 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	
	Atovaquone Oral 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 atovaquone oral 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 atovaquone oral suspension or aerosolized pentamidine.

Rash occurred more often in subjects treated with atovaquone oral suspension (46%) than in subjects treated with aerosolized pentamidine (28%). Treatment-limiting adverse reactions occurred in 25% of subjects treated with atovaquone oral 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 atovaquone oral 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 ($\geq 20\%$) of Subjects with Selected Adverse Reactions in the Aerosolized Pentamidine Comparative PCP Prevention Trial

Adverse Reaction	Atovaquone Oral 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 $\geq 10\%$ of subjects receiving the recommended dose of atovaquone oral 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 atovaquone tablet formulation: 1) a randomized, double-blind trial comparing atovaquone 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 atovaquone 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 atovaquone 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 atovaquone and 24% of subjects who received TMP-SMX discontinued therapy due to an adverse reaction. Among the subjects who discontinued, 4% of subjects receiving atovaquone and 8% of subjects in the TMP-SMX group discontinued therapy due to rash.

The incidence of adverse reactions with atovaquone oral 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	Atovaquone Tablets (n = 203) %	TMP-SMX (n = 205) %
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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 atovaquone 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 atovaquone 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 atovaquone reported adverse reactions than subjects who received pentamidine (63% vs. 72%). However, only 7% of subjects discontinued treatment with atovaquone due to adverse reactions, while 41% of subjects who received pentamidine discontinued treatment for this reason. Of the 5 subjects who discontinued therapy with atovaquone, 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	Atovaquone 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 atovaquone, and in 14 of 71 subjects (20%) who received pentamidine. One subject (1%) receiving atovaquone 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 atovaquone tablets or pentamidine, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of atovaquone oral 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

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7.1 Rifampin/Rifabutin

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

7.2 Tetracycline

Concomitant administration of tetracycline and atovaquone oral 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 atovaquone oral suspension. Monitor patients for potential loss of efficacy of atovaquone 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 atovaquone oral suspension with indinavir due to the decrease in trough concentrations of indinavir. Monitor patients for potential loss of efficacy of indinavir if coadministration with atovaquone oral suspension is necessary.

8 USE IN SPECIFIC POPULATIONS

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8.1 Pregnancy

Risk Summary

Available data from postmarketing experience with use of atovaquone in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnant women with HIV who are infected with PCP are at increased risk of adverse pregnancy outcomes (see *Clinical Considerations*). Atovaquone given orally by gavage to pregnant rats and rabbits during organogenesis did not cause fetal malformations at plasma concentrations up to 3 times and 0.5 times, respectively, the estimated human exposure based on steady-state plasma concentrations (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women with HIV who are infected with PCP are at increased risk of severe illness and maternal death associated with PCP compared with non-pregnant women.

Data

Animal Data: Atovaquone administered in oral doses of 250, 500, and 1,000 mg/kg/day to pregnant rats during organogenesis (Gestation Day [GD] 6 to GD15) did not cause maternal or embryo-fetal toxicity at doses up to 1,000 mg/kg/day corresponding to maternal plasma concentrations approximately 3 times the estimated human exposure during the treatment of PCP based on steady-state plasma concentrations. In pregnant rabbits, atovaquone administered in oral doses of 300, 600, and 1,200 mg/kg/day during organogenesis (GD6 to GD18) caused decreased fetal body length at a maternally toxic dose of 1,200 mg/kg/day corresponding to a plasma concentration that is approximately 0.5 times the estimated human exposure based on steady-state plasma concentrations. In a pre- and post-natal study in rats, atovaquone administered in oral doses of 250, 500, and 1,000 mg/kg/day from GD15 until Lactation Day (LD) 20

did not impair the growth or developmental effects in first generation offspring at doses up to 1,000 mg/kg/day corresponding to approximately 3 times the estimated human exposure based on steady-state plasma concentrations during the treatment of PCP. Atovaquone crossed the placenta and was present in fetal rat and rabbit tissue.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. There are no data on the presence of atovaquone in human milk, the effects on the breastfed child, or the effects on milk production. Atovaquone was detected in rat milk when lactating rats were administered oral atovaquone (see *Data*). When a drug is present in animal milk, it is likely the drug will be present in human milk. Because of the potential for HIV-1 transmission to HIV-negative infants, instruct mothers with HIV-1 not to breastfeed if they are taking atovaquone for the prevention or treatment of PCP.

Data

In a rat study with doses of 10 and 250 mg/kg given orally by gavage on postpartum Day 11, atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma at both doses. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk

8.3 Pediatric Use

Evidence of safety and effectiveness in pediatric patients (aged 12 years and younger) has not been established. In a trial of atovaquone oral 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 Atovaquone Oral 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.

8.4 Geriatric Use

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

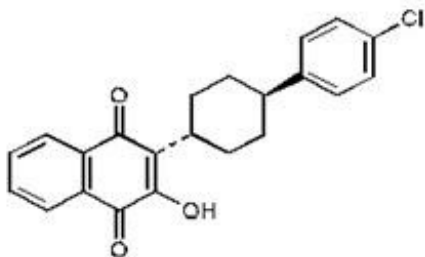
9 OVERDOSAGE

Overdoses up to 31,500 mg of atovaquone have been reported. In one patient who also 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

10 DESCRIPTION

Atovaquone oral suspension USP is a quinone antimicrobial drug. 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:



Atovaquone oral suspension USP is a formulation of micro-fine particles of atovaquone, USP.

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

11 CLINICAL PHARMACOLOGY

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11.1 Mechanism of Action

Atovaquone is a quinone antimicrobial drug [*see Microbiology (11.4)*] .

11.2 Pharmacodynamics

Relationship between Plasma Atovaquone Concentrations and Clinical Outcome

In a comparative clinical trial, HIV/AIDS subjects received atovaquone tablets 750 mg 3 times daily or TMP-SMX for treatment of mild-to-moderate PCP for 21 days [*see Clinical*

Studies (14.2)] ; the relationship between atovaquone plasma concentrations and successful treatment outcome from 113 of these subjects for whom both steady-state drug concentrations and outcome data were available is shown in Table 6.

Steady-State Plasma Atovaquone Concentrations (mcg/mL)	Successful Treatment^a No. of Successes/No. in Group (%)
0 to <5	0/6 (0%)
5 to <10	18/26 (69%)
10 to <15	30/38 (79%)
15 to <20	18/19 (95%)
≥20	24/24 (100%)

^a Successful treatment outcome 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, and severity scores for cough, dyspnea, and chest pain/tightness.

Cardiac Effects

The effect of atovaquone oral suspension on the QT interval is unknown in humans.

11.3 Pharmacokinetics

Plasma atovaquone concentrations do not increase proportionally with dose following ascending repeat-dose administration of atovaquone oral suspension in healthy subjects. When atovaquone oral suspension was administered with food at dosage regimens of 500 mg once daily, 750 mg once daily, and 1,000 mg once daily, mean (\pm SD) steady-state plasma atovaquone concentrations were 11.7 ± 4.8 , 12.5 ± 5.8 , and 13.5 ± 5.1 mcg/mL, respectively. The corresponding mean (\pm SD) C_{\max} concentrations were 15.1 ± 6.1 , 15.3 ± 7.6 , and 16.8 ± 6.4 mcg/mL.

Absorption

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

Effect of Food: Administering atovaquone oral suspension with food enhances atovaquone bioavailability. Sixteen healthy subjects received a single 750-mg dose of atovaquone oral suspension after an overnight fast and following a meal (23 g fat: 610 kCal). The mean (\pm SD) atovaquone AUC under fasting and fed conditions were 324 ± 115 and 801 ± 320 h•mcg/mL, respectively, representing a 2.6 ± 1.0 -fold increase.

Distribution

Following IV administration of atovaquone, the mean (\pm SD) 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 mean (\pm SD) half-life of was 62.5 ± 35.3 hours after IV administration and ranged from 67.0 ± 33.4 to 77.6 ± 23.1 hours following administration of atovaquone oral suspension.

Metabolism: The metabolism of atovaquone is unknown.

Excretion: Following oral administration of ^{14}C -labelled atovaquone to healthy subjects, greater than 94% of the dose was recovered as unchanged atovaquone in the feces over 21 days.

Specific Populations

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

HIV-Infected Subjects: When atovaquone oral suspension was administered to 5 HIV-1-infected subjects at a dose of 750 mg twice daily, the mean (\pm SD) steady-state plasma atovaquone concentration was 21.0 ± 4.9 mcg/mL and mean (\pm SD) C_{max} was 24.0 ± 5.7 mcg/mL. The mean (\pm SD) minimum plasma atovaquone concentration (C_{min}) associated with the 750-mg twice-daily regimen was 16.7 ± 4.6 mcg/mL.

In an open-label PCP trial in 18 HIV-1-infected subjects, administration of atovaquone oral suspension 750 mg twice daily with meals resulted in a mean (\pm SD) steady-state plasma atovaquone concentration of 22.0 ± 10.1 mcg/mL.

The mean (\pm SD) plasma clearance of atovaquone following IV administration in 9 HIV-1-infected subjects was 10.4 ± 5.5 mL/min (0.15 ± 0.09 mL/min/kg).

Drug Interaction Studies

Rifampin/Rifabutin: In a trial with 13 HIV-1-infected volunteers, the oral administration of rifampin 600 mg every 24 hours with atovaquone oral suspension 750 mg every 12 hours resulted in a $52\% \pm 13\%$ decrease in the mean (\pm SD) steady-state plasma atovaquone concentration and a $37\% \pm 42\%$ increase in the mean (\pm SD) 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 atovaquone oral suspension 750 mg twice daily resulted in a 34% decrease in the mean steady-state plasma atovaquone concentration and a 19% decrease in the mean 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 a 50% reduction in steady-state atovaquone plasma concentrations.

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 (TMP-SMX): Concomitant administration of atovaquone oral suspension 500 mg once daily (not the approved dosage) and TMP-SMX in 6 HIV-infected adult subjects did not result in significant changes in either atovaquone or TMP-SMX exposure.

Zidovudine: The administration of atovaquone tablets 750 mg every 12 hours with zidovudine 200 mg every 8 hours to 14 HIV-1 infected subjects resulted in 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.

11.4 Microbiology

Mechanism of Action

Atovaquone is a hydroxy-1,4-naphthoquinone, an analog of ubiquinone, with antipneumocystis activity. The mechanism of action against *Pneumocystis jirovecii* 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.

Antimicrobial Activity

Atovaquone is active against *P. jirovecii* [see *Clinical Studies (14)*].

Resistance

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

12 NONCLINICAL TOXICOLOGY

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12.1 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.

Impairment of Fertility

Atovaquone administered by oral gavage in doses of 100, 300, or 1,000 mg/kg/day to adult male rats from 73 days prior to mating until 20 days after mating and to adult female rats from 14 days prior to mating until LD20 did not impair male or female fertility or early embryonic development at doses up to 1,000 mg/kg/day corresponding to plasma exposures of approximately 3 times the estimated human exposure based on steady-state plasma concentrations.

13 CLINICAL STUDIES

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13.1 Prevention of PCP

The indication for prevention of PCP is based on the results of 2 clinical trials comparing atovaquone oral 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 atovaquone oral 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 atovaquone oral suspension 1,500 mg once daily (n = 175), atovaquone oral 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		
	Atovaquone Oral Suspension 1,500 mg/day (n = 527)	Dapsone 100 mg/day (n = 510)	Atovaquone Oral Suspension 750 mg/day (n = 188)	Atovaquone Oral Suspension 1,500 mg/day (n = 172)	Aerosolized Pentamidine 300 mg/day (n = 169)
%	15	19	23	18	17
Relative Risk ^b	0.77		1.47	1.14	
(CI) ^c	(0.57, 1.04)		(0.86, 2.50)	(0.63, 2.06)	

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

^b Relative risk <1 favors atovaquone and values >1 favor comparator. Trial results did not show superiority of atovaquone 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 HOW SUPPLIED/STORAGE AND HANDLING

Atovaquone oral suspension USP (bright yellow, tutti frutti flavored) containing 750 mg atovaquone per 5 mL.

Store at 15°C to 25°C (59°F to 77°F). Do not freeze.

15 PATIENT COUNSELING INFORMATION

Administration Instructions

Instruct patients to:

- Ensure the prescribed dose of atovaquone oral suspension is taken as directed.
- Take their daily doses of atovaquone oral suspension with food, as food will significantly improve the absorption of the drug.
- Shake atovaquone oral suspension gently before use each time.

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk [see *Use in Specific Populations (8.2)*].

Manufactured by: PAI Pharma LLC

Greenville, SC 29605

QUESTIONS OR COMMENT?

Call 1-800-845-8210

16 Principal Display Panel

Delivers 5 mL

NDC 63739-203-01

Atovaquone Oral Suspension USP

750 mg/5 mL

Package Not Child-Resistant

RX ONLY



ATOVAQUONE

atovaquone suspension

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:63739-203
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ATOVAQUONE (UNII: Y883P1Z2LT) (ATOVAQUONE - UNII:Y883P1Z2LT)	ATOVAQUONE	750 mg in 5 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63739-203-18	3 in 1 CASE	04/19/2024	
1		6 in 1 TRAY		
1	NDC:63739-203-05	5 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product		
2	NDC:63739-203-42	7 in 1 CASE	04/19/2024	

2		6 in 1 TRAY		
2	NDC:63739-203-05	5 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
ANDA	ANDA214272		04/19/2024	

Labeler - McKesson Corporation dba SKY Packaging (140529962)

Registrant - PAI Holdings, LLC dba Pharmaceutical Associates, Inc. (044940096)

Establishment			
Name	Address	ID/FEI	Business Operations
PAI Holdings, LLC dba Pharmaceutical Associates, Inc. and dba PAI Pharma		044940096	analysis(63739-203) , label(63739-203) , manufacture(63739-203) , pack(63739-203)

Revised: 2/2024

McKesson Corporation dba SKY Packaging