CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020500/S005

CHEMISTRY REVIEW(S)

HFD-590 Atkins

JUL 21 1998

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION: HFD-590	2. NDA NUMBER: 20-500

3. NAME AND ADDRESS OF APPLICANT: *(City and State)*
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

4. AF NUMBER:

5. SUPPLEMENT(S):

NUMBER(S)	DATE(S)
SCP-004	January 21, 1998

6. NAME OF DRUG:
MEPRON® (atovaquone) Suspension

7. NONPROPRIETARY NAME:
Atovaquone

8. SUPPLEMENT(S) PROVIDES FOR:
Introduction of 5 and 10 mL unit dose sachet to be packaged at

9. AMENDMENTS/REPORTS:
February 23, 1998
July 14, 1998

10. PHARMACOLOGICAL CATEGORY:
Antiprotozoal

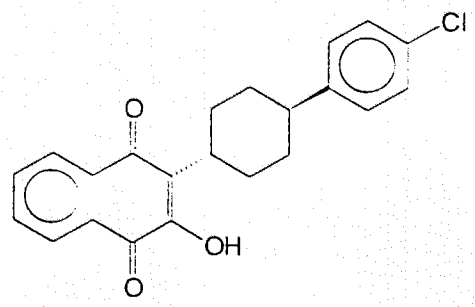
11. HOW DISPENSED:
[X] Rx [ ]OTC

12. RELATED IND/NDA/DMF(S):
DMF
DMF

13. DOSAGE FORM(S):
Oral suspension

14. POTENCY(IES):
750 mg/5mL (150 mg/mL)

15. CHEMICAL NAME AND STRUCTURE:
trans-2-[4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone



16. MEMORANDA:

17. COMMENTS:

18. CONCLUSIONS AND RECOMMENDATIONS: It is acceptable to substitute content uniformity for fill volume and sedimentation for this packaging configuration. Sedimentation is more appropriately applied to multiple-use containers. The product appears to be stable in this packaging configuration. Although six months of stability data would not ordinarily support an 18 month shelf life, it is acceptable in this case based on the supporting data in similar packaging. The sponsor was asked to provide data concerning the amount of drug recovered from the sachet by the average patient. It is apparent that they do not have such information. Appropriate directions for use should be provided so that the patient receives the proper dosage. The site inspections are complete and all have been rated as acceptable by OC. This supplement is approvable. The applicant will need to provide appropriate directions for use on the unit dose sachet.

19. REVIEWER: NAME	SIGNATURE	DATE COMPLETED
Gene W. Holbert, Ph.D.	/S/	7-21-98

20. CONCURRENCE: /S/ 7/21/98

DISTRIBUTION:						
	X	Original: NDA 20-500	X	HFD-590: NSchmuff	X	HFD-590: BAtkins
	X	Division File HFD-590	X	HFD-590: GHolbert	X	HFD-830: CChen

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020500/S005

MICROBIOLOGY REVIEW(S)

DRAFT

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-500

REVIEWER	: Shukal Bala
CORRESPONDENCE DATE	: 03-05-98
CDER RECEIPT DATE	: 03-06-98
REVIEW ASSIGN DATE	: 03-17-98
REVIEW COMPLETE DATE	: 09-09-98

SPONSOR: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park
NC 27709

SUBMISSION REVIEWED: SE1-005

DRUG CATEGORY: Anti-protozoal

INDICATION: Prevention of *Pneumocystis carinii* pneumonia

DOSAGE FORM: Suspension for oral administration

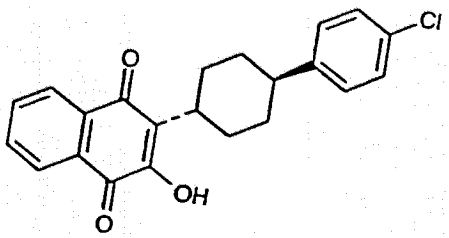
PRODUCT NAMES:

a. **PROPRIETARY:** Mepron

b. **NONPROPRIETARY:** Atovaquone (566C8O)

c. **CHEMICAL:** trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-l,4-naphthoquinone

STRUCTURAL FORMULA:



Molecular weight: 366.84
Empirical formula: $C_{22}H_{19}ClO_3$

SUPPORTING DOCUMENTS: IND
NDA # 20-259

BACKGROUND:

The subject of this NDA is Mepron, approved for the treatment of mild to moderate *Pneumocystis carinii* Pneumonitis (PCP) in subjects who are intolerant to trimethoprim-sulfamethoxazole (TMP-SMX). In this NDA supplement the sponsor has request approval for the use of Mepron (1500 mg/day) for prevention of PCP in patients who are intolerant to TMP-SMX.

SUMMARY:

The preclinical studies demonstrating activity of atovaquone against *Pneumocystis* were reviewed earlier (for details see the microbiology review of NDA # 20-259, dated 10/30/92). No additional preclinical microbiology studies have been provided in this submission. A brief summary of the activity of atovaquone against *Pneumocystis* is as follows:

The 50% inhibitory concentrations of atovaquone effective *in vitro* against the *P. carinii* trophozoite and/or cyst stage have been shown to be in the range of 0.1 - 3 ug/ml (0.3 to 7.5 uM). Although these *in vitro* studies were performed in the presence of 10 - 20% fetal bovine serum, it is important to recognize that atovaquone is a protein binding compound and therefore the concentrations shown to be effective *in vitro* may not be relevant to the *in vivo* situation. Nevertheless, these studies do suggest a direct anti-pneumocystis effect of atovaquone on the trophozoite and/or cyst stage of the parasite.

Atovaquone has been shown to be effective as a therapeutic and prophylactic agent in the immunosuppressed rat model. Therapeutic studies indicate that treatment with atovaquone (100 mg/kg) after 4 or 6 weeks of immunosuppression was effective in curing *P. carinii* pneumonitis in 89% of rats. At a dose of 100 mg/kg atovaquone was also effective in preventing the development of *P. carinii* pneumonitis in about 95% of the test animals. Lower doses of atovaquone (10-50 mg/kg) were less effective in preventing the infection. Concentrations of atovaquone in plasma plateau between the dose of 50 to 100 mg/kg. Plasma concentrations of atovaquone at the end of therapy were measured and found to correlate with the anti-pneumocystis activity. At the end of the study, animals remaining negative for *P. carinii* pneumonitis had an atovaquone plasma concentration > 60 (range 60-94) ug/ml.

Studies evaluating the potential for drug interactions between AZT and atovaquone suggest no adverse effects of atovaquone on the anti-retroviral activity of AZT. It has also been shown that at the doses tested AZT had no adverse effect on the anti-pneumocystis activity of atovaquone when administered as a prophylactic agent.

Mechanism of Action:

The mechanism of action of atovaquone has been investigated using mitochondrial proteins from *Plasmodium* species. The site of action appears to be the bc_1 complex. The mechanism by which atovaquone inhibits the activity of *P. carinii* was not evaluated. Although the sponsor was requested to investigate the mechanism by which atovaquone exhibits activity against *P. carinii* (see NDA # 20-259 microbiology review dated 10/30/92 and memorandum of telephone facsimile correspondence dated 11/12/92) no additional studies have been provided in this submission.

A study by Ittarat *et al.*, 1995 (Antimicrob. Agents Chemother. 39: 325) shows that atovaquone inhibits the activity of dihydroorotate dehydrogenase (DHOD), derived from *P. carinii* crude homogenate, by about 76% at a concentration of 100 μM (Table 1). These values are much higher than the concentrations required to inhibit the growth of *P. carinii in vitro* (minimum inhibitory concentration (MIC) values of 0.3 to 7.5 μM). Also, the concentration of atovaquone required to inhibit the enzyme activity of DHOD derived from *Plasmodium* is much lower (about 1 nM) than that shown for *P. carinii* thereby suggesting that *Plasmodium* sp. may be more sensitive to the drug. Although these studies indicate that atovaquone inhibits the activity of DHOD, a key enzyme for conversion of dihydroorotate to orotate which in turn is important for *de novo* pyrimidine biosynthesis and is also linked to the mitochondrial electron transport chain (bc_1 mitochondrial enzymes), the possibility of another drug target cannot be ruled out.

TABLE 1. Effects of chemotherapeutic agents on *P. carinii* DHOD activity

Inhibitor	Concn (μM)	% Inhibition (no.)[a]
Atovaquone	1	0.7 ± 1.0 (2)
	10	36.5 ± 6.2 (4)
	100	76.3 ± 5.2 (4)
Pentamidine	10	−15.7 ± 2.3 (2)
5H6DP	10	−3.9 ± 10.8 (2)
	100	−11.9 ± 17.5 (2)

[a] Values are means ± standard deviations.

Resistance:

Development of resistance by microorganisms after prolonged drug exposure is a likely event to occur. In the original NDA submission the sponsor stated that strains of *Plasmodium* were isolated *in vitro* and *in vivo* and the mechanism of resistance involved changes in the DHOD enzyme. Studies related to selection of strains of *Toxoplasma gondii* generated under drug pressure were in

progress. However, the details of the studies were not submitted for review. The sponsor was requested to provide the methodologies used and the data generated showing the development of resistance in *Plasmodium* and *Toxoplasma* species for future consideration when updating the microbiology section of the label (NDA # 20-259 review dated 10/30/92). Although the sponsor has not requested to update the microbiology section of the label and has not provided any additional information, it is important to consider the potential for development of resistance in patients who are at risk of developing PCP and are undergoing prophylaxis therapy.

Studies reported in the literature show that *P. falciparum* (a protozoan) can develop drug resistance *in vitro*. Studies also show treatment of patients with malaria with atovaquone alone may lead to an initial clinical and parasitological cure followed by relapse. For example, a study by Looareesuwan *et al.*, 1996 (Am. J. Trop. Med. Hyg. 54 (1): 62-66) shows that about one-third of the patients with falciparum malaria treated with atovaquone failed therapy despite an initial clinical and parasitological response. Paired isolates from these subjects demonstrated a 1499 times increase in 50% inhibitory concentration (IC_{50}) values after therapy (from 3.3 ng/ml to 4947 ng/ml).

Toxoplasma gondii (also a protozoon) mutants with resistance to atovaquone have also been generated under drug pressure (Pfefferkorn *et al.*, 1993, J. Parasitol. 79: 559-564).

A recent study by Walker *et al.*, 1998 (J. Inf. Dis. in press) in 10 subjects on PCP prophylaxis with atovaquone showed that 4 patients failed prophylaxis. The period of prophylaxis varied from 2 to 15 months. All 4 patients who failed atovaquone prophylaxis showed changes in the nucleotide sequence in the cytochrome b region (Table 2). However, the changes in amino acid sequence were observed in only 2 of the 4 patients (Table 2). It would have been worthwhile to correlate changes in nucleotide and amino acid sequences with *in vitro* susceptibility to the drug. The authors have stated that due to the limitations of culture methods for clinical isolates (*P. carinii* sp. *hominis*) the *in vitro* susceptibility of the *P. carinii* was not tested. The reports of maintenance *of in vitro* culture of *P. carinii* derived from clinical subjects with PCP are not very common. However, reports do exist. For example, in a study by Cirioni, O. *et al.*, 1997 (J. Antimicrob. Chemother. 39: 45) the *in vitro* susceptibility of 5 clinical isolates to atovaquone and other drugs was tested using the A549 (human lung carcinoma) cell line. In the absence of *in vitro* susceptibility data, the changes in nucleotide and amino acid sequences are only suggestive of a potential for development of drug resistance in samples from patients who fail drug therapy. It would also be worthwhile to do genotypic and phenotypic analyses of strains obtained from patients with PCP before initiation of treatment and at different time intervals after therapy.

Table 2. Nucleotide substitutions in cytochrome b from atovaquone-treated patients.

		Nucleotide				
	Patient	279	362	369	516	1032
—	wild type	C	C	G	C	T
+(7)	UM33	T (Ile→Ile)	C	G	T (Ile→Ile)	T
—	D262	C	C	G	C	A (Gly→Gly)
+(15)	UC1	C	T (Thr→Ile)	G	C	T
+(2)	UC2	T (Ile→Ile)	C	T (Leu→Phe)	T (Ile→Ile)	T

SPONSOR'S PROPOSED LABEL

No changes have been made in the Microbiology section of the label.

CONCLUSIONS:

Atovaquone has been shown to be active against *P. carinii in vitro* and *in vivo*. The sponsor has proposed no changes in the Microbiology section of the revised label.

Based on studies available in the literature it appears that a potential for development of resistance exists upon treatment with atovaquone in patients with malaria or PCP. Although the study in *P. carinii* is based on a very small number of samples and no correlation has been established between the observed changes in genotype and phenotype, nevertheless the study does suggest a potential for development of resistance in individuals who fail atovaquone prophylaxis. Therefore, the sponsor should be requested to conduct studies to further investigate the genotypic and amino acid changes in paired isolates collected prior to initiation of treatment and at different time intervals after discontinuation of treatment. Attempts should also be made to correlate such changes with *in vitro* susceptibility and clinical outcome. It is also recommended that the potential for development of resistance be discussed in the microbiology section of the label.

Proposed change in the microbiology section of the label:

RECOMMENDATIONS:

This NDA is approvable with respect to microbiology pending an acceptable version of the label. If additional (post-marketing) clinical trials are planned the sponsor should consider the following:

1. Please evaluate the potential for development of resistance using samples collected from patients before and after treatment with Mepron. Attempts should also be made to correlate such changes with *in vitro* susceptibility and clinical outcome.

APPEARS THIS WAY
ON ORIGINAL

/S/
Shukal Bala
Microbiologist, HFD-590

CONCURRENCES:
HFD-590/Deputy Dir. _____ Signature _____ Date
HFD-590/MicroTL /S/ Signature 9/10/98 Date
CC:
HFD-590/Original NDA # 20-500
HFD-590/Division File
HFD-590/MO
HFD-590/Pharm
HFD-590/Chem
HFD-590/Micro TL
HFD-590/Review Micro
HFD-590/CSO/AtkinsB

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020500/S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-500 (SE1-005)
Atovaquone Suspension
Mepron®
Glaxo Wellcome Inc

Submission Dates: March 5,1998; May 12, 1998
Review Date: December 16, 1998
Reviewers: Kellie S. Reynolds, Pharm.D.
Roopa Viraraghavan, M.D.
Type of submission: Efficacy Supplement

IV. Study ACTG 227 - Pharmacokinetics of Atovaquone in Pediatric Patients Treated with Atovaquone Suspension

1. PK Background of Atovaquone

Note: For more details on atovaquone pharmacokinetics, see the Biopharmaceutics/ Pharmacokinetics Reviews for NDA 20-259 (atovaquone tablet) and NDA 20-500 (atovaquone suspension). Both reviews were written by Dr. John A. Lazor.

Introduction

Atovaquone suspension is approved for the acute oral treatment of mild-to-moderate *Pneumocystis carinii* pneumonia (PCP) in patients who are intolerant to trimethoprim-sulfamethoxazole (TMP-SMX). In the current efficacy supplement, the applicant is seeking approval of atovaquone suspension for the prevention of PCP in patients who are intolerant to TMP-SMX. This supplement also includes atovaquone pharmacokinetic information for 24 HIV infected pediatric patients (9 patients, in addition to the 15 patients described previously in NDA 20-500).

Previous studies with atovaquone tablets (NDA 20-259) in adults revealed that there is a relationship between the average steady-state concentration ($C_{avg,ss}$) of atovaquone in plasma and the probability of being treated successfully for PCP. Adult PCP patients with a $C_{avg,ss}$ greater than 15 µg/mL have a 95% or better chance of being treated successfully. A similar relationship between atovaquone concentrations and successful treatment was observed in NDA 20-500 (atovaquone suspension). Based on the results from the pivotal efficacy studies with the tablet, the goal of the new suspension formulation was to achieve average plasma atovaquone concentrations of 15-25 µg/mL. Across several studies submitted in NDA 20-500, mean ± SD atovaquone $C_{avg,ss}$ ranged from 21.0 ± 4.9 to 21.8 ± 9.6 µg/mL for patients receiving 750 mg twice daily.

A target concentration of atovaquone has not yet been established for PCP prophylaxis, but the proposed total daily dose of atovaquone suspension in adults is the same for prophylaxis (1500 mg once daily) as for treatment (750 mg twice daily).

Medical Officer's Comments: *Based on the above information, the Applicant postulates that the daily dose of atovaquone suspension should also be the same for prophylaxis and treatment of PCP in children.*

Study 115 (NDA 20-500) Atovaquone Suspension: Relative Bioavailability/Food Effect

Limited clinical trial experience has been obtained with the suspension formulation of atovaquone. The suspension has greater oral bioavailability than the tablet. In a single-dose, cross-over pharmacokinetic study of the tablet and suspension in healthy volunteers (Study 115), single doses of 750 mg atovaquone tablets (3 tablets) or 750 mg atovaquone suspension (5 mL) were administered under fasting and fed (23 gram fat breakfast) conditions. The 23 gram fat breakfast increased AUC 2.6 ± 1.0 fold and Cmax 3.6 ± 1.0 fold, when atovaquone suspension was administered. Similar increases in AUC and Cmax were observed for atovaquone tablets, fed vs. fasting. Following administration of the suspension under fasting conditions, atovaquone AUC and Cmax were 2.3 ± 0.8 and 2.4 ± 0.9 fold higher, respectively, than following administration of the tablet formulation under fasting conditions. Following administration of the suspension under fed conditions, atovaquone AUC and Cmax were 2.2 ± 0.6 and 2.3 ± 0.7 fold higher, respectively, than following administration of the tablet formulation under fed conditions.

Medical Officer's/Clinical Pharmacology Reviewer's Comment: *This study demonstrated that the suspension formulation has substantially greater oral bioavailability than the tablet formulation. The effect of food on atovaquone plasma concentrations is similar for the suspension and tablet formulations.*

The results from this study are consistent with the results from Study 301 (NDA 20-500). The absolute bioavailability of the tablet formulation was 23 ± 11%. The absolute bioavailability of the suspension formulation was 47 ± 15%.

Cross Study Comparison of Dosage Regimens (NDA 20-500)

The following results were obtained across studies when atovaquone suspension was administered with food by various dosage regimens for 14-21 days.

Study	Regimen	Subjects	N	Cmax (μg/mL)	Cavg (μg/mL)	Cmin (μg/mL)
201	500 mg QD	HIV+, $CD_4 \leq 200$	19	15.1 ± 6.1	11.7 ± 4.8	9.1 ± 3.8
201	750 mg QD	HIV+, $CD_4 \leq 200$	9	15.3 ± 7.6	12.5 ± 5.8	9.3 ± 4.2
201	1000 mg QD	HIV+, $CD_4 \leq 200$	14	16.8 ± 6.4	13.5 ± 5.1	10.1 ± 4.2
202		HIV+, PCP	19	not determined	10.8 ± 6.1	not determined
104		HIV+, $CD_4 < 200$	5	24.2 ± 12.1	22.9 ± 12.0	15.7 ± 6.6
202	1500 mg QD	HIV+, PCP	5	not determined	22.6 ± 10.0	not determined
201	750 mg BID	HIV+, $CD_4 \leq 200$	5	24.0 ± 5.7	21.0 ± 4.9	16.7 ± 46
202		HIV+, PCP	16	not determined	21.6 ± 10.7	not determined
104	1000 mg BID	HIV+, $CD_4 < 200$	3	41.3 ± 8.7	32.3 ± 6.2	25.6 ± 4.7
202		HIV+, PCP	9	not determined	25.7 ± 8.1	not determined

2. Study 115-213 – Relationship Between Plasma Atovaquone Concentration and Efficacy (Prophylaxis of PCP)

Study 115-213 is one of the two clinical trials conducted to evaluate the efficacy of atovaquone suspension for the prevention of PCP in patients who are intolerant to TMP-SMX. Patients were randomized to one of three treatments: atovaquone suspension 750 mg once daily (n = 188), atovaquone suspension 1500 mg once daily (n = 175), or aerosolized pentamidine 300 mg once monthly (n = 187). In study 115-213, steady-state plasma atovaquone concentration results were available for 102 of 363 (28%) patients in the atovaquone treatment groups. Patients were scheduled to have pre-dose concentrations determined at weeks 4 and 12 and every 12 weeks thereafter. The steady-state pre-dose concentration (Ctrough,ss) values are summarized in the following table.

Patients	Statistic	Ctrough,ss values for each treatment (µg/mL)	
		750 mg atovaquone	1500 mg atovaquone
All patients	N (patients with conc. data/ total) mean ± sd range	51/188 12.97 ± 8.59 1.10 – 39.30	51/175 16.12 ± 7.52 0.61 – 32.96
Patients with PCP event	N (patients with conc. data/ total) mean ± sd range	14/47 10.83 ± 8.59 3.39 – 32.45	14/39 15.65 ± 7.90 0.61 – 32.96
Patients with no PCP event	N (patients with conc. data/ total) mean ± sd range	37/141 13.78 ± 8.60 1.10 – 39.3	37/136 16.30 ± 7.47 5.39 – 32.91

Clinical Pharmacology Reviewer's Comment: *Based on the data in the above table, there was very little difference in atovaquone plasma concentrations between the two treatment groups. However, these data, in combination with the data submitted with NDA 20-500, indicate that patients receiving atovaquone 1500 mg once daily are more likely to have Cavg,ss greater than 15 µg/mL than patients receiving 750 mg once daily. Cavg,ss values are higher than Ctrough,ss values.*

These results must be viewed with caution for several reasons. Plasma samples were scheduled to be obtained at infrequent intervals (at weeks 4 and 12 and every 12 weeks thereafter). Results are available for less than one-third of patients in the study; for many of these patients, results are available for only a minority of their scheduled samples. Very few patients had samples obtained at or shortly before PCP was diagnosed.

Atovaquone Dosage for PCP Prophylaxis

The optimal atovaquone plasma concentration for PCP prophylaxis is unknown; however, data from PCP treatment studies have demonstrated a relationship between steady-state plasma concentrations and successful therapy with atovaquone. The mean steady-state plasma concentration of atovaquone achieved in patients enrolled in the trimethoprim-sulfamethoxazole comparative trial (NDA 20-259, atovaquone tablets)

was 14.0 ± 6.9 µg/mL. The variability of plasma concentrations among patients in this trial was substantial, with a 10-fold difference in steady-state plasma concentrations observed among patients. A strong relationship was demonstrated between the effectiveness of atovaquone in curing PCP and the steady-state plasma concentrations, with a concentration of 13.9 µg/mL (95% CI = 11.9, 18.1 µg/mL) predicted to result in a 90% probability of successful treatment.[i]

3. ACTG 227 (Pediatric Pharmacokinetic Study)

Protocol Description

ACTG 227 was a Phase I, multiple dose, dose-escalation, safety, tolerability, and pharmacokinetic study of MEPRON (atovaquone) Suspension in HIV-infected infants and children, conducted under IND _____ A manuscript describing this study has been accepted for publication.[ii]

Medical Officer's Note: *This was a multi-center study. None of the investigators are on the FDA's August 22, 1997 list for disqualified or restricted principal investigators.*

The objective of the present study was to identify the dose of MEPRON Suspension that was capable of producing $C_{avg,ss}$ >15µg/mL in infants and children. Subjects were stratified by age (1 to 3 months, 3 to 24 months, and 2 to 12 years) and MEPRON Suspension was administered at a dose of 10, 30, or 45 mg/kg body weight once daily for 12 days. Because atovaquone absorption is enhanced by food, subjects were to take their doses with food or formula. Concentrations of atovaquone in plasma were obtained before dosing on days 1, 3, 5, 7, 9, and 12. After the last dose of atovaquone (day 12), concentrations were determined at the following times: hours 2, 4, 6, 8, 12, 24, 72, 144, 216, and 288. Steady-state pharmacokinetic parameters were estimated from plasma concentrations obtained on the last day of dosing, using non-compartmental methods.

Results:

MEPRON Suspension was well tolerated by all study subjects. The average steady-state plasma atovaquone concentrations are presented below.

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 µg/mL (mean ± SD)		
1-3 months	5.9 (n=1)	27.8 ± 5.8 (n=4)	-
> 3-24 months	5.8 ± 5.1 (n=4)	9.9 ± 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)	-

As indicated in Appendix 1/Figure 1, apparent clearance following oral doses of atovaquone suspension is higher and more variable in the subjects less than 2 years of age. Figures 2-4 in Appendix 1 illustrate the average steady state plasma atovaquone concentrations in individual pediatric patients, by dose level. These figures indicate:

1. Age 1-3 months: The 10 mg/kg dose (n=1) was too low to reach a Cavg,ss of 15 μg/mL. Following the 30 mg/mg dose (n=4), two patient had a Cavg,ss value higher than the range typically observed in adults (15-25 μg/mL) and two subjects had values between 15 and 25 μg/mL. The applicant recommends a dose of 30 mg/kg for this age group.

2. Age >3-24 months: Following the 10 mg/kg (n=4) and 30 mg/kg (n=4) doses, all patients in this age group had Cavg,ss values less than 15 μg/mL. Following the 45 mg/kg dose (n=4), two patients had Cavg,ss values less than 15 μg/mL and two had values between 15-25 μg/mL. The applicant recommends a dose of 45 mg/kg for this age group.

3. Age >2-13 years: Following the 10 mg/kg dose (n=4), three patients had Cavg,ss values between 15-25 μg/mL and one patient had a value less than 15 μg/mL. Following the 30 mg/kg dose (n=3), all three patients had Cavg,ss values greater than 25 μg/mL. The applicant recommends a dose of 30 mg/kg for this age group.

Medical Officer's Comments and Conclusions:

1. *Dosage recommendations by the Applicant, in pediatric patients with PCP are based on efficacy data in adults and pharmacokinetic data in infants and children.*

2. *The sample size in each of the three dose/kg categories is low.*

3. *Explanation as to why a dose of 45 mg/kg is required in the 3-24 months age group has not been provided.*

Clinical Pharmacology Reviewer's Comments and Conclusions:

1. *The dosing recommendations are not appropriate, based on the pharmacokinetic data collected in pediatric patients. The doses recommended by the applicant did not result in atovaquone Cavg,ss values between 15-25 μg/mL.*

2. *It is not appropriate to include atovaquone dosing recommendations for pediatric patients in the labeling. The table containing the atovaquone Cavg,ss values for each age group at each dose should be included in the CLINICAL PHARMACOLOGY section of the label. The PRECAUTIONS: Pediatric Use section of the label should indicate that safety and effectiveness have not been established in pediatric patients and should refer the reader back to the CLINICAL PHARMACOLOGY section.*

/S/ 12/16/98

Kellie S. Reynolds, Pharm.D.
Reviewer
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

Concurrence:

/S/ 12/16/98

Funmi Ajayi, Ph.D.
Team Leader
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

/S/ 12/17/98

Roopa Viraraghavan, M.D.
Medical Officer,
DSPIDP- HFD 590

Concurrence:

/S/ 12/16/98

Robert Hopkins, M.D.
Medical Team Leader
DSPIDP- HFD 590

cc:
Division File: NDA 20-500
HFD-590 (M. Goldberger, Div. Dir.)
HFD-590 (R. Hopkins, MO Team Leader)
HFD-590 (R. Viraraghavan, MO)
HFD-590 (B. Atkins, CSO)
HFD-880 (K. Reynolds, PK Reviewer)
HFD-880 (F. Ajayi, PK Team Leader)
HFD-880 (Division File)
CDR (B. Murphy)

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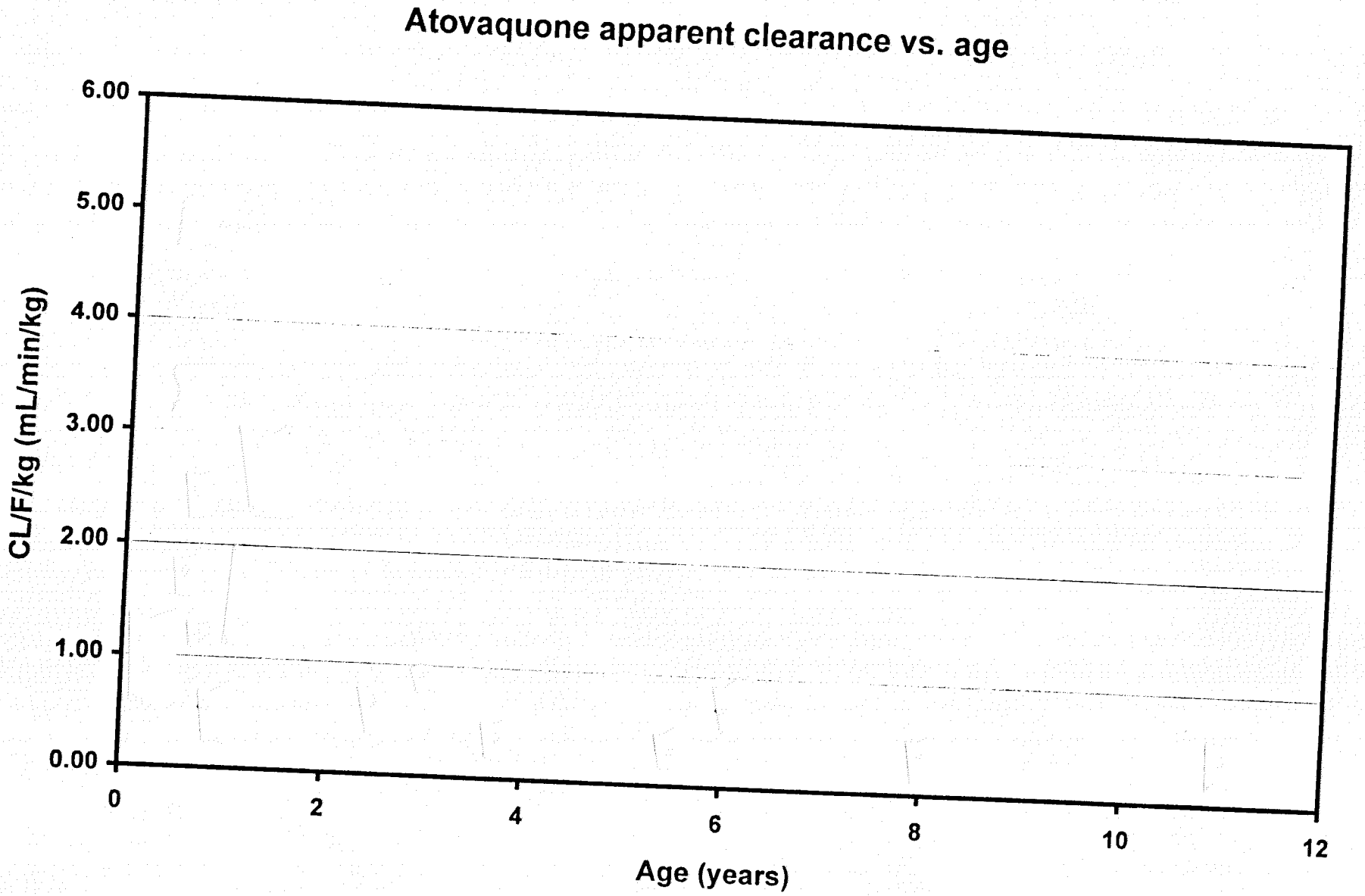
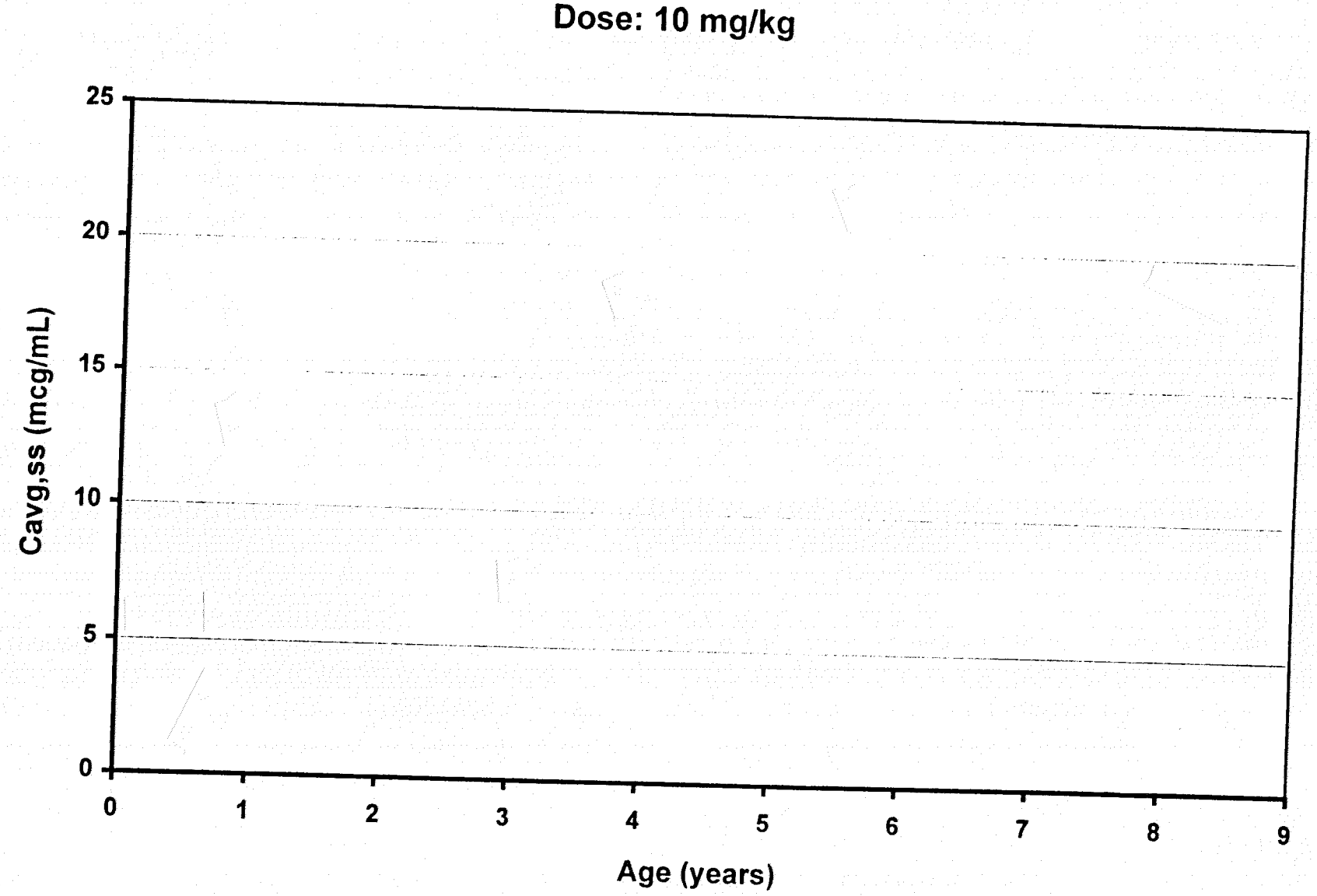
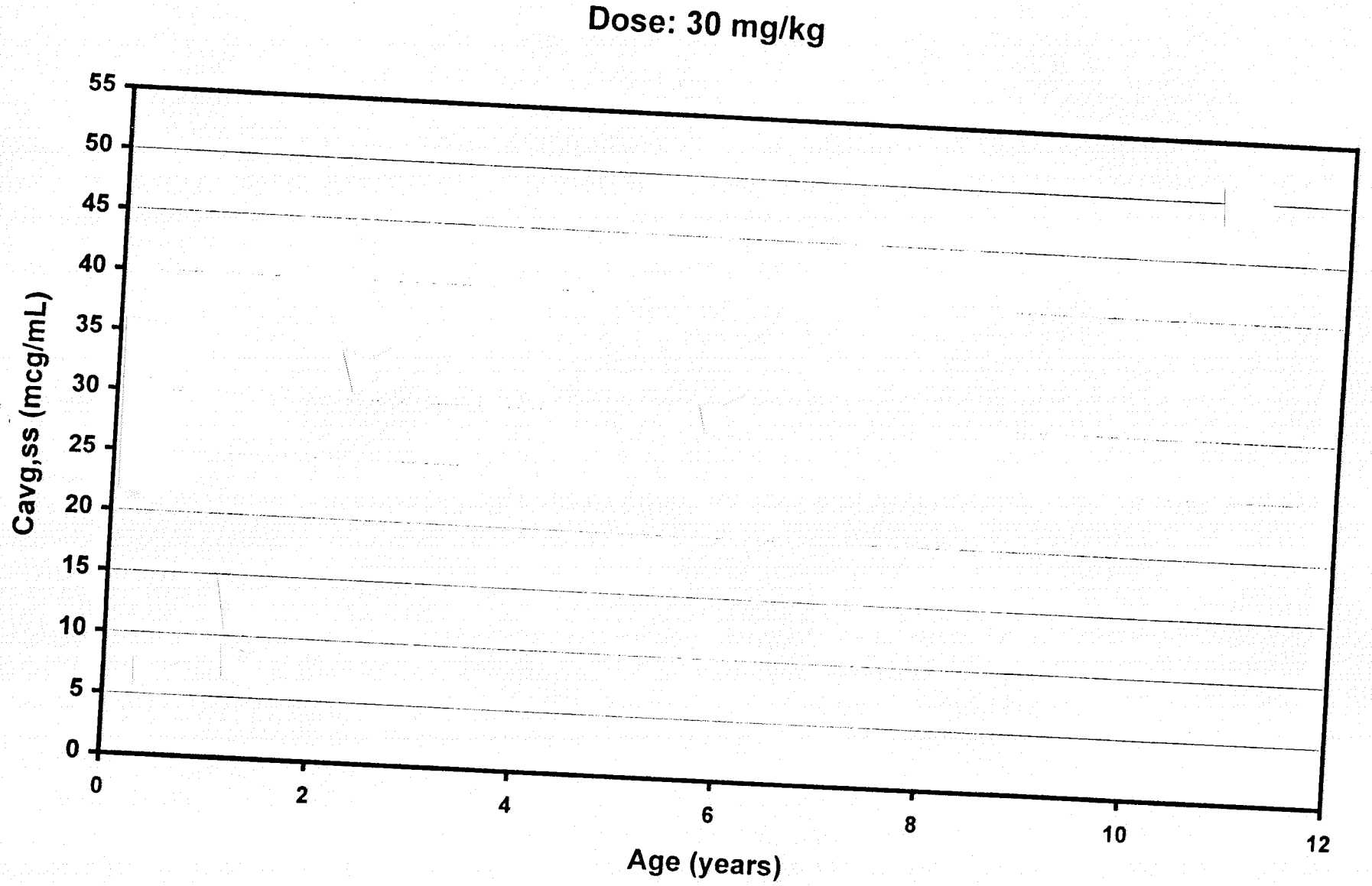
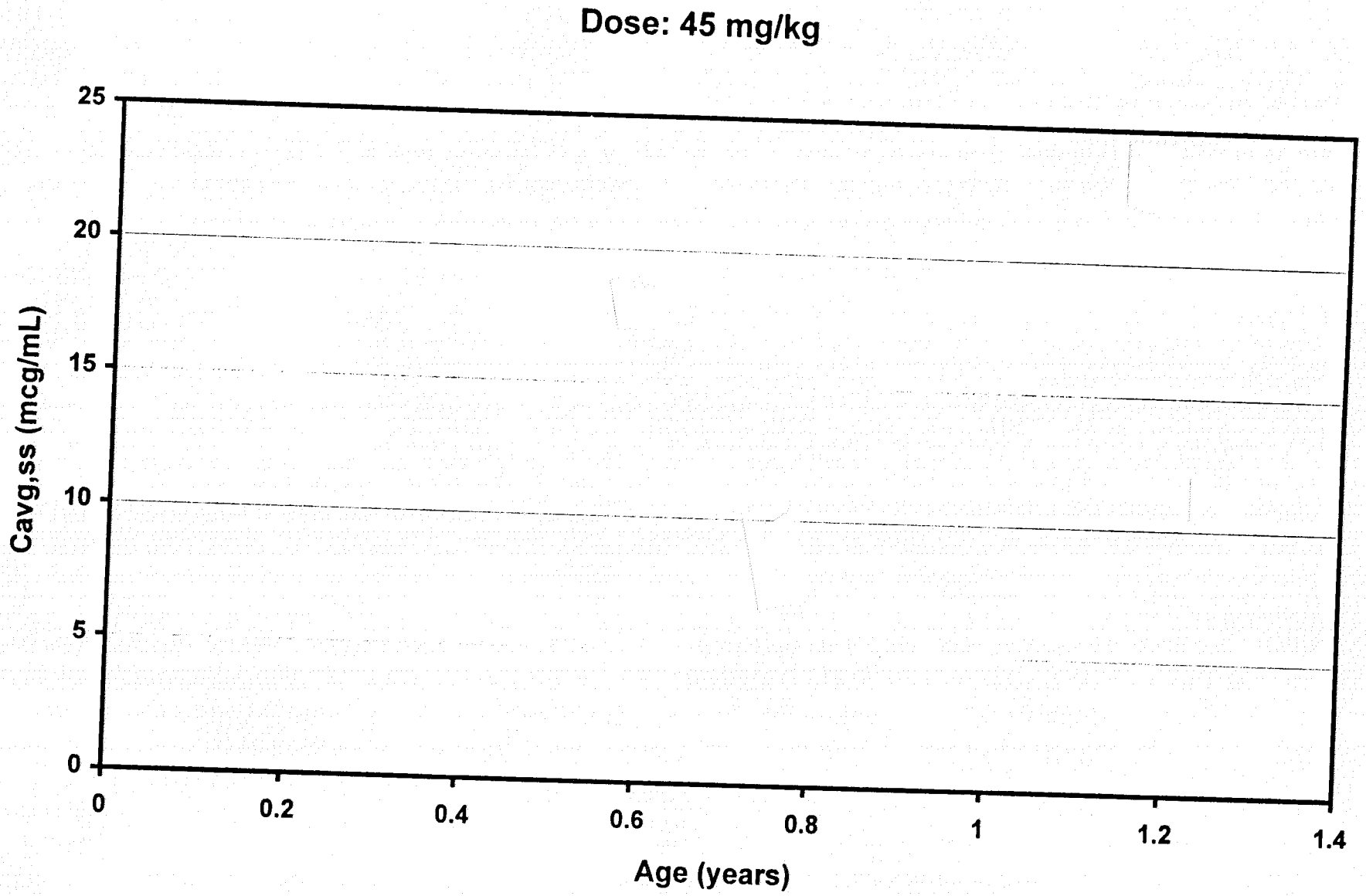
[i] Hughes W, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. N Eng J Med 1993;328:1521-7.

[ii] Hughes W, Dorenbaum A, Yogev R, Diaz C, Xu J, McNamara J, Moye J, Purdue L, van Dyke R, Rogers M, Sadler B. A phase I safety and pharmacokinetics study of micronized atovaquone in human immunodeficiency virus (HIV)-infected infants and children. Antimicrob Agents Chemother (in press).


Atovaquone apparent clearance vs. age
CL/F/kg (mL/min/kg)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0
2
4
6
8
10
12
Age (years)


Dose: 10 mg/kg
Cavg,ss (mcg/mL)
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
9
Age (years)


Dose: 30 mg/kg
Cavg,ss (mcg/mL)
55
50
45
40
35
30
25
20
15
10
5
0
0
2
4
6
8
10
12
Age (years)


Dose: 45 mg/kg
Cavg,ss (mcg/mL)
25
20
15
10
5
0
0
0.2
0.4
0.6
0.8
1
1.2
1.4
Age (years)

MEMORANDUM
Jan. 30, 1995

TO: File
FROM: Kenneth L. Hastings, Dr.P.H.
SUBJECT: NDA 20-500 (Mepron® suspension)

This submission did not contain new nonclinical pharmacology/toxicology data and no review is needed. However, a change in the label is indicated based on the improved bioavailability of the suspension formulation compared to the previously marketed tablet formulation.

According to the label,

Since the new formulation increases oral bioavailability from 23% to 47%, the relative exposure estimate needs to be changed accordingly
Also:

be changed to " should

A new version of the Mepron® suspension label was received by facsimile on 1/11/95. The sponsor's new label contained the corrections suggested above. No other action is indicated.

concurrences:
HFD-530/Dep Dir/DFreema /S/ 2/13/95
HFD-530/SPharm/JFarrell /S/ 1/31/95

cc:
HFD-530 Original NDA
HFD-530 Division File
HFD-530/CSO/MTarosky
HFD-530/MO/DBirnkrant

APPEARS THIS WAY
ON ORIGINAL