本文書は３通作成し、１通は厚生労働省エイズ治療薬研究班事務局へ書留郵便で提出し、他は患者、主治医がそれぞれ保管してください。（同一薬剤の継続時は初回のみ必要です。）

（4）患者同意書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

フリガナ 申請者（主治医）氏名		病院名・〒住所	
診療科名			
職　責			
患者氏名（イニシャル）　姓［　　］. 名［　　］.		男　・　女	
カルテ番号［　　］	生年月日	年　月　日	

上記の患者さんに対して、以下の内容について十分に説明したうえ同意を得ました。

同意書

私は私の病気（　　）の治療のために、厚生労働省エイズ治療薬研究班から治療薬（　　）の提供を受けることに関して、上記の担当医師から下記の内容について説明を受け、また質問する機会も得て理解いたしましたので、この治療を受けることに同意いたします。

説明内容

1.この治療の目的と意義
2.予期される効果と副作用
3.他の治療法の有無とその内容
4.同意しない場合でも今後の治療に不利益を受けないこと。
5.同意した場合でも随時これを撤回でき今後の治療に不利益を受けないこと。
6.わからない点は、いつでも質問し説明を受けられること。
7.プライバシーは厳重に守られること。

同意取得日	年　月　日			
フリガナ 患者氏名 （自署）	印	フリガナ 代諾者氏名 （自署）	印	続柄
生年月日	年　月　日			
住所		代諾者住所		

本文書は薬剤を受け取り次第、念書とともに厚生労働省エイズ治療薬研究班事務局へ郵便で提出してください。

（5）薬剤受領書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

薬　剤　名	数　量

上記の薬剤を確かに受領いたしました。

フリガナ 受領者（主治医） 氏名	印
診療科名	
職　責	
病院名・〒住所	

班長連絡先　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
〒160-0023 東京都新宿区西新宿 6-7-1
TEL03-3342-6111 EXT5086　FAX 03-3340-5448
事務局連絡先　パレクセル・インターナショナル株式会社
エイズ治療薬研究班事務局担当者
〒104-0033 東京都中央区新川 1-17-21　茅場町ファーストビル 6F
TEL：03-3537-5902　FAX：03-3552-0452

（6）臨床研究使用成績調査票（1）

臨床経過と検査値の推移を各ポイント記載する毎に本表のコピーも事務局へお送り下さい

主治医氏名	印	病院名・〒住所	
診療科名			
職　責			
電話番号	（　）	FAX番号	（　）
E－Mail			

患者氏名（イニシャル）　姓［　］．名［　］．	男・女	身長　cm
カルテ番号［　］	生年月日	年　月　日
合併症　1．無し 2．慢性肝炎 3．肝硬変 4．腎障害 5．糖尿病 6．高脂血症 7．血友病 8．その他（　）		

今回使用した研究班の薬（研究班の薬剤を全てを記載して下さい。）

薬剤名	含有量・剤形	1日量と投与回数	投与期間（年/月/日）
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /

研究班の薬剤を投与中に使用した併用薬を全て記載してください。

薬剤名	剤形	1日量と投与回数	投与期間（年/月/日）
		/日　回/日	/ /　－　/ /
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		/日　回/日	/ /　－　/ /
		/日　回/日	/ /　－　/ /

(7) 臨床研究使用成績調査票 (2)

臨床経過と臨床検査値の推移　　ポイント毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　　責			
患者氏名（イニシャル）　姓 [　　]. 名 [　　].		男 ・ 女	
カルテ番号 [　　]		生年月日	年　　月　　日

検査ポイント	投与前	開始後　　ヶ月	開始後　　ヶ月	開始後　　ヶ月
検査日	年　月　日	年　月　日	年　月　日	年　月　日
外来・入院	外来・入院	外来・入院	外来・入院	外来・入院
体重	Kg	Kg	Kg	Kg
体温	℃	℃	℃	℃
血圧	/　mmHg	/　mmHg	/　mmHg	/　mmHg
症状の程度	3+・2+・1+・−	3+・2+・1+・−	3+・2+・1+・−	3+・2+・1+・−
CD4細胞数	/μl	/μl	/μl	/μl
HIV-RNA量	×10　/ml	×10　/ml	×10　/ml	×10　/ml
白血球数 WBC	/μl	/μl	/μl	/μl
赤血球数 RBC	/μl	/μl	/μl	/μl
Hb	g/dl	g/dl	g/dl	g/dl
Htc	%	%	%	%
血小板数	/μl	/μl	/μl	/μl
好中球%	%	%	%	%
好酸球%	%	%	%	%
好塩基球%	%	%	%	%
リンパ球%	%	%	%	%
単球%	%	%	%	%
TP	g/dl	g/dl	g/dl	g/dl
T-Bil	mg/dl	mg/dl	mg/dl	mg/dl
GOT	IU/L	IU/L	IU/L	IU/L
GPT	IU/L	IU/L	IU/L	IU/L
γGTP	IU/L	IU/L	IU/L	IU/L
BUN	mg/dl	mg/dl	mg/dl	mg/dl
クレアチニン	mg/dl	mg/dl	mg/dl	mg/dl
尿酸	mg/dl	mg/dl	mg/dl	mg/dl
総コレステロール	mg/dl	mg/dl	mg/dl	mg/dl
中性脂肪	mg/dl	mg/dl	mg/dl	mg/dl
グルコース	mg/dl	mg/dl	mg/dl	mg/dl
尿蛋白	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿糖	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿潜血反応	−・+−・+・++	−・+−・+・++	−・+−・+・++	−・+−・+・++
尿沈さ異常と内容	無・(　　)	無・(　　)	無・(　　)	無・(　　)

(8) 臨床研究使用成績調査票 (3)

その他の重要な臨床検査成績

XP，CT，MRI，シンチグラム等

検査毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	病院名・〒住所		
診療科名				
職　　責				
患者氏名（イニシャル）　姓 [　　]. 名 [　　].			男 ・ 女	
カルテ番号 [　　]		生年月日	年　　月　　日	

（9）有害事象発生報告書

年　月　日

有害事象が発生したら直ちに記入して、FAXで事務局03-3518-6014へお送り下さい。

主治医氏名	印	病院名・〒住所	
診療科名			
職　責			
患者氏名（イニシャル）　姓［　　］．名［　　］．		男・女	
カルテ番号［　　］		生年月日	年　月　日

有害事象の内容		
発生日時	年　月　日　午前・午後　時	
経過と処置		
程度（主治医判断）	軽症　・　中等度　・　重篤	
薬剤との因果関係	1.関連有り　2．関連が否定出来ない　3．関連無し　4．不明	
関連有ると思われる薬剤	薬剤名	理由

転帰報告書

転帰を判定したら直ちに記入し事務局へお送り下さい。

判定日時	年　月　日　午前・午後　時
転　帰	回復　・　軽快　・　死亡　・　後遺症
死因・後遺症	
薬剤との因果関係	1．関連有り　2．関連が否定出来ない　3．関連無し　4．不明

［別紙第２号様式］

念　　書

平成　　年　　月　　日

厚生労働大臣　殿

輸入業者（受取人）氏名（法人にあっては名称及び代表者の氏名）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿印

同住所（法人にあっては主たる事務所の所在地）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

今般、別紙輸入報告書により報告いたしました下記 医薬品は（　医師個人用　）として使用するもので、他に販売、授与するものではありません。
つきましては、本品の通関手続に関しよろしくお取り計らい願います。
上述のとおり、後日のため念書差入れます。

記

品　　名	数　　量

（この様式の大きさは日本工業規格Ａ４とすること）

念書の取扱についてのお願い

厚生労働省エイズ治療薬研究班
主任研究者(班長)　福武　勝幸

この念書は医師個人輸入の手続きにおいて厚生労働省へ必ず提出しなければならないものです。研究班の存続のために最も重要な書類ですので、遅滞なく班長へご返送いただきますようお願いいたします。

当研究班においては、厚生労働省の特別な配慮により薬剤を班長名であらかじめ輸入し通関しておりますが、本念書をご提出いただくことにより、各主治医か個人輸入したのと同等に扱うこととなり、薬事法に抵触することなく各医師へ薬剤をお届けする形で研究班が機能できる仕組みになっております。(この念書は当研究班専用のもので、一般の個人輸入の書式とは異なります。)

記載上の注意

日付欄には薬剤をお受け取りになった日付をご記入ください。輸入業者(受取人)氏名(法人にあっては名称及び代表者の氏名)の欄には、薬剤を研究班へ申請された医師の所属施設と氏名をご記入ください。また、同住所(法人にあっては主たる事務所の所在地)の欄には、医師の所属する施設の住所を御記載ください。お受け取りになった薬剤の品名と数量をご記載ください。

念書返送先

班長連絡先　東京医科大学病院　臨床検査医学科　主任教授　福武　勝幸
〒160-0023 東京都新宿区西新宿 6-7-1
TEL03-3342-6111 EXT5086　FAX 03-3340-5448

薬剤受領書返送先

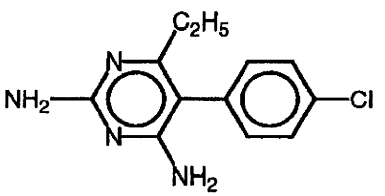
事務局連絡先　パレクセル・インターナショナル株式会社
エイズ治療薬研究班事務局担当者
〒104-0033 東京都中央区新川 1-17-21
茅場町ファーストビル 6F
TEL：03-3537-5902　FAX：03-3552-0452

DARAPRIM®
(pyrimethamine)
25-mg Scored Tablets

DESCRIPTION

DARAPRIM (pyrimethamine) is an antiparasitic compound available in tablet form for oral administration. Each scored tablet contains 25 mg pyrimethamine and the inactive ingredients corn and potato starch, lactose, and magnesium stearate.

Pyrimethamine, known chemically as 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine, has the following structural formula:



$C_{12}H_{13}ClN_4$
Mol. Wt 248.71

CLINICAL PHARMACOLOGY

Pyrimethamine is well absorbed with peak levels occurring between 2 to 6 hours following administration. It is eliminated slowly and has a plasma half-life of approximately 96 hours. Pyrimethamine is 87% bound to human plasma proteins.

Microbiology: Pyrimethamine is a folic acid antagonist and the rationale for its therapeutic action is based on the differential requirement between host and parasite for nucleic acid precursors involved in growth. This activity is highly selective against plasmodia and *Toxoplasma gondii.*

Pyrimethamine possesses blood schizonticidal and some tissue schizonticidal activity against malaria parasites of humans. However, the 4-amino-quinoline compounds are more effective against the erythrocytic schizonts. It does not destroy gametocytes, but arrests sporogony in the mosquito.

The action of pyrimethamine against *Toxoplasma gondii* is greatly enhanced when used in conjunction with sulfonamides. This was demonstrated by Eyles and Coleman[1] in the treatment of experimental toxoplasmosis in the mouse. Jacobs et al[2] demonstrated that combination of the 2 drugs effectively prevented the development of severe uveitis in most rabbits following the inoculation of the anterior chamber of the eye with toxoplasma.

INDICATIONS AND USAGE

Treatment of Toxoplasmosis: DARAPRIM is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.

Treatment of Acute Malaria: DARAPRIM is also indicated for the treatment of acute malaria. It should not be used alone to treat acute malaria. Fast-acting schizonticides such as chloroquine or quinine are indicated and preferable for the treatment of acute malaria. However, conjoint use of DARAPRIM with a sulfonamide (e.g., sulfadoxine) will initiate transmission control and suppression of susceptible strains of plasmodia.

Chemoprophylaxis of Malaria: DARAPRIM is indicated for the chemoprophylaxis of malaria due to susceptible strains of plasmodia. However, resistance to pyrimethamine is prevalent worldwide. It is not suitable as a prophylactic agent for travelers to most areas.

CONTRAINDICATIONS

Use of DARAPRIM is contraindicated in patients with known hypersensitivity to pyrimethamine or to any component of the formulation. Use of the drug is also contraindicated in patients with documented megaloblastic anemia due to folate deficiency.

WARNINGS

The dosage of pyrimethamine required for the treatment of toxoplasmosis is 10 to 20 times the recommended antimalaria dosage and approaches the toxic level. If signs of folate deficiency develop (see ADVERSE REACTIONS), reduce the dosage or discontinue the drug according to the response of the patient. Folinic acid (leucovorin) should be administered in a dosage of 5 to 15 mg daily (orally, IV, or IM) until normal hematopoiesis is restored.

Data in 2 humans indicate that pyrimethamine may be carcinogenic: a 51-year-old female who developed chronic granulocytic leukemia after taking pyrimethamine for 2 years for toxoplasmosis,[3] and a 56-year-old patient who developed reticulum cell sarcoma after 14 months of pyrimethamine for toxoplasmosis.[4]

Pyrimethamine has been reported to produce a significant increase in the number of lung tumors in mice when given intraperitoneally at doses of 25 mg/kg.[5]

DARAPRIM should be kept out of the reach of infants and children as they are extremely susceptible to adverse effects from an overdose. Deaths in pediatric patients have been reported after accidental ingestion.

PRECAUTIONS

General: The recommended dosage for chemoprophylaxis of malaria should not be exceeded. A small "starting" dose for toxoplasmosis is recommended in patients with convulsive disorders to avoid the potential nervous system toxicity of pyrimethamine. DARAPRIM should be used with caution in patients with impaired renal or hepatic function or in patients with possible folate deficiency, such as individuals with malabsorption syndrome, alcoholism, or pregnancy, and those receiving therapy, such as phenytoin, affecting folate levels (see Pregnancy subsection).

Information for Patients: Patients should be warned that at the first appearance of a skin rash they should stop use of DARAPRIM and seek medical attention immediately. Patients should also be warned that the appearance of sore throat, pallor, purpura, or glossitis may be early indications of serious disorders which require treatment with DARAPRIM to be stopped and medical treatment to be sought.

Women of childbearing potential who are taking DARAPRIM should be warned against becoming pregnant. Patients should be warned to keep DARAPRIM out of the reach of children. Patients should be advised not to exceed recommended doses. Patients should be warned that if anorexia and vomiting occur, they may be minimized by taking the drug with meals.

Concurrent administration of folinic acid is strongly recommended when used for the treatment of toxoplasmosis in all patients.

Laboratory Tests: In patients receiving high dosage, as for the treatment of toxoplasmosis, semiweekly blood counts, including platelet counts, should be performed.

Drug Interactions: Pyrimethamine may be used with sulfonamides, quinine and other antimalarials, and with other antibiotics. However, the concomitant use of other antifolic drugs or agents associated with myelosuppression including sulfonamides or trimethoprim-sulfamethoxazole combinations, proguanil, zidovudine, or cytostatic agents (e.g., methotrexate), while the patient is receiving pyrimethamine, may increase the risk of bone marrow suppression. If signs of folate deficiency develop, pyrimethamine should be discontinued. Folinic acid (leucovorin) should be administered until normal hematopoiesis is restored (see WARNINGS). Mild hepatotoxicity has been reported in some patients when lorazepam and pyrimethamine were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section for information on carcinogenesis.

Mutagenesis: Pyrimethamine has been shown to be nonmutagenic in the following in vitro assays: the Ames point mutation assay, the Rec assay, and the *E. coli* WP2 assay. It was positive in the L5178Y/TK +/- mouse lymphoma assay in the absence of exogenous metabolic activation.[6] Human blood lymphocytes cultured in vitro had structural chromosome aberrations induced by pyrimethamine.

In vivo, chromosomes analyzed from the bone marrow of rats dosed with pyrimethamine showed an increased number of structural and numerical aberrations.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Pyrimethamine has been shown to be teratogenic in rats when given in oral doses 7 times the human dose for chemoprophylaxis of malaria or 2.5 times the human dose for treatment of toxoplasmosis. At these doses in rats, there was a significant increase in abnormalities such as cleft palate, brachygnathia, oligodactyly, and microphthalmia. Pyrimethamine has also been shown to produce terata such as meningocele in hamsters and cleft palate in miniature pigs when given in oral doses 170 and 5 times the human dose, respectively, for chemoprophylaxis of malaria or for treatment of toxoplasmosis.

There are no adequate and well-controlled studies in pregnant women. DARAPRIM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Concurrent administration of folinic acid is strongly recommended when used for the treatment of toxoplasmosis during pregnancy.

Nursing Mothers: Pyrimethamine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pyrimethamine and from concurrent use of a sulfonamide with DARAPRIM for treatment of some patients with toxoplasmosis, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS and PRECAUTIONS: Pregnancy).

Pediatric Use: See DOSAGE AND ADMINISTRATION section.

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

ADVERSE REACTIONS

Hypersensitivity reactions, occasionally severe (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and anaphylaxis), and hyperphenylalaninemia, can occur particularly when pyrimethamine is administered concomitantly with a sulfonamide. Consult the complete prescribing information for the relevant sulfonamide for sulfonamide-associated adverse events. With doses of pyrimethamine used for the treatment of toxoplasmosis, anorexia and vomiting may occur. Vomiting may be minimized by giving the medication with meals; it usually disappears promptly upon reduction of dosage. Doses used in toxoplasmosis may produce megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia, atrophic glossitis, hematuria, and disorders of cardiac rhythm. Hematologic effects, however, may also occur at low doses in certain individuals (see PRECAUTIONS: General).

Pulmonary eosinophilia has been reported rarely.

OVERDOSAGE

Following the ingestion of 300 mg or more of pyrimethamine, gastrointestinal and/or central nervous system signs may be present, including convulsions. The initial symptoms are usually gastrointestinal and may include abdominal pain, nausea, severe and repeated vomiting, possibly including hematemesis. Central nervous system toxicity may be manifest by initial excitability, generalized and prolonged convulsions which may be followed by respiratory depression, circulatory collapse, and death within a few hours. Neurological symptoms appear rapidly (30 minutes to 2 hours after drug ingestion), suggesting that in gross overdosage pyrimethamine has a direct toxic effect on the central nervous system.

The fatal dose is variable, with the smallest reported fatal single dose being 375 mg. There are, however, reports of pediatric patients who have recovered after taking 375 to 625 mg.

There is no specific antidote to acute pyrimethamine poisoning. In the event of overdosage, symptomatic and supportive measures should be employed. Gastric lavage is recommended and

is effective if carried out very soon after drug ingestion. Parenteral diazepam may be used to control convulsions. Folinic acid should also be administered within 2 hours of drug ingestion to be most effective in counteracting the effects on the hematopoietic system (see WARNINGS). Due to the long half-life of pyrimethamine, daily monitoring of peripheral blood counts is recommended for up to several weeks after the overdose until normal hematologic values are restored.

DOSAGE AND ADMINISTRATION

For Treatment of Toxoplasmosis: The dosage of DARAPRIM for the treatment of toxoplasmosis must be carefully adjusted so as to provide maximum therapeutic effect and a minimum of side effects. At the dosage required, there is a marked variation in the tolerance to the drug. Young patients may tolerate higher doses than older individuals. Concurrent administration of folinic acid is strongly recommended in all patients.

The adult *starting* dose is 50 to 75 mg of the drug daily, together with 1 to 4 g daily of a sulfonamide of the sulfapyrimidine type, e.g., sulfadoxine. This dosage is ordinarily continued for 1 to 3 weeks, depending on the response of the patient and tolerance to therapy. The dosage may then be reduced to about one half that previously given for each drug and continued for an additional 4 to 5 weeks.

The pediatric dosage of DARAPRIM is 1 mg/kg/day divided into 2 equal daily doses; after 2 to 4 days this dose may be reduced to one half and continued for approximately 1 month. The usual pediatric sulfonamide dosage is used in conjunction with DARAPRIM.

For Treatment of Acute Malaria: DARAPRIM is NOT recommended alone in the treatment of acute malaria. Fast-acting schizonticides, such as chloroquine or quinine, are indicated for treatment of acute malaria. However, DARAPRIM at a dosage of 25 mg daily for 2 days with a sulfonamide will initiate transmission control and suppression of non-falciparum malaria. DARAPRIM is only recommended for patients infected in areas where susceptible plasmodia exist. Should circumstances arise wherein DARAPRIM must be used alone in semi-immune persons, the adult dosage for acute malaria is 50 mg for 2 days; children 4 through 10 years old may be given 25 mg daily for 2 days. In any event, clinical cure should be followed by the once-weekly regimen described below for chemoprophylaxis. Regimens which include suppression should be extended through any characteristic periods of early recrudescence and late relapse, i.e., for at least 10 weeks in each case.

For Chemoprophylaxis of Malaria:

Adults and pediatric patients over 10 years — 25 mg (1 tablet) once weekly
Children 4 through 10 years — 12.5 mg (1/2 tablet) once weekly
Infants and children under 4 years — 6.25 mg (1/4 tablet) once weekly

HOW SUPPLIED

White, scored tablets containing 25 mg pyrimethamine, imprinted with "DARAPRIM" and "A3A" in bottles of 100 (NDC 0173-0201-55).

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

REFERENCES

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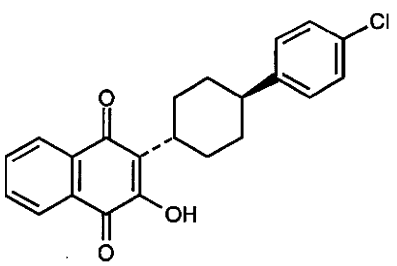
MEPRON®

(atovaquone)

Suspension

DESCRIPTION

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



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

MICROBIOLOGY

Mechanism of Action: Atovaquone is a hydroxy-1,4-naphthoquinone, an analog of ubiquinone, with antipneumocystis activity. The mechanism of action against *Pneumocystis carinii* has not been fully elucidated. In *Plasmodium* species, the site of action appears to be the cytochrome bc_1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain

via ubiquinone. Inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis.

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

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

CLINICAL PHARMACOLOGY

Pharmacokinetics: *Absorption*: Atovaquone is a highly lipophilic compound with low aqueous solubility. The bioavailability of atovaquone is highly dependent on formulation and diet. The suspension formulation provides an approximately 2-fold increase in atovaquone bioavailability in the fasting or fed state compared to the previously marketed tablet formulation. The absolute bioavailability of a 750-mg dose of MEPRON Suspension administered under fed conditions in 9 HIV-infected (CD4 >100 cells/mm^3) volunteers was 47% ± 15%. In the same study, the bioavailability of a 750-mg dose of the previously marketed tablet formulation was 23% ± 11%.

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

plasma atovaquone concentration (C_{max}) was 15.1 ± 6.1 and 8.8 ± 3.7 mcg/mL when atovaquone was administered with food and under fasting conditions, respectively.

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

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

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

Special Populations: ***Pediatrics:*** In a study of MEPRON Suspension in 27 HIV-infected, asymptomatic infants and children between 1 month and 13 years of age, the pharmacokinetics of atovaquone were age dependent. These patients were dosed once daily with food for 12 days. The

average steady-state plasma atovaquone concentrations in the 24 patients with available concentration data are shown in Table 1.

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

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)	_____

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

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

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

Trimethoprim/Sulfamethoxazole (TMP-SMX): The possible interaction between atovaquone and TMP-SMX was evaluated in 6 HIV-infected adult volunteers as part of a larger multiple-dose, dose-escalation, and chronic dosing study of MEPRON Suspension. In this crossover study, MEPRON Suspension 500 mg once daily, or TMP-SMX tablets (160 mg trimethoprim and 800 mg sulfamethoxazole) twice daily, or the combination were administered with food to achieve

steady state. No difference was observed in the average steady-state plasma atovaquone concentration after coadministration with TMP-SMX. Coadministration of MEPRON with TMP-SMX resulted in a 17% and 8% decrease in average steady-state concentrations of trimethoprim and sulfamethoxazole in plasma, respectively. This effect is minor and would not be expected to produce clinically significant events.

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

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

Table 2. Relationship Between Plasma Atovaquone Concentration and Successful Treatment

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

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

† Based on logistic regression analysis.

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

INDICATIONS AND USAGE

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

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