ATOVAQUONE- atovaquone suspension
American Health Packaging

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ATOVAQUONE ORAL SUSPENSION safely and effectively. See full prescribing information for ATOVAQUONE ORAL SUSPENSION.
ATOVAQUONE oral suspension
Initial U.S. Approval: 1992

INDICATIONS AND USAGE
Atovaquone oral suspension is a quinone antimicrobial drug indicated for:

- Prevention of Pneumocystis jirovecii 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 atovaquone oral suspension has not been studied.
- The efficacy of atovaquone oral suspension 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 Bottles: 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 atovaquone oral suspension. (4)

WARNINGS AND PRECAUTIONS
- Failure to administer atovaquone oral 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 Hetero Labs Limited at 1-866-495-1995 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 atovaquone oral 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 atovaquone 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)

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Revised: 6/2018
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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)DO$_2$] ≤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 & 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. 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 Oral Suspension**
Shake gently before administering the recommended dosage.

### 3 DOSAGE FORMS & STRENGTHS
Atovaquone oral suspension, USP is a yellow homogenous suspension containing 750 mg of atovaquone USP per 5 mL.

### 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 suspension.

### 5 WARNINGS AND PRECAUTIONS

#### 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 oral suspension.

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/mm$^3$ 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Atovaquone Oral Suspension 1,500 mg/day (n = 536)</th>
<th>All Subjects</th>
<th>Dapsone 100 mg/day (n = 521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>6.3</td>
<td></td>
<td>8.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.1</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.2</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.2</td>
<td></td>
<td>0.6</td>
</tr>
</tbody>
</table>

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, 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 (≥20%) of Subjects with Selected Adverse Reactions in the Aerosolized Pentamidine Comparative PCP Prevention Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Atovaquone Oral Suspension 1,500 mg/day (n = 175)</th>
<th>Aerosolized Pentamidine (n = 186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>Rash</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Fever</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>24</td>
<td>17</td>
</tr>
</tbody>
</table>

Other reactions occurring in ≥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 ≥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 (≥10%) of Subjects with Selected Adverse Reactions in the TMP-SMX Comparative PCP Treatment Trial
### Table 4. Percentage (≥10%) of Subjects with Selected Adverse Reactions in the Pentamidine Comparative PCP Treatment Trial (Primary Therapy Group)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Atovaquone Tablets (n = 73)</th>
<th>Pentamidine (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>Insomnia</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Sweat</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Monilia, oral</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

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

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

8.1 Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Atovaquone 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 $^{14}$C-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 atovaquone 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 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

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose of Atovaquone Oral Suspension</th>
<th>Average C$_{ss}$ in mcg/mL (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg/kg</td>
<td>30 mg/kg</td>
</tr>
<tr>
<td>1-3 months</td>
<td>5.9 (n = 1)</td>
<td>27.8 ± 5.8 (n = 4)</td>
</tr>
<tr>
<td>&gt;3-24 months</td>
<td>5.7 ± 5.1 (n = 4)</td>
<td>9.8 ± 3.2 (n = 4)</td>
</tr>
<tr>
<td>&gt;2-13 years</td>
<td>16.8 ± 6.4 (n = 4)</td>
<td>37.1 ± 10.9 (n = 3)</td>
</tr>
</tbody>
</table>

C$_{ss}$ = Concentration at steady state.

8.5 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.

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

Atovaquone oral suspension is a quinone antimicrobial drug. The chemical name of atovaquone is 1,4-
Naphthalenedione, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-, trans. Atovaquone USP is a yellow colored powder that is freely soluble in tetrahydrofuran, soluble in chloroform and sparingly soluble in acetone. 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:

![Structural formula of atovaquone](image)

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 USP and the inactive ingredients benzyl alcohol, flavor, hypromellose, poloxamer, 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 atovaquone oral suspension administered under fed conditions in 9 HIV-1-infected (CD4 >100 cells/mm\(^3\)) volunteers was 47% ± 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 atovaquone oral 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 under fasting and fed conditions were 324 ± 115 and 801 ± 320 h•mcg/mL, respectively, representing a 2.6 ± 1-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/mm\(^3\)) receiving daily doses of 500 mg atovaquone oral suspension. AUC values under fasting and fed conditions were 169 ± 77 and 280 ± 114 h•mcg/mL, respectively. Maximum plasma atovaquone concentration (C\(_{\text{max}}\)) 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 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, 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\(_{\text{max}}\) concentrations were 15.1 ± 6.1, 15.3 ± 7.6, and 16.8 ± 6.4 mcg/mL. When atovaquone oral 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 ± 4.9 mcg/mL and C\(_{\text{max}}\) was 24 ± 5.7 mcg/mL. The minimum plasma atovaquone concentration (C\(_{\text{min}}\)) 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\(_{d_{\text{ss}}}\)) 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 \pm 5.5 \text{ mL/min} (0.15 \pm 0.09 \text{ mL/min/kg}). The half-life of atovaquone was $62.5 \pm 35.3 \text{ hours}$ after IV administration and ranged from $67 \pm 33.4$ to $77.6 \pm 23.1 \text{ hours}$ across trials following administration of atovaquone oral 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 $13.9 \pm 6.9 \text{ mcg/mL}$ ($n = 133$). 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

<table>
<thead>
<tr>
<th>Steady-state Plasma Atovaquone Concentrations (mcg/mL)</th>
<th>Successful Treatment*</th>
<th></th>
<th>Predicted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed No. Successes/No. in Group (%)</td>
<td></td>
<td>Predicted</td>
</tr>
<tr>
<td>0 to &lt;5</td>
<td>0/6</td>
<td>0%</td>
<td>1.5/6</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>18/26</td>
<td>69%</td>
<td>14.7/26</td>
</tr>
<tr>
<td>10 to &lt;15</td>
<td>30/38</td>
<td>79%</td>
<td>31.9/38</td>
</tr>
<tr>
<td>15 to &lt;20</td>
<td>18/19</td>
<td>95%</td>
<td>18.1/19</td>
</tr>
<tr>
<td>20 to &lt;25</td>
<td>18/18</td>
<td>100%</td>
<td>17.8/18</td>
</tr>
<tr>
<td>25+</td>
<td>6/6</td>
<td>100%</td>
<td>6/6</td>
</tr>
</tbody>
</table>

* 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.

† Based on logistic regression analysis.

A dosing regimen of atovaquone oral 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 atovaquone oral 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 $22 \pm 10.1 \text{ mcg/mL}$ ($n = 18$).

**Drug Interactions**

*Rifampin/Rifabutin:* In a trial with 13 HIV-1-infected volunteers, the oral administration of rifampin 600 mg every 24 hours with atovaquone oral 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 $82 \pm$
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 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 atovaquone oral suspension. In this crossover trial, atovaquone oral 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 atovaquone 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% ± 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.

### 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 jirovecii* has not been fully elucidated. In *Plasmodium* species, the site of action appears to be the cytochrome b_{c1} 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 IC_{50} (50% inhibitory concentration) of atovaquone against *P. jirovecii* to be 0.1 to 3 mcg/mL.

#### Drug 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.

### 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 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) *

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Aerosolized Pentamidine 300 mg/month (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atovaquone Oral Suspension 1,500 mg/day (n = 527)</td>
<td>Atovaquone Oral Suspension 750 mg/day (n = 188)</td>
<td>Atovaquone Oral Suspension 1,500 mg/day (n = 172)</td>
</tr>
<tr>
<td></td>
<td>Dapsone 100 mg/day (n = 510)</td>
<td></td>
<td>Aerosolized Pentamidine 300 mg/month</td>
</tr>
<tr>
<td>%</td>
<td>15</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Relative Risk †</td>
<td>0.77 (0.57, 1.04)</td>
<td>1.47 (0.86, 2.50)</td>
<td>1.14 (0.63, 2.06)</td>
</tr>
</tbody>
</table>

* Those events occurring during or within 30 days of stopping assigned treatment.
† Relative risk <1 favors atovaquone and values >1 favor comparator. Trial results did not show superiority of atovaquone to the comparator.
‡ 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 2 efficacy trials: a randomized, double-blind trial comparing atovaquone tablets with TMP-SMX in subjects with HIV/AIDS and mild-to-moderate PCP (defined in the protocol as [(A-a)DO₂] ≤45 mm Hg and PaO₂ ≥60 mm Hg on room air) and a randomized open-label trial comparing atovaquone 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 oral suspension and tablet formulations established the currently recommended oral 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 atovaquone 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 atovaquone (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 atovaquone 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 atovaquone and 7 (3.4%) deaths among subjects treated with TMP-SMX (P = 0.051). Of the 13 subjects with confirmed PCP and treated with atovaquone 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%) of the 49 subjects with Day 4 plasma atovaquone concentrations ≥5 mcg/mL died.

Sixty-two percent of subjects on atovaquone 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**

<table>
<thead>
<tr>
<th>Outcome of Therapy*</th>
<th>Number of Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atovaquone Tablets</td>
</tr>
<tr>
<td></td>
<td>(n = 160)</td>
</tr>
<tr>
<td>Therapy success</td>
<td>99</td>
</tr>
<tr>
<td>Therapy failure due to:</td>
<td></td>
</tr>
<tr>
<td>-Lack of response</td>
<td>28</td>
</tr>
<tr>
<td>-Adverse reaction</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>33</td>
</tr>
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</table>
Required alternate PCP therapy during trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Atovaquone (n=70)</th>
<th>Pentamidine (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy success</td>
<td>32 (57%)</td>
<td>21 (40%)</td>
</tr>
<tr>
<td>Therapy failure due to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lack of response</td>
<td>16 (29%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>- Adverse reaction</td>
<td>2 (3.6%)</td>
<td>19 (36%)</td>
</tr>
<tr>
<td>- Unevaluable</td>
<td>6 (11%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Required alternate PCP therapy during trial</td>
<td>19 (34%)</td>
<td>29 (55%)</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>11 (12.5%)</td>
<td>12 (14%)</td>
</tr>
</tbody>
</table>

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Atovaquone oral suspension, USP is a yellow homogenous suspension containing 750 mg atovaquone USP per 5 mL, supplied in:
- 5 mL unit dose cups: 42 cups (7 x 6) NDC 60687-534-78
Store at 15°C to 25°C (59°F to 77°F). Do not freeze.

DO NOT USE IF SEAL IS BROKEN.

17 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.

PACKAGING INFORMATION

American Health Packaging unit dose cups (see How Supplied section) contain drug product from Camber Pharmaceuticals, Inc. as follows:
(750 mg per 5 mL / 42 UD) NDC 60687-534-78 packaged from NDC 31722-629

Distributed by:
American Health Packaging
Columbus, OH 43217
8453478/0620F

Package/Label Display Panel – Tray

Atovaquone
Oral Suspension, USP
Rx Only
FOR INSTITUTIONAL USE ONLY

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

8453478/0620F

Atovaquone
Oral Suspension, USP
Rx only
FOR INSTITUTIONAL USE ONLY
Rx Only
NDC 60687- 534-40
Atovaquone
Oral Suspension, USP
750 mg/5 mL
Delivers 5 mL
DO NOT FREEZE.
SHAKE GENTLY BEFORE USING.
See package insert for full prescribing information and storage.
For Institutional Use Only.
American Health Packaging
Columbus, OH 43217
0453478/0620

ATOVAQUONE
atovaquone suspension

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<td>ATOVAQUONE (UNII: Y883P1Z2LT)</td>
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### Product Characteristics

| Color | yellow |
| Shape |        |
| Flavor | STRAWBERRY |

### Packaging

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<td>6 in 1 TRAY</td>
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Revised: 7/2020