CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50739

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS, HFD-520

NDA#: 50-739 (000)

SPONSOR: Parke-Davis Pharmaceutical Company
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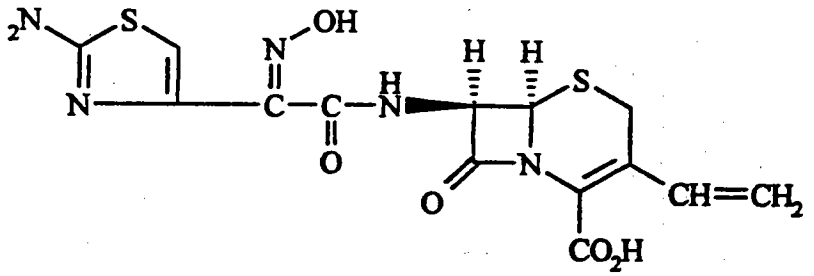
DRUG NAME: Cefdinir (Omnicef ™) Capsules [CI-983]

OTHER NAME(s): [6R-[6α,7β(Z)]]-7][[(2-amino4-thiazolyl)(hydroxyimino)acetyl]amino-3-ethnyl-8-oxo-5-thia- 1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

CATEGORY: Extended Spectrum, Semisynthetic, β-lactam Cephalosporin Antibiotic for Oral Administration

STRUCTURAL FORMULA:



The empirical formula is $C_{14}H_{13}N_5O_5S_2$

RELATED SUBMISSIONS: IND[DMFs[

NUMBER OF VOLUMES: 22

INFORMATION CONVEYED TO THE SPONSOR: YES (X), NO ( )

DATE CDER RECEIVED: September 4, 1996

DATE ASSIGNED: September 10, 1996

DATE REVIEW STARTED: November 15, 1996

DATE 1st DRAFT COMPLETED: April 2, 1997

DATE REVIEW ACCEPTED BY SUPERVISOR: April 22, 1997

REVIEW OBJECTIVES:

To review an original New Drug Application submitted in support of Cefdinir (Omnicef™) proposed to be used for the control of mild to moderate bacterial infection caused by susceptible strains.

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Oral dosage of 300 mg BID for ten days.

PRECLINICAL DATA:

Preclinical studies submitted in support of this NDA 50-739 have been, in most part, previously reviewed in connection with IND { }. The aforementioned reviews are attached to the present review. The preclinical pharmacology/toxicology studies submitted to support NDA 50-739 which have not been previously reviewed are reviewed and evaluated in this document. The locations of laboratories conducting these studies (both foreign and local) and their adherence to the GLP provisions are also stated.

PHARMACOLOGY

Cefdinir is an extended-spectrum, semisynthetic, β-lactam antibiotic of the cephalosporin class for oral administration in

the treatment of mild to moderate bacterial infections. Cefdinir has bactericidal activity against gram-positive and gram-negative bacteria by inhibiting the bacterial cell wall synthesis.

A. ***GENERAL SAFETY PHARMACOLOGY:***

The general pharmacology of cefdinir was investigated in mice, rats, guinea pigs, rabbits, and dogs. The following are the general summary of the safety pharmacology studies conducted and submitted into the NDA application.

*1. **Central Nervous System:** A few episodes of vomiting were observed during and immediately following dosing at 320 or 1000 mg/kg, i.v. of cefdinir. Cefdinir at 1000 mg/kg produced frequent urination in dogs, a slight inhibition of acetic acid-induced writhing episodes in mice, a transient drowsy electroencephalographic (EEG) patterns in rabbits, and a slight elevation of body temperature in rabbits. At the highest dose of 1000 mg/kg, cefdinir **did not** produce any effects on general behavior in rats, locomotor activities in the traction test in mice, sleeping time induced by hexobarbital in mice, electroshock- and pentylenetetrazol-induced convulsions in mice, the analgesic test in mice, the conditioned avoidance response in rats, and the spinal reflex in rabbits.*

2. Autonomic Nervous System: Cefdinir at the highest dose of 1000 mg/kg slightly potentiated the acetylcholine-induced hypotensive response in the conscious rats. Cefdinir at concentrations of 10 mg/ml slightly inhibited serotonin-induced contraction of rat stomach strip and electrically-induced contraction of the phrenic nerve-diaphragm preparation, and dose-dependently reduced the resting tonus of isolated guinea pig tracheal muscle. At the highest doses (1000 mg/kg in vivo; 10,000 µg/ml in vitro), cefdinir had no effect on the epinephrine-induced hypertensive response in rats, the contractile response of isolated guinea pig ileum to acetylcholine or histamine, the contractile response of isolated rat vas deferens to norepinephrine, sympathetic transmission in dogs, or salivary secretion in dogs.

3. Respiratory and Cardiovascular Systems: Cefdinir at 320 and 1000 mg/kg, i.v. produced transient disturbances in respiration followed by moderate tachypnea and a slight increase in blood pressure and heart rate during or after vomiting episodes in dogs. Cefdinir at the highest dose of 1000 mg/kg had a slight and transient inhibitory effect on heart rate in conscious rats. Cefdinir at 10,000 µg/ml caused a slight and transient inhibitory effect followed by slight potentiating effect on the contractile force of isolated guinea pig atria, a very slight inhibitory effect on contractile rate of isolated guinea pig atria, and a very slight relaxing effect on KCl-induced contraction of isolated canine saphenous artery. At the highest dose of

1000 mg/kg, cefdinir had no effects on blood pressure in conscious dogs, anesthetized dogs, and conscious rats; heart rate in conscious and anesthetized dogs; ECG in conscious dogs; and blood flow in the common carotid artery and femoral artery.

4. Gastrointestinal Tract: Cefdinir increased spontaneous jejunal movement in anesthetized dogs and bile secretion in rats at 1000 mg/kg. Cefdinir at the highest concentration of 10,000 μg/ml also increased spontaneous contraction of isolated rabbit ileum. At the highest dose of 1000 mg/kg, cefdinir had no effect on gastric secretion, restraint stress ulcer, and intestinal charcoal meal transit in rats.

5. Hematological System: Cefdinir produced a dose-dependent inhibition of ADP- and collagen-induced aggregation of human platelets, with IC_{50}'s of 3.9×10^{-3} g/ml and 4.3×10^{-3} g/ml, respectively. Cefdinir had no effect on bleeding time in mice and coagulation time in rats at the 1000 mg/kg, i.v. dose, and there was no hemolysis in rabbit blood in the presence of a 20% concentration of cefdinir.

6. Urinary System and Others: Cefdinir increased urine volume and excretion of Na^+ and K^+ in rats at 1000 mg/kg. At the highest doses (1000 mg/kg in vivo and 10,000 μg/ml in vitro), cefdinir had no effects on the spontaneous contraction of isolated nonpregnant and pregnant rat uterus.

B. *PHARMACOKINETIC AND ADME STUDIES ON CEFDINIR:*

The following are the general summary of the pharmacokinetic and ADME studies not reviewed as part of the original IND submission.

1. *Bioavailability of cefdinir in mice by oral dosing, Report # RR 764-02261 dated December 22, 1994.*

The pharmacokinetics of Cefdinir were studied in the male ICR mice. A single 20-mg/kg dose, i.v. or orally was administered and serum samples were obtained up to 2 hrs post-dose by cardiac puncture (10 mice/time point). Urine samples from additional mice were collected for 24 hours after a single 20-mg/kg, i.v. or oral dose. Serum and urine cefdinir concentrations were determined.

Comments: *After the i.v. dosing, cefdinir serum concentrations declined exponentially, suggesting that the distribution was rapid. Volume of distribution (V_d) approximated extracellular fluid volume. The terminal half-life ($T_{\frac{1}{2}}$) was longer following oral administration than after i.v. dosing, suggesting that the absorption rate was slower than the elimination rate. The majority of an i.v. dose (76.1%) was eliminated unchanged in urine as systemic clearance was largely accounted for by renal excretion. Urinary recovery after oral dosing was 9.8% of the dose, suggesting limited oral absorption. Based on AUC(0-∞) values and urinary recovery ratios, absolute oral bioavailability of cefdinir was 13.1% and 12.9%, respectively.*

2. Bioavailability of cefdinir in rats, rabbits, and dogs by oral dosing, Report # RR 764-02365 dated June 26, 1995.

I. Single-dose Pharmacokinetics in Rats.

Cefdinir pharmacokinetics were determined in male Sprague-Dawley (SD) rats. A single 20-mg/kg i.v. or p.o. dose was administered, and heparinized plasma samples were obtained up to 2 (for i.v.) and 6 (for p.o.) hrs post-dose by cardiac puncture (10 animals/time point). Urine samples from additional rats (10/route) were collected for 24 hours after a single 20-mg/kg, i.v. or p.o. dose. Plasma and urine were also collected after the administration of single 2.5, 5, 10, 20, 40, or 80 mg/kg, p.o., suspension of cefdinir. Plasma and urine cefdinir concentrations were determined by a standardized assay.

Comments: *Cefdinir pharmacokinetics in rats were similar to that already described for the mice. Cefdinir plasma concentrations declined linearly following the i.v. dosing, indicating rapid drug distribution. The volume of distribution was equivalent to the extracellular fluid volume. The terminal half-life (T½) was longer following oral administration than after i.v. dosing, suggesting that the absorption rate was slower than the elimination rate. The majority of administered compound (80.0%) by the i.v. route was eliminated unchanged in urine and the systemic clearance was largely accounted for by renal excretion. The urinary recovery following oral dosing was 15.5% of the dose, indicating limited oral absorption of cefdinir. Based on AUC(0-∞) values and urinary recovery ratios, absolute oral bioavailability of cefdinir was 17.0% and 19.4%, respectively.*

ii. Single-dose Pharmacokinetics in Rabbits.

The pharmacokinetics of Cefdinir were assessed in male Japanese White rabbits. A single 20 mg/kg, i.v. or p.o. dose was administered, and heparinized plasma samples were obtained serially from an ear vein in each animal through 3 (for i.v.) and 6 (for p.o.) hours post-dose (5 rabbits/route). Plasma and urine were also collected after the administration of single 1.25, 2.5, 5, 10, or 20 mg/kg, p.o., suspension of cefdinir. Plasma, urine, and bile samples were collected from each rabbit for 24 hours post-dose. These samples for cefdinir concentrations were determined by an established assay.

Comments: *The pharmacokinetics of Cefdinir in rabbits were similar to those already reported for mice and rats. Cefdinir plasma concentrations declined exponentially after i.v. dosing indicating rapid distribution. Volume of distribution (V_d) was equivalent to the extracellular fluid volume. Elimination terminal half-life (T½) was longer after oral than after i.v. dosing, suggesting that the absorption rate was slower than the elimination rate. The major portion of the i.v.-administered compound (80.0%) was eliminated unchanged in urine and the systemic clearance was largely accounted for by renal excretion. The urinary recovery following oral dosing was 45.8% of the dose, indicating limited oral absorption of cefdinir. Based on AUC(0-∞) values and urinary recovery ratios, the absolute oral bioavailability of cefdinir was 42.2% and 53.3%, respectively.*

iii. Single-dose Pharmacokinetics in the Dog.

The pharmacokinetics of Cefdinir were assessed in male beagle dogs. A single 20 mg/kg, i.v. or p.o. dose was administered, and heparinized plasma samples were obtained serially from each animal through 24 hours post-dose from a cephalic vein (5 dogs per route). Plasma and urine were also collected after the administration of single 2.5, 5, 10, 20, or 40 mg/kg, p.o., suspension of cefdinir. Plasma, urine, and biliary samples were also collected from each dog for 24 hours post-dose. The plasma, bile, and urine cefdinir concentrations were determined by a standardized microbiological assay.

Comments: *The pharmacokinetics of Cefdinir in dogs was significantly different from those already described for mice, rats, and rabbits. The decline in the Cefdinir plasma concentrations followed a linear but biphasic pattern following i.v. dosing. The volume of distribution was equivalent to the reported for the extracellular fluid volume. The elimination terminal half-life (T½) values following i.v. and oral dosing were similar and were significantly longer in the dogs as compared to other species. Furthermore, the systemic clearance in the dogs was 10 to 30 folds lower than in mice, rats, and rabbits. A significant portion of the i.v. dose of cefdinir (68.1%) was eliminated unchanged in urine and the systemic clearance was largely accounted for by renal excretion. The urinary recovery following oral dosing was 41.3% of the dose, indicating limited oral absorption of cefdinir. Based on AUC(0-∞) values and urinary recovery ratios, the absolute oral*

bioavailability of cefdinir was 70.5% and 60.6%, respectively.

3. Effect of developmental age on cefdinir pharmacokinetics. (I). Plasma and kidney concentrations of cefdinir after oral dosing in infant rats. Study # RR 764-02305 dated February 23, 1995.

The pharmacokinetics of Cefdinir were determined in studies in young and adult male Sprague Dawley rats. A single oral dose of cefdinir at 100 mg/kg was administered to rats aged 4 days, 21 days, and 6 weeks. Heparinized plasma samples were collected and analyzed for cefdinir concentrations using microbiological assay.

Comments: Cefdinir plasma concentrations and C_{max}, $T_{\frac{1}{2}}$, and $AUC_{(0-\infty)}$ values were generally highest in the 4-day-old rats and decreased progressively with age in 21-day-old and 6-week-old animals (see Table).

Age	Pharmacokinetic Parameters			
	Cmax	Tmax	T½	AUC(0-∞)
4 Days	23.3	6.0	3.8	294.5
21 Days	3.64	6.0	2.9	50.1
6 Weeks	5.40	1.0	1.9	17.9

Cmax = Maximum observed plasma concentration (μg/ml).
Tmax = Time of Cmax (hr).
T½ = Elimination half-life (hr).
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinity (μg·hr/ml).

The long T½ in 4-day-old rats may suggests that the kidney's tubular secretion was negligible in these animals. However, as tubular secretion and glomerular filtration function developed to maturity, T½ decreased progressively with age. The age-related decrease in cefdinir exposure could be attributed to the increase in renal clearance which would accompany post-natal development of renal elimination processes.

(ii). Plasma concentrations of cefdinir after single oral dosing in infant dogs. Study # RR 764-02314 dated February 24, 1995.

The pharmacokinetics of cefdinir were evaluated in young and adult beagle dogs. Six 3-week old dogs (3/sex) and 5 male dogs aged 9 to 24 years were fasted for 1 day prior to receiving a single oral dose of cefdinir suspension at 20 mg/kg. Heparinized plasma was obtained serially from the cephalic vein through 24 hrs post-dose, and cefdinir concentrations were determined by microbiological assay.

Comments: *There were no reported consistent sex differences in plasma concentrations or pharmacokinetic parameters, and in the combined-sex mean data (see Table).*

Age	N	Mean Pharmacokinetic Parameters			
		Cmax	tmax	T½	AUC(0-∞
3 Weeks	3/Sex	32.5	5.0	4.15[a]	347[a]
9 to 24 Months	5 Male	47.5	4.0	4.06	482

Cmax = Maximum observed plasma concentration (μg/ml).
Tmax = Time of Cmax (hr).
T½ = Mean elimination half-life (hr).
AUC(0-∞) = Area under the plasma concentration-time curve extrapolated to infinite time (μg·hr/ml).
[a] N = 2 male, 3 female.

The mean C_{max} and $AUC_{(0-\infty)}$ values observed in the juvenile dogs were ca. 30% lower than in the adults, while the T_{max} and T½ values were similar in both age groups. Sponsor suggested that this may be due to a higher volume of distribution in the juvenile dogs, which have greater extracellular water volume per kilogram body weight as compared to the adult dogs.

Conclusions on the pharmacokinetics of cefdinir in juvenile animals: Plasma cefdinir concentrations in the juvenile rats were higher and in juvenile dogs were lower than in their respective adults, probably attributable to the effects of age on renal clearance (tubular secretion) and volume of distribution, respectively.

C. TOXICOKINETIC STUDIES ON CEFDINIR:

The following are the general summary of the toxicokinetic studies not reviewed as part of the original IND submission.

1. Toxicokinetics of Cefdinir in male and female Sprague-Dawley rats, Report # RR 764-02580 dated July 26, 1996.

The toxicokinetics of Cefdinir were studied in male and female S.D. rats following oral 0, 100, 320, or 1000 mg/kg/day doses for 7 days. Heparinized plasma samples were collected by cardiac puncture on Day 7 at 1 hour post-dose from the vehicle control group (4/sex) and through 24 hrs post-dose in cefdinir-treated rats (4/sex/time point/dose). Plasma cefdinir concentrations were determined by [ ] and plasma cefdinir pharmacokinetic parameters were determined using mean concentrations at each time point.

Comments:

Cefdinir was not detectable in plasma samples from vehicle controls. Cefdinir elimination half-life (T½) increased above 320 mg/kg. Increases in C_{max} values were less linear with increasing dose in both male and female rats. $AUC_{(0-24)}$ values increased linearly with the dose in males but less linear with dose in females. In the female rats, C_{max} and $AUC_{(0-24)}$ values were 1.4 to 2.1-folds greater, respectively, than in the male rats. These results are summarized below:

Cefdinir pharmacokinetic parameters following once-daily administration of 100, 320, or 1000 mg/kg Cefdinir to SD Rats for 7 Days.

Dose[a]	Sex	Cmax	NCmax	tmax	t½	AUC(0-24)	NAUC
100	Male	2.68	0.0268	1	1.5	10.7	0.107
320		6.35	0.0198	1	1.4	31.8	0.0994
1000		14.1	0.0141	2	3.3	97.3	0.0973
100	Female	5.67	0.0567	1	1.5	19.7	0.197
320		10.3	0.0322	1	1.3	45.7	0.143
1000		23.8	0.0238	1	3.7	179	0.179

Cmax = Maximum observed plasma concentration (μg/ml).
Ncmax = Cmax (μg/ml) normalized to a 1-mg/kg dose.
tmax = Time of Cmax (hr).
t½ = Elimination half-life (hr).
AUC(0-24) = Area under the plasma concentration-time curve from time zero to 24 hours post-dose (μg·hr/ml).
NAUC = AUC(0-24) (μg·hr/ml) normalized to a 1-mg/kg dose.
[a] Milligrams/kilograms

2. Tissue distribution of radioactivity in rats dosed with [^{14}C]cefdinir, Report # RR 764-02104 dated January 19, 1994.

Tissue distribution of [^{14}C]cefdinir was investigated in the rats. Male S.D. rats received a single 10-mg/kg (30 μCi/kg), p.o. [^{14}C]cefdinir dose and were sacrificed at 1, 6, and 24 hours post-dose (3 rats/time point). Blood, plasma, and tissues samples were collected and solubilized, and blood and tissues were bleached. Radioactivity was determined by

Blood, plasma, and tissue radioequivalents and tissue:plasma radio-equivalent ratios were determined.

Comments: Radioactivity peaked at 1 hour post-dose in all of the tissues sampled. The highest [^{14}C]cefdinir radio-equivalents (tissue:plasma ratio) were observed in the small intestine at 3.95, stomach at 3.14, urinary bladder at 1.81, and kidney at 1.52. From this study, it was determined that the radioactivity was distributed to most tissues in the body except for brain, bone marrow, and thyroid.

At 6 hrs post-dose, radioactivity declined in all tissues except in the large intestine, where [^{14}C]cefdinir radio-equivalents remained comparable to those at 1 hr post-dose levels. The highest radioactivity was observed in kidney.

At 24 hours post-dose, radioactivity was not detectable in most tissues. The radioequivalent levels in kidney were 60% lower at 24 hours than at 6 hours, while radioactivity in the large intestine had declined only slightly.

In summary, [^{14}C]cefdinir distributed widely to most tissues in the body, except for brain, bone marrow, and thyroid. The highest radio-equivalents were observed in the GI tract, urinary bladder, and kidney. Radioactivity declined rapidly in all tissues and organs except the large intestine, where radio-equivalents remained stable for the duration of the study.

3. Plasma concentrations and tissue concentrations of cefdinir by oral dosing in rabbits, comparison with other antibiotics, Report # RR 764-02367 dated July 10, 1995.

Tissue concentrations of Cefdinir were determined in male Japanese White rabbits. A single 20 mg/kg, p.o. dose was administered to the rabbits and the animals were sacrificed at 0.5, 1, and 2 hrs post-dose (3 rabbits/time point). Plasma samples were collected and heparinized aliquots of the plasma samples were saved for analysis. Liver, kidney, lungs, heart, and spleen samples were removed, rinsed, homogenized, centrifuged, and the supernatant saved for analysis. Cefdinir was quantified in plasma and tissue homogenate supernatants using a standardized microbiological assays.

Comments: *The relative tissue cefdinir concentrations in rabbits were comparable to that already described for rats. The reported mean cefdinir concentrations were highest in kidney, followed by the plasma, liver, lung, heart, and spleen. At 1 hour post-dose, the mean cefdinir tissue:plasma concentration ratios were determined to be 6.95, 0.30, 0.28, 0.13, and 0.08 in the kidney, liver, lung, heart, and spleen, respectively. The respective tissue:plasma* $AUC_{(0-2)}$ *ratios were also determined to be 6.57, 0.28, 0.28, 0.13, and 0.10.*

TOXICOKINETICS SUMMARY:

Toxicokinetic data in animal studies indicated that Cefdinir was distributed rapidly and widely throughout the body, with a volume of distribution equivalent to that of extracellular fluid volume. Following oral administration in rats, $[^{14}C]$*cefdinir distributed to most tissues in the body, except for brain, bone marrow, and*

thyroid. The highest radio-equivalents were observed in the GI tract, urinary bladder, and kidney. Radioactivity declined rapidly in all tissues and organs except the large intestine, where the radio-equivalents remained stable for at least 24 hours. Radio-equivalents in urinary bladder and kidney were higher and persisted longer than in most other tissues. Following an intravenous dosing, systemic radioactivity was higher, but relative radioactivity distribution and elimination were similar to that observed following oral dosing. After administration of non-radiolabeled cefdinir to rats or rabbits, cefdinir concentrations in the kidney were 2 to 7 folds higher, while concentrations in liver, lung, heart, and spleen were only 10% to 30% of concurrent plasma concentrations. Cefdinir penetration into rat milk was minimal.

The lower systemic radioactivity, coupled with high and persistent radio-equivalents in the gastrointestinal tract after oral dosing, reflected low oral cefdinir absorption in rats. Furthermore, high and persistent cefdinir concentrations and radio-equivalents in urinary bladder and kidney were consistent with the primary role of renal excretion in cefdinir elimination.

D. TOXICOLOGY STUDIES

The following are the toxicology studies either not submitted or not reviewed as part of the original IND submission.

1. Twenty-six-week oral toxicity study of cefdinir in rats. Report # RR 745-01758 dated March 14, 1991. Conducted at

GLP Status: Yes.

Dosages: 0, 100, 320, or 1000 mg/kg Cefdinir, p.o. for 26 weeks.

Comments: No clinical signs were observed at 100 mg/kg. All animals at higher doses (320 and 1000 mg/kg) were reported to show persistent dark-red feces, from Day 2 at 1000 mg/kg and during Weeks 6 or 7 at 320 mg/kg. No drug-related deaths occurred. Body weight gain decreased 13% in females at 1000 mg/kg at termination and food consumption increased 7% to 10% in males at the same dose from Weeks 20 to 26. Ophthalmic examinations were unremarkable.

Significant clinical laboratory findings were as follows: At 1000 mg/kg, serum iron decreased 30% in females without changes in hematology parameters or histopathology of hematopoietic organs. Peripheral white blood cell counts decreased 17% to 22% and urine pH decreased in both sexes. Increased proteinuria and a 30% prolongation of prothrombin time were noted in males. At necropsy, cecal enlargement was observed in some rats at 320 mg/kg and most rats at 1000 mg/kg. In males at 1000 mg/kg, absolute and relative kidney weights increased 12% and 18%, respectively, correlating with exacerbation of nephropathy in male rats. Slight to mild thickening of the mucosa of the stomach was observed microscopically in both sexes at 1000 mg/kg. Plasma cefdinir concentrations increased with increasing dose and no differences were noted between the concentrations at Weeks 5, 12, and 26 or between males and females at any time point (see

summary in the table):

Plasma Cefdinir Concentrations in Rats Given Oral Doses for 26 Weeks[a]

Week	Plasma Cefdinir Concentrations (μg/ml)					
	100 mg/kg		320 mg/kg		1000 mg/kg	
	Male	Female	Male	Female	Male	Female
5	6.72 ± 0.77	7.63 ± 1.44	14.3 ± 0.89	17.2 ± 2.10	22.6 ± 1.20	28.0 ± 4.07
12	8.58 ± 0.67	6.69 ± 0.92	14.3 ± 1.25	12.6 ± 1.15	26.4 ± 2.46	25.7 ± 1.94
26	7.55 ± 1.35	6.71 ± 0.42	13.8 ± 0.87	13.7 ± 1.30	21.0 ± 1.46	27.1 ± 0.74

a Samples obtained 1 hour post-dose from 3 animals/sex; mean ± standard error.

It is concluded that oral treatment with cefdinir at 100 mg/kg, p.o., for 26 weeks was well tolerated and this dose (100 mg/kg) was the determined NOEL in this study.

2. Twenty-six-week oral toxicity study and toxicokinetics of cefdinir in dogs. Report # RR 745-01759 dated March 14, 1991. Conducted at(

( ) GLP Status: Yes.

Dosages: 0, 200, 400, or 800 mg/kg Cefdinir, p.o. for 26 weeks, 4/sex/group.

Comments: The dogs were given cefdinir in gelatin capsules at 200, 400, or 800 mg/kg for 26 weeks. All treated dogs were reported to have reddish-brown feces throughout the study. Soft or mucoid feces were noted occasionally at 800 mg/kg. Salivation occurred sporadically in a few animals at 400 mg/kg, and almost

daily in most animals at 800 mg/kg. Emesis was observed sporadically in both treated and control groups with test substance occasionally present in the vomitus from treated animals. No mortalities was reported and there were no drug-related changes in body weight, food consumption, blood pressure, electrocardiograms, ophthalmic examinations, clinical laboratory, hepatic or renal function parameters, organ weights, or histopathology. No significant differences were observed between males and females or respective time points in plasma cefdinir concentrations obtained on Day 1 or in Weeks 13 and 26 (see table).

Plasma Cefdinir Concentrations in Dogs Given Oral Doses for 26 Weeks[a]

Day or Week	Plasma Cefdinir Concentrations (μg/ml)					
	200 mg/kg		400 mg/kg		800 mg/kg	
	Male	Female	Male	Female	Male	Female
Day 1						
2 Hours	45.5±15.7	114.7±12.5	81.9±16	104.4±9.40	99.0±11	142.3±26.1
24 Hours	7.64±3.25	2.18±0.16	9.05±5	4.55±0.76	11.0±2	5.35±1.20
Week 13						
2 Hours	78.0±25.2	83.3±24.0	74.6±22	94.3±9.20	54.9±19	94.2±11.8
24 Hours	3.19±0.75	2.85±0.35	4.06±1	3.37±0.40	8.88±4	5.71±1.69
Week 26						
2 Hours	84.2±6.70	74.1±2.0	96.3±13	63.6±13.4	83.4±11	95.1±16.9
24 Hours	11.4±7.40	3.03±0.74	2.37±0	5.20±1.69	6.87±3	7.04±3.20

a Samples obtained from 4 dogs/sex; mean ± standard error.

Stool samples from dogs given 800 mg/kg in this 26-week oral toxicity study were analyzed using[ ]techniques to determine the composition of the dark-red pigment in feces after cefdinir administration. Occult blood tests on these stools were negative.

The pigment was found to contain iron complexed with cefdinir.

Toxicokinetics:

The toxicokinetic profile of cefdinir was determined in dogs treated with given 200, 400, or 800 mg/kg by gavage for 7 days. No deaths were observed, emesis occurred sporadically (usually within 1 to 2 hrs post-dose and occasionally contained test substance) in all groups, but with apparent dose-related frequency in males. Reddish-brown feces were observed daily throughout the study in all dogs and salivation within minutes of dosing was frequently observed in 5 of 6 dogs at 800 mg/kg. Cefdinir C_{max} and $AUC_{(0-24)}$ increased non-linearly with increasing dose in males and females dogs, however, no sex-related differences were noted (see table of toxicokinetic parameters).

Toxicokinetic parameters in dogs given oral doses of cefdinir for 7 Days[a]

Dose (mg/kg)	Cmax (µg/ml)		AUC(0-24) (µghr/ml)	
	Male	Female	Male	Female
200	103 ± 6.20	91.1 ± 23.0	936 ± 95.0	831 ± 93.8
400	107 ± 18.0	111 ± 1.73	1324 ± 219	1352 ± 311
800	128 ± 13.1	121 ± 19.1	1403 ± 631	1612 ± 70.9

Cmax = Maximum plasma concentration; AUC(0-24) = Area under the plasma concentration-time curve from 0 to 24 hrs.

a Plasma samples obtained 0.5, 1, 2, 4, 6, and 24 hours post-dose on Day 7 from 3 animals/sex; mean ± standard deviation.

Conclusions:

Cefdinir was well-tolerated in the dogs at doses up to 800 mg/kg, for 26 weeks without any histopathologic changes attributable to cefdinir. The observed emesis in dogs and changes in fecal consistency following repeated administration of cefdinir were not uncommon effects observed with antibiotics. Dark-red stools

observed in the dogs following cefdinir administration was believed to have resulted from the presence of iron complexed with cefdinir related substances in the gastrointestinal tract. No other significant associated toxicities were observed in this study.

3. Nephrotoxicity study of Cefdinir in rats. Report # RR 745-01760 dated October, 1990. Conducted at[

] GLP Status: Yes.

Dosages: 0, 180, 320, or 560 mg/kg Cefdinir, p.o. for 14 days, 5 males S.D. rats/group. Additional rats were given s.c. injections of furosemide at 100 mg/kg alone or immediately after administration of cefdinir for 14 days.

Comments: Urine volume decreased, and specific gravity and osmolarity increased slightly in all groups treated with cefdinir on Day 1. Similar changes were observed in groups given cefdinir alone at 560 mg/kg, furosemide alone, or cefdinir and furosemide on Day 7 and in groups given furosemide alone or with cefdinir at 320 mg/kg on Day 14. Changes in urinalysis parameters were most pronounced on Day 1. At necropsy, relative kidney weights increased at least 10% in groups given furosemide alone or cefdinir and furosemide. No gross or histopathologic renal changes were observed in the rats treated with cefdinir alone. In animals receiving furosemide alone or in combination with cefdinir, there were similarities in the incidence and severity of the cortico-medullary-junction focal lesions and necrosis and

calcification of renal tubular epithelium. However, cefdinir did not induce nephrotoxicity or exacerbate the renal effects of furosemide.

4. Local irritation studies by cefdinir in rabbits (eye mucosa and primary skin irritation). Report # RR 745-01768 dated July, 1986. Conducted at

GLP Status: Yes.

Comments: *The potential of topically-applied cefdinir to induce ocular or skin irritation was assessed in rabbits.*
Ocular *- Rabbits were given 0.1 ml of a 1% or 10% solution of cefdinir once in the left eye while the right eye remained untreated. Additional animals received 0.9% NaCl in the left eye and served as controls. Ophthalmic examinations were perfpormed at 2, 24, 48, and 72 hrs after treatment. Results showed no injuries to the cornea, iris, or conjunctiva were observed. Cefdinir is therefore considered a non-ocular irritant.*
Dermal *- To assess skin irritation potential, 0.5 ml of a 1% or 10% cefdinir solution was applied to chemically-depilated intact or abraded skin of rabbits. A 5% solution of sodium lauryl sulfate (SLS) was evaluated as a positive control. Application sites were occluded for 24 hours and then washed with distilled water. Skin reactions were graded at 24 and 72 hrs after the application using the Draize scale, and the primary irritation index was calculated. At 24 hrs, very slight erythema (Grade 1 -*

barely perceptible) was observed on the abraded skin of 2 animals treated with the 1% solution. Similar results were observed on intact skin of 1 animal and on abraded skin of 4 animals treated with the 10% solution. At 72 hours, very slight erythema was observed on abraded skin of 1 animal treated with the 10% solution. The mean primary irritation scores were 0.1 at 1% and 0.3 at 10%. In contrast, moderate to severe erythema (Grade 3) and slight to moderate edema (Grade 2 to 3) were observed on intact and abraded skin of all animals treated with the positive control, SLS with a mean primary irritation score of SLS was 3.6. Therefore, cefdinir is considered to have a low dermal irritation potential.

E. REPRODUCTIVE TOXICOLOGY STUDIES

The following are the reproductive toxicology studies either not submitted or not reviewed as part of the original IND submission.

1. Fertility and general reproductive performance study of cefdinir in rats. Report # RR 745-01574 dated December 24, 1987. Conducted at (

GLP Status: Yes.

Dosages: *0, 100, 320, or 1000 mg/kg Cefdinir, p.o.*

Male and female rats were given cefdinir at 100, 320, or 1000 mg/kg by gavage to determine the effects on fertility, general reproductive performance, and offspring development. Males were treated for 64 days prior to and through the 14-day mating period; half of the females were treated for 15 days prior to mating and through gestation Day 13; the remaining females

were treated through lactation Day 21. Reproductive parameters were assessed in females sacrificed on gestation Day 13. Females treated through lactation Day 21 were allowed to deliver and rear their young. Offspring evaluations were conducted. Skeletal evaluations were performed only on offspring that died during the lactation period. At necropsy, the cecum was removed from parental animals and weighed.

***Comments:** All males at 100 and 320 mg/kg, 1 female at 320 mg/kg, and 3 females at 1000 mg/kg had soft feces early in the dosing period. At 1000 mg/kg, all males and most females had dark-red soft feces throughout the dosing duration. No drug-related deaths were reported at any dose level. No significant differences in body weight changes were observed in males or females treated until gestation Day 13. During gestation, body weight gain decreased 11% in females at 1000 mg/kg treated until lactation Day 21; food consumption decreased on gestation Days 1 to 3. However, weight gain and food consumption were comparable to controls during the lactation period. Cecal enlargement was reported in some animals of both sexes at 320 mg/kg, and in all males and most females at 1000 mg/kg. Absolute and relative cecal weights increased in all treated animals except in few females at 100 mg/kg from the group allowed to deliver.*

There were no significant drug-related effects observed on mating time, copulation, fertility index, or maternal reproductive parameters. No cefdinir-associated effects occurred on viability, body weight, behavior, or development of offspring and no internal, external, or skeletal malformations were observed.

2. Two phase oral teratology and toxicokinetic studies of cefdinir in rats. Report # RR 745-01648 and RR 745-02262 dated May, 1990. Conducted at |

| GLP

Status: Yes.

Dosages: *0, 100, 320, or 1000 mg/kg Cefdinir, p.o. in pregnant rats on gestation Days 7 to 17. On Gestation Day 20, two-thirds of the females were sacrificed and examined for gross pathologic changes. Maternal reproductive parameters were assessed and fetal evaluations were also conducted. The remaining females were allowed to deliver their offspring and were later sacrificed on lactation Day 21. The number of implantation sites was recorded. Offspring evaluations included evaluation of F_1 reproductive function. The F_2 fetuses were weighed, sexed, and evaluated for external abnormalities.*

The toxicokinetic profile of cefdinir was also determined in the pregnant and lactating rats given 32, 100, 320, or 1000 mg/kg by gavage on gestation Day 7 through lactation Day 13. These were identical doses to those used in the teratology study. In addition, milk was collected on lactation Day 13 and analyzed for the presence of cefdinir.

Comments: *No mortalities were reported. All females treated at 1000 mg/kg had reddish feces during the treatment period. During gestation, body weight gain decreased ca. 15% from Days 14 to 20 and food consumption decreased ca. 13% from Days 9 to 17 at all doses. During lactation, body weight gain and food consumption increased at all doses. No effects on maternal reproductive*

parameters were observed on gestation Day 20 or lactation Day 21 and no gross pathologic findings were noted. In the rats sacrificed on gestation Day 20, placental weights decreased by ca. 10% and fetal weights decreased by ca. 5% at all doses. No cefdinir-related effects on offspring survival, growth, development, behavior, fertility, or F_2 fetal evaluations were observed. Cefdinir was not considered to be teratogenic in rats as low incidences of wavy ribs and delayed ossification of the pubic bone were observed in both the treatment and control groups.

Toxicokinetics:

Toxicokinetic Parameters in Pregnant and Lactating Rats Given Oral Doses of Cefdinir on Gestation Day 7 through Lactation Day 13[a]

Dose (mg/kg)	Gestation Day 17 Plasma		Lactation Day 13 Plasma	
	Cmax (µg/ml)	AUC(0-24) (µg·hr/ml)	Cmax (µg/ml)	AUC(0-24) (µg·hr/ml)
32	2.09±0.42	12.3±3.33	3.99±2.50	30.3±16.0
100	6.06±0.76	39.5±3.66	10.6±3.25	82.1±30.7
320	10.8±2.08	72.9±19.8	35.5±11.2	337±15.3
1000	22.5±1.76	247±20.3	ND	ND

Cmax = Maximum plasma concentration; AUC(0-24) = Area under the concentration-time curve from 0 to 24 hours; ND = Not determined.

a Plasma samples obtained 0.25, 1, 2, 4, 6, and 24 hours post-dose from 5 animals; mean ± standard deviation.

Cefdinir C_{max} increased proportionately with the dose from 32 to 100 mg/kg and less linear from 100 to 1000 mg/kg whereas $AUC_{(0-24)}$ increased proportionately with dose from 32 to 1000 mg/kg (see the PK table). Cefdinir concentrations in rats' milk were

detectable but very low (see data in the table below).

Cefdinir Milk Concentrations and Milk-to-Plasma Ratios in Rats on Lactation Day 13[a]

Dose (mg/kg)	Milk (μg/ml)	Plasma (μg/ml)	Milk-to-Plasma Ratio
32	0.016±0.04	3.76±2.1	0.002±0.005
100	0.186±0.06	10.0±3.4	0.019±0.004
320	0.427±0.16	26.6±5.0	0.016±0.004

a Samples obtained 1 hour post-dose from 5 animals; mean ± standard deviation.

3. Oral teratology and toxicokinetic studies of cefdinir in rabbits. Report # RR 745-01645 and RR 745-02378 dated September 6, 1990. Conducted at [redacted]

[redacted] GLP Status: Yes.

Dosages: 0, 1, 3.2, or 10 mg/kg Cefdinir, p.o. in pregnant rabbits on gestation Days 6 to 18. On gestation Day 29, females were sacrificed and examined for gross pathologic changes. Maternal reproductive parameters were assessed and fetal evaluations were also conducted. The toxicokinetic profile of cefdinir was also determined in pregnant rabbits given 1, 3.2, or 10 mg/kg by gavage on gestation Days 6 through 14.

Comments:

No clinical signs or drug-related deaths were observed in all groups. At 10 mg/kg, body weight gain decreased by 94% and was associated with approximately 39% decrease in food consumption during the dosing period. However, food consumption in this group was comparable to controls by gestation Day 24. No effects were

observed on maternal reproductive or fetal parameters and no drug-related gross pathologic changes were noted. Low incidence of lobar abnormality of the lung in 1 fetus and thymic remnant in the neck of 3-5 fetuses of the control, 3.2, and 10 mg/kg groups were observed. Abnormal sutura frontalis was also seen in 1 fetus of the 3.2 mg/kg group, fusion of lumber vertebral arches and absence of lumbar vertebral body in another fetus was seen in the same group. Low incidence of the thirteenth rib and delayed ossification of the frontal and interparietal bones were observed in both the treatment and control groups. These findings were considered not uncommon in the New Zealand White rabbits. Therefore, cefdinir was considered not teratogenic in rabbits.

Toxicokinetics: Cefdinir C_{max} increased proportionately with dose from 1 to 3.2 mg/kg but less linear with dose from 3.2 to 10 mg/kg; $AUC_{(0-24)}$ increased more than proportionately from 1 to 3.2 mg/kg and less linear from 3.2 to 10 mg/kg (see table).

Toxicokinetic Parameters in Pregnant Rabbits Given Oral Doses of Cefdinir on Gestation Days 6 Through 14[a]

Dose (mg/kg)	Cmax (µg/ml)	AUC(0-24) (µghr/ml)
1	0.40 ± 0.20	0.59 ± 0.28
3.2	1.34 ± 0.19	2.57 ± 0.50
10	3.33 ± 0.85	6.71 ± 2.11

Cmax = Maximum plasma concentration; AUC(0-24) = Area under the plasma concentration-time curve from 0 to 24 hours.

[a] Plasma samples obtained 0.25, 1, 2, 4, 6, and 24 hours post-dose on Gestation Day 14 from 5 animals; mean ± standard deviation.

Conclusions: Based on the rat and rabbit data, cefdinir exhibited

no adverse effects on fertility or general reproduction. Cefdinir was determined not to be teratogenic in rats or rabbits. It did not affect offspring survival, development, behavior, or reproduction. Fetal weight in the rat teratology study and birth/body weight in the perinatal/postnatal study were decreased but without any significant adverse effects.

SUMMARY AND EVALUATION

1. General Safety Pharmacology:

(a). Central Nervous System Effects: At the highest dose of 1000 mg/kg studied, Cefdinir did not produce any effects on general behavior in rats, locomotor activities in the traction test in mice, sleeping time induced by hexobarbital in mice, electroshock- and pentylenetetrazol-induced convulsions in mice, the analgesic test in mice, the conditioned avoidance response in rats, and the spinal reflex in rabbits.

(b). Autonomic Nervous System Effects: At the highest doses (1000 mg/kg in vivo; 10,000 μg/ml in vitro), cefdinir had no effect on the epinephrine-induced hypertensive response in rats, the contractile response of isolated guinea pig ileum to acetylcholine or histamine, the contractile response of isolated rat vas deferens to norepinephrine, sympathetic transmission in dogs, or salivary secretion in dogs.

(c). Respiratory and Cardiovascular System Effects: At the highest dose of 1000 mg/kg, cefdinir had no effects on blood pressure in conscious dogs, anesthetized dogs, and conscious rats; heart rate in conscious and anesthetized dogs; ECG in

conscious dogs; and blood flow in the common carotid artery and femoral artery.

(d). Gastrointestinal Tract: At the highest dose of 1000 mg/kg, cefdinir had no effect on gastric secretion, restraint stress ulcer, and intestinal charcoal meal transit in rats.

(d). Hematological System: Cefdinir produced a dose-dependent inhibition of ADP- and collagen-induced aggregation of human platelets, with IC_{50}'s of 3.9×10^{-3} g/ml and 4.3×10^{-3} g/ml, respectively. Cefdinir had no effect on bleeding time in mice and coagulation time in rats at the 1000 mg/kg, i.v. dose, and there was no hemolysis in rabbit blood in the presence of a 20% concentration of cefdinir.

(e). Urinary System and Others: Cefdinir increased urine volume and excretion of Na^+ and K^+ in rats at 1000 mg/kg, p.o. At the highest doses (1000 mg/kg in vivo and 10,000 µg/ml in vitro), cefdinir had no effects on the spontaneous contraction of isolated nonpregnant and pregnant rat uterus.

2. Pharmacokinetic and ADME studies on Cefdinir:

(a). Following i.v. dosing, cefdinir distribution is rapid. The volume of distribution (V_d) approximated extracellular fluid volume. The terminal half-life ($T_{\frac{1}{2}}$) is longer following oral administration than after i.v. dosing, suggesting that the absorption rate was slower than the elimination rate. The majority of an i.v. dose (76.1%) was eliminated unchanged in urine as systemic clearance was largely accounted for by renal

excretion.

(b). Plasma cefdinir concentrations in the juvenile rats were higher and in juvenile dogs were lower than in their respective adults, probably due to the effects of age on renal clearance (tubular secretion) and volume of distribution, respectively.

3. Toxicokinetic studies on Cefdinir: Study data indicated that Cefdinir was distributed rapidly and widely throughout the body, with a volume of distribution equivalent to that of extracellular fluid volume. Following oral administration of [^{14}C]cefdinir in rats, cefdinir was distributed to most tissues in the body, except for brain, bone marrow, and thyroid. The highest radio-equivalents were observed in the GI tract, urinary bladder, and kidney. Radio-equivalents in urinary bladder and kidney were higher and persisted longer than in most other tissues. Following an intravenous dose, radioactivity distribution and elimination were similar to that observed following an oral dose. The high and persistent cefdinir concentrations and radio-equivalents in urinary bladder and kidney were consistent with the primary role of renal excretion in cefdinir elimination.

4. Toxicology studies on Cefdinir:

(a). Twenty-six-week oral toxicity study of cefdinir in rats. Rats of both sexes were treated orally at 0, 100, 320, or 1000 mg/kg Cefdinir for 26 weeks. The NOEL level was determined to be 100 mg/kg, p.o. from this study. All animals at higher doses (320 and 1000 mg/kg) were reported to show persistent dark-red feces.

No drug-related deaths occurred at any dose level. Ophthalmic examinations were unremarkable. At necropsy, cecal enlargement was observed in some rats at 320 mg/kg and most rats at 1000 mg/kg. In males at 1000 mg/kg, the absolute and relative kidney weights increased 12% and 18%, respectively, correlating with exacerbation of nephropathy in male rats.

(b). Twenty-six-week oral toxicity study and toxicokinetics of cefdinir in dogs. Dogs of both sexes were given cefdinir in gelatin capsules at 0, 200, 400, or 800 mg/kg for 26 weeks. Cefdinir was well-tolerated in the dogs at doses up to 800 mg/kg for 26 weeks without any histopathologic changes attributable to cefdinir. Dark-red stools observed in the dogs following cefdinir administration was attributed to have resulted from the presence of iron complexed with cefdinir related substances in the gastrointestinal tract. No other significant associated toxicities were observed in this study.

c. Nephrotoxicity study of Cefdinir in rats. Male S.D. rats (5/group) were treated orally at 0, 180, 320, or 560 mg/kg Cefdinir, for 14 days. Additional rats were given s.c. injections of furosemide at 100 mg/kg alone or immediately after administration of cefdinir for 14 days. Decreased urine volume, slight increased specific gravity and osmolarity were observed in all groups treated with cefdinir on Day 1. Similar changes were observed in groups given either cefdinir alone at 560 mg/kg, furosemide alone, or cefdinir and furosemide on Day 7 and in

groups given furosemide alone or with cefdinir at 320 mg/kg on Day 14. No gross or histopathologic renal changes were observed in the rats treated with cefdinir alone. In animals receiving furosemide alone or in combination with cefdinir, there were similarities in the incidence and severity of the cortico-medullary-junction focal lesions and necrosis and calcification of renal tubular epithelium. However, cefdinir did not induce nephrotoxicity or exacerbate the renal effects of furosemide.

(d). Local irritation studies by cefdinir in rabbits (eye mucosa and primary skin irritation). *The potential of topically-applied cefdinir to induce ocular or skin irritation was assessed in rabbits. Rabbits were given 0.1 ml of a 1% or 10% solution of cefdinir once in the left eye while the right eye remained untreated. In another group rabbits, 0.5 ml of a 1% or 10% cefdinir solution was applied to chemically-depilated intact or abraded skin of rabbits. A 5% solution of sodium lauryl sulfate (SLS) was evaluated as a positive control. Application sites were occluded for 24 hours and then washed with distilled water. Skin reactions were graded at 24 and 72 hrs after the application using the Draize scales. Results showed no injuries to the cornea, iris, or conjunctiva were observed. Cefdinir is therefore considered a non-ocular irritant. Cefdinir produced mean primary irritation scores of 0.1 at 1% and 0.3 at 10% as compared to a mean primary irritation score of 3.6 for the positive control. Therefore, cefdinir is considered to have a low dermal irritation potential.*

5. Reproductive Toxicology studies on Cefdinir: Cefdinir exhibited no adverse effects on fertility or general reproduction. Cefdinir was determined not to be teratogenic in rats or rabbits. It did not affect offspring survival, development, behavior, or reproduction. Fetal weight in the rat teratology study and birth/body weight in the perinatal/postnatal study were decreased but without any significant adverse effects.

RECOMMENDATION:

I. Cefdinir is an extended-spectrum, semisynthetic, β-lactam antibiotic of the cephalosporin class for oral administration in the treatment of mild to moderate bacterial infections. Cefdinir has bactericidal activity against gram-positive and gram-negative bacteria by inhibiting the bacterial cell wall synthesis. The recommended dosage is 300 mg, BID for 10 days.

II. Based on the information from submitted and reviewed safety pharmacology, pharmacokinetic and ADME, acute and subchronic toxicity, toxicokinetic, reproductive toxicology, and genotoxicity studies on the test compound, cefdinir is relatively non-toxic and tolerated at high doses in the in-vivo animal studies

III. In the labeling section, sponsor should express all of the recommended human dose as a ratio of the relevant animal studies in terms of the total body surface area in milligram/meter^2 unless AUC ratios can be calculated from animal and human values.

IV. From the standpoint of pharmacology and toxicology, NDA 50-739 for Cefdinir (Omnicef ™) Capsules should be approved.

/S/ 4/21/97

Oluwadare M. Adeyemo, Ph.D.
Pharmacologist, HFD-520

cc: NDA 50-739 (000)
HFD-340
HFD-520/Pharm/MAdeyemo
HFD-520/MO/HHamilton
HFD-520/Chem/SPagay
HFD-520/CSO/CDeballas
HFD-520/Micro/SAltaie
HFD-520/Biopharm/PColangelo
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Concurrence Only:
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RE0 4/22/97

16 4/24/97