CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-130

21-131

21-132

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 18 2000

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-130, 21-131, 21-132
Submission date:	October 15, 1999, 1P
Product:	Linezolid (U-100766)
Dosage Form:	Tablet, IV injection and Suspension
Sponsor:	Pharmacia & Upjohn Company 7000 Portage Road Kalamazoo, Michigan 49001
Type of submission:	Original New Drug Application
Reviewer:	Jenny Zheng, Ph.D.
Date received:	June-10-1999

1. INTRODUCTION

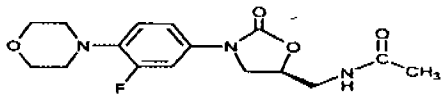
The sponsor submitted three New Drug Applications, 21-130, 21-131, 21-132, to seek approval of linezolid as an oral tablet, intravenous injection and oral suspension. The intended treatments are community-acquired pneumonia, nosocomial pneumonia, uncomplicated skin and skin structure infection, complicated skin and soft tissue infection, vancomycin-resistant *E faecium* and *faecalis* infections (VRE). Twenty-seven studies were conducted in phase 1 and 2 to characterize the pharmacokinetics of linezolid. The results were submitted as Section 6 of this application.

2. SYNOPSIS (question based)

What is linezolid?

Linezolid (U-100766, PNU100766, (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl) phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide), is an antibacterial agent of the oxazolidinone class. Linezolid is composed of a single enantiomer with the asymmetric center at C-5 of the oxazolidinone ring.

PNU-100766



Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

What are the physical chemical properties of linezolid?

The aqueous solubility is approximately 3 mg/mL. Linezolid is a weak base with a pKa of 1.8, which indicates that linezolid is not ionized in aqueous media, including blood and urine, with pH>4.

What are the clinical indications?

1. Community-acquired pneumonia
2. Nosocomial pneumonia
3. Uncomplicated skin and skin structure infection
4. Complicated skin and soft tissue infection
5. Vancomycin-resistant *E faecium* and *faecalis* infections (VRE).

How does linezolid work (Mode of Action)?

Oxazolidinones inhibit the initiation phase of bacterial protein synthesis most likely by inhibiting 30S subunit mediated initiation. The components of the [redacted] targeted by the oxazolidinones are not recognized by other antibiotics since no cross-resistance has been found in bacterial strains resistant to multiple drugs or with strains resistant to other translational inhibition antibiotics. This suggests that oxazolidinones have a different mode of action than other antibiotics. They appear to be largely bacteriostatic in action, although against *Streptococcus pneumoniae* they may be bactericidal.

Linezolid, a derivative of the template compound of the series, is effective in vitro against a range of gram positive organisms (*Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Enteroccus faecium, Streptococcus pyogenes, Streptococcus pneumoniae, Listeria monocytogenes, and Moraxella catarrhalis*) including both fully sensitive and multiple-drug resistant strains.

Does linezolid work in animal models?

Yes. Numerous animal models have been used to establish efficacy of linezolid. Linezolid has proven to be efficacious in mouse lethal systemic infections by both oral and parenteral routes of administration. Activity has been demonstrated for staphylococci, enterococci, and pneumococci. Linezolid has been used effectively in combination with other agents to treat monomicrobic MRSA infections and polymicrobic infections in mice. Linezolid was efficacious in the treatment of soft tissue infections in mice due to staphylococci, enterococci, and pneumococci, as well as polymicrobic soft tissue infections due to *Escherichia coli*, and *Enterococcus faecalis*.

Was a PK/PD relationship established in animal models?

Yes. The major pharmacodynamic parameter responsible for linezolid in vivo activity was determined in a mouse thigh infection model; the major parameter determining efficacy for both *Staphylococcus aureus* and *Streptococcus pneumoniae* was "Time Above MIC." Efficacy was achieved when the drug concentration was maintained above the MIC for ~ 40% of the dosing interval.

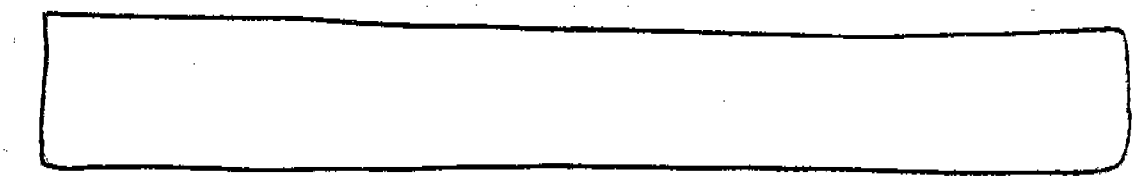
What *in vitro* or animal studies were conducted to identify important drug-drug interaction issues?

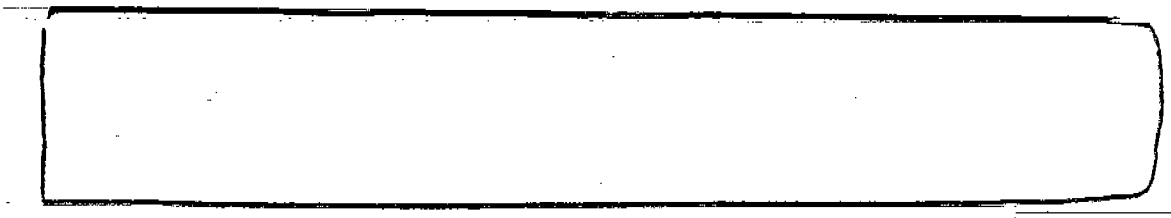
1. The initial investigation into the mechanism of linezolid metabolism was with the cytochrome P450 system. In vitro metabolism studies using specific probe substrates and cDNA expressed human cytochrome P450 isoforms showed that linezolid is not an inhibitor of the activities of clinically significant human cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. No meaningful induction of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A, and CYP4A was observed in studies of rat livers from the 90-day oral toxicology study. Therefore, clinically significant drug interactions mediated through inhibition or induction of cytochrome P450 isoforms by linezolid are not expected.

   Further investigation into the mechanism of linezolid metabolism was conducted in vitro. It was found that the metabolism of linezolid was mediated by non-enzymatic

chemical oxidation to the unstable hemiacetal PNU-143011, the precursor of the major human metabolite, PNU-142586.

2. It was found that linezolid was a mild, reversible monoamine oxidase inhibitor in vitro, but no stable sensitive animal models could be found.





How was the first dose selected for human study?

The first dose in humans was selected based on toxicity data obtained from animals. In the subchronic/chronic animal studies, the NOAELs were generally in the range of 10-20 mg/kg/day. The starting single dose of 50 mg in human was approximately 0.833 mg/kg/day, which is 1/24 of 20 mg/kg/day. Therefore, the first human dose was considered safe.

How were the initial human tolerance, safety and PK determined?

Six studies were conducted to study the safety, tolerance and basic PK characteristics.

1. single oral doses of 50 mg to 500 mg;
2. multiple oral doses of 100 mg to 750 mg given every 8 hours for up to 10 days;
3. single IV doses (30-minute infusion) of 250 mg to 750 mg;
4. multiple IV doses of 250 mg to 500 mg given every 8 hours for up to 7 days;
5. multiple oral doses of 125 mg to 625 mg given every 12 hours for 14 days;
6. multiple IV doses of 500 mg and 625 mg given every 12 hours for 7 days

What are the pharmacokinetics characteristics of linezolid?

1. Linezolid is rapidly and extensively absorbed after oral administration. Maximum concentrations (C_{max}) are reached approximately 1-2 hours after dosing.
2. After single or multiple IV doses, the total systemic elimination clearance (CL) averaged about 100-200 mL/minute. About 35% of the dose is eliminated as unchanged linezolid in the urine. Renal clearance (CLr) averaged about 30-50 mL/minute, which suggests net tubular reabsorption. The nonrenal clearance (CLnr), calculated as the difference between CL and CLr, averaged about 70-150 mL/minute and is more variable than CLr.
3. The variability of linezolid CL was high.
4. CL was decreased when dose was increased, indicating nonlinear PK.

5. The distribution of linezolid appears to approximate total body water, as the steady-state volume of distribution (Vss) averaged about 40-50 L (0.6-0.7 L/kg).
6. The elimination half-life averaged about 5-7 hours.
7. In both iv and oral multiple dose studies, it was found that a dose of 750 mg every 8 hours and could not be tolerated due to the increase of serum creatinine.

How was the clinical dose regimen selected?
Based on a 625mg bid, multiple dose PK study, the trough linezolid concentration was higher than 4 μg/mL (MIC_{90} of *Staphylococcus aureus)*. Therefore, linezolid 600 mg every 12 hours was selected as the dose regimen for phase II studies.

Is the dose versus exposure proportional within therapeutic range?
There is a small degree of nonlinearity with higher doses of linezolid. The total clearance for the 625-mg dose is about 25%-35% lower than would be predicted from the 125-mg dose. The decrease in CL was accounted for by decreases in both CLr and CLnr. The studied doses were 125 mg, 375 mg and 625 mg.

What is the bioavailability?
The average relative bioavailability was 103% (ranged from 78% to 133%) for oral dosage forms.

Does food affect the bioavailability?
Yes, the T_{max} is delayed from 1.5 hours to 2.2 hours when high fat food was given with linezolid. The C_{max} was 23% lower (6.2 μg/mL vs 7.6 μg/mL) when high fat food was given with linezolid. The difference is statistically significant. But similar $AUC_{0-\infty}$ values were measured under both conditions. The sponsor claimed no food effect on oral formulation considering the high intrinsic variability of linezolid pharmacokinetics.

How many formulations have been used in the drug development process? Are these formulations bioequivalent?
Twelve oral formulations were used in clinical trial studies including tablet, suspension and capsule. Capsules were prepared by placing tablets in hard shell capsule. Oral tablet and suspension formulations are bioequivalent, but bioequivalence between the tablet and capsule used in the clinical trials was not studied. Another bioequivalence study demonstrated bioequivalence between the capsule containing milled bulk and the compressed tablet, indicating the bioavailability of linezolid was not sensitive to the encapsulation.

How does the linezolid distribute in the body?
The distribution of linezolid appears to be limited to the volume of total body water as the steady-state volume of distribution (V_{ss}) determined following intravenous administration averaged about 40-50 L (0.6-0.7 L/kg). Values for volume of distribution following oral administration (V_z) were comparable to V_{ss}.
Concentrations of linezolid in the saliva were highly correlated with plasma concentrations of drug measured at the same time points. The saliva concentrations were consistently 23%-30% higher than those in plasma.

Sweat concentrations of linezolid were determined as an indicator of distribution of linezolid in skin. Concentrations of linezolid in sweat samples correlated well with those of the plasma. The sweat concentrations were 55% of those in plasma.

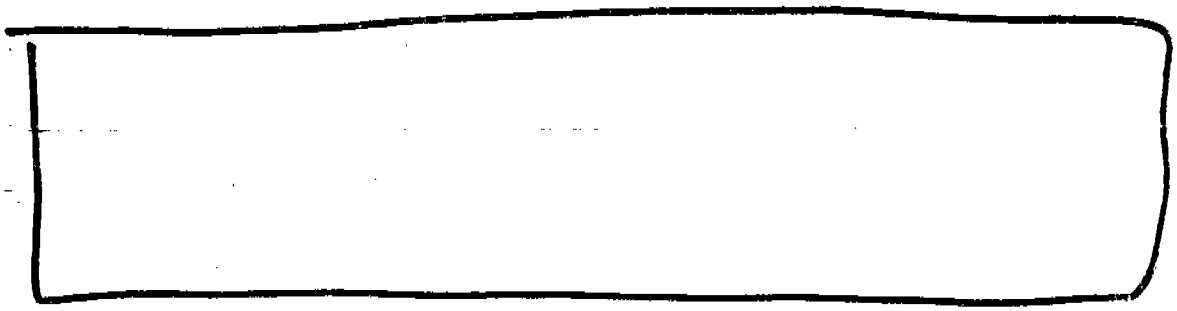
How is linezolid metabolized in humans?
The three major drug-related compounds in excreta are linezolid and metabolites PNU-142586 and PNU-142300. Both major metabolites are derived from oxidation of the morpholine ring which results in the ring-opened carboxylic acid metabolites. Nonrenal clearance generally accounts for approximately 65% of the total clearance of linezolid. Of these two major nonrenal elimination pathways, PNU-142300 represents a relatively constant and low 9% to 11% of the dose. In vitro studies showed that formation of the major metabolite, PNU-142586, is mediated by a chemical oxidation that is a nonenzymatic (noncatalytic) process. The enzymes or oxidants that contribute to PNU-142586 formation in vivo have not been elucidated.

Are the metabolites active?
Both major metabolites are not active.

Are the metabolites toxic?
The toxicity of the metabolites is unknown. In vitro studies demonstrated that the Ki for monoamine amine oxidase was high (1 mM), indicating metabolites are less likely to have MAOI effect.

How is linezolid excreted?
The mass balance measurements accounted for approximately 94% of the dose in urine and feces. Approximately, 35% of dose was accounted for as parent drug in the urine, and approximately 50% of the dose was accounted for as the two major metabolites in the urine (approximately 40% as PNU-142586 and 10% as PNU-142300). Approximately 10% of the dose was found as the two major metabolites in the feces.

Is there a difference in linezolid PK between males and females?
After a single dose of 600 mg linezolid, there was a significant difference between males and females, with mean $AUC_{0-\infty}$ for females being ~ 64% greater than mean $AUC_{0-\infty}$ for males. There were no significant differences between males and females in mean apparent elimination-rate constant or half-life. There was a significant difference in mean apparent oral clearance (CL_{PO}) between males and females. CL_{PO} for females was ~37% lower than mean CL_{PO} for males when not corrected for body weight. Correcting for differences in weight reduced this difference to ~20%. Overall, females had a slightly lower volume of distribution than males.



How different is the PK among various ethnic groups?
No pharmacokinetics studies have been conducted. However, in a population pharmacokinetics study, it was found that non-Caucasian patients had a slightly higher elimination of linezolid through the linear pathway than Caucasian patients. The contribution of linear clearance is rather small, and the total clearance for non-Caucasian patients was similar to that of white patients.

Is dose adjustment needed in elderly?
No significant differences were found between the young and elderly for $AUC_{0-\infty}$, C_{max}, CL_{PO} , V_z, elimination rate constant, or half-life.

Is dosage adjustment needed in patients with renal impairment?
No. The $AUC_{0-\infty}$ was not different over the range of renal function tested (CLcr> 10 mL/min). For the end stage renal failure patient, total apparent oral clearance increased in subjects on dialysis from 76.6 mL/minute on their off-dialysis day to 130 mL/minute on their on-dialysis day. Hemodialysis was a significant source of elimination of linezolid in the end-stage renal failure patient. Although patients with different levels of impaired renal function seemed to have similar exposure, the exposure to the two metabolites was significantly different. For metabolite PNU-142300, compared with the exposure in healthy volunteers, total exposures measured as AUC are 53%, 631%, and 3516% greater in moderate renal impaired (CLcr: 40-79 mL/min), severely renal impaired (CLcr:10-39 mL/min), and anuric patients, respectively. Accordingly, the half-lives of the metabolite PNU-142300 are increased in renal impaired patients. For metabolite PNU-142586, even more exposure was observed. Compared with the exposure in healthy volunteers, the total exposures measured as AUC are 68%, 566% and 4744% greater in moderate renal impaired, severely renal impaired, and anuric patients, respectively. The half-lives of the metabolites are significantly increased. The increased half-life would result in more significant accumulation when repeated doses are given.

Is dosage adjustment needed in patients with hepatic impairment?
No statistically significant differences in linezolid pharmacokinetic parameters were observed for patients with mild-to-moderate liver disease relative to healthy volunteers. But severe hepatic impaired patients were not studied. The two metabolites did not appear to accumulate in patients studied.

What are the drug-drug interaction concerns based on the available information?

(i) Although in vitro and animal study demonstrated that linezolid is not cytochrome P-450 substrate, inducer or inhibitor. However, cytochrome P-450 isoform 2C9 (CYP2C9) is not expressed in the rat and therefore possible induction of CYP2C9 could not be examined in this species. Therefore, the drug-drug interaction study with warfarin was conducted in human. Both pharmacokinetics and pharmacodynamics measured as International Normalized Ratio (INR) were evaluated. The mean $AUC_{0-\infty}$ value for S-warfarin during linezolid treatment was significantly greater (20%) than the value following linezolid alone. There were no significant differences for either enantiomer in mean C_{max} or t_{max}, and no significant differences for (R)-warfarin in mean $AUC_{0-\infty}$ or CL_{PO} during concomitant linezolid therapy as compared to warfarin administration alone. There were significant differences in CL_{PO} for (S)-warfarin (mean value during linezolid therapy was 15% less than value determined during warfarin alone). Statistically significant reductions in mean maximum INR and area under the INR versus time curve during linezolid therapy were observed. However, the magnitude of these differences was very small; the percent reduction in mean maximum INR was only 9.9% and the percent reduction in area under the INR versus time curve was only 4.6%.

(ii) Since linezolid is only active for Gram positive organisms, without identifying the organisms, linezolid will likely be used with antibiotics which are active to Gram negative organisms such as aztreonam, and gentamicin. Therefore, drug-drug interaction studies were conducted and showed that linezolid has no PK drug-drug interaction with either aztreonam or gentamicin.

(iii) Since it was found from in vitro studies that linezolid was a mild reversible MAO-A and MAO-B inhibitor, three drug-drug interaction studies with pseudoephedrine, phenylpropanolamine and dextromethorphan were conducted. The results indicted that pharmacokinetics of linezolid was not affected by these three drugs. Linezolid had minimal effect upon the pharmacokinetics of pseudoephedrine with an approximate 10% increase in plasma concentrations. However, linezolid did affect the pharmacodynamics of phenylpropanolamine and pseudoephedrine as measured by systolic blood pressure. The mean increase in the maximum positive change in systolic blood pressure over the test period was 18 mmHg (range 5-39 mmHg) during pseudoephedrine administration and 32 mmHg (range 20-52 mmHg) during co-administration of linezolid with pseudoephedrine. A mean increase of 11 mmHg (range 0-27 mmHg) was observed for the placebo treatment. Likewise, an increased response was observed in the mean increase in the maximum systolic blood pressure attained when linezolid was administered with pseudoephedrine. A mean maximum value of 151 mmHg (range 131-174) was observed following the combination versus a mean maximum value of 133 mmHg (range 104-161) during pseudoephedrine administration, and a value of 130 mmHg (range 101-152) during the placebo treatment. Similarly, linezolid increased the AUC of phenylpropanolamine by about 22% and C_{max} by about 20%. The mean increase in the maximum positive change in systolic blood pressure over the test period was 14 mmHg (range 0-40

mmHg) during phenylpropanolamine administration and 38 mmHg (range 18-79 mmHg) during co-administration of linezolid with phenylpropanolamine. A mean increase of 8 mmHg (range 0-26 mmHg) was observed for the placebo treatment. Likewise, an increased response was observed in the mean increase in the maximum systolic blood pressure attained when linezolid was administered with phenylpropanolamine. A mean maximum value of 147 mmHg (range 129-176) was observed following the combination, versus a mean maximum value of 125 mmHg (range 106-139 mmHg) during phenylpropanolamine administration, and a value of 121 mmHg (range 103-158 mmHg) during the placebo treatment. Similar increases were observed in the area under the response curve for systolic pressure and the diastolic pressure response.

No significant differences in body temperature, digit symbol substitution (a measure of cognitive function), nurse-rated sedation, blood pressure, or pulse were noted with dextromethorphan alone versus dextromethorphan given during linezolid use indicating no evidence of serotonin syndrome effects.

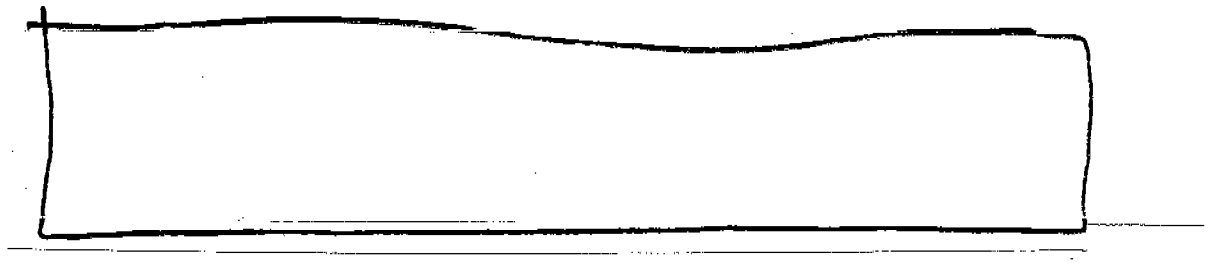
The sponsor proposed the changes in blood pressure are within normal daily activity, however, the significance of the changes is being assessed by the clinical division.

Due to the MAO inhibitory effect of linezolid, the interaction with tyramine contained in the food was investigated. It was found that at least 100 mg tyramine was necessary to increase the systolic blood pressure by 30 mmHg under linezolid treatment. Therefore, the interaction was found to be not significant. The patients using linezolid should avoid consumption of large amounts of tyramine containing food.

How has the sponsor integrated PPK and PK/PD information in phase II studies?

The sponsor conducted one population pharmacokinetics study. But due to the high variability and nonlinear pharmacokinetics of linezolid, the model could not describe the data well. Therefore, this study was not successful. The PK/PD relationship was investigated. The derived PK parameters were correlated with clinical outcome. It was found that the AUC/MIC is the efficacy predictor, which is not consistent with animal study. However, due to the unsuccessful PPK studies, the PK/PD relationship was found to be not reliable.

Another PK/PD was conducted in phase II. The eradication of *Staphylococcus aureus* from the nose was the clinical endpoint. However, due to the high eradication rate (44 from 48), no PK/PD relationship was found.



3. COMMENTS (To be sent to the sponsor):

i. Drug-drug interaction study with antioxidants
It has been found from in vitro studies that the linezolid is oxidized by free radicals generated from the liver. This pathway metabolized 40% of administered linezolid. If antioxidants, such as vitamin E or C are taken with linezolid, an interaction is likely. In vitro evidence that the formation of linezolid oxidized product is inhibited by 60% when the antioxidant butylated hydroxyanisole (BHA) is present, appears to support the likelihood of an interaction conclusion.

ii The sponsor should consider a pharmacokinetics study to investigate the difference due to race between Oriental and Caucasian. Only one male oriental subject was included in phase 1 studies and the CL of this subject was 33 mL/min. The average CL of other male subjects (15 Caucasian and 1 Hispanic) from the same study at the same dose was 96.1 mL/min. The difference in CL could be a race effect.

iii. The mechanism of the metabolite elimination should be further studied. It was found that the two primary metabolites accumulated in renal impaired patients. It was also found in the mass balance study that the metabolites accumulated in females after multiple doses. It should be determined if the elimination of the metabolites is active secretion in order to exclude potential drug-drug interactions.

iv. For the suspension, more than 90% of drug is dissolved at 15 minutes therefore, the specification is suggested to be not less than 85% (Q=[redacted]) dissolved at 15 minutes instead of 30 minutes which was suggested by the sponsor for both tablet and suspension.

v. It was found that the CL corrected by body weight in pediatric patients is higher than CL in adults. Additional pharmacokinetics studies in pediatric patients should be conducted in order to choose an adequate dose regimen.

COMMENTS (not sent to the sponsor)

It was found from the "use-test" study that air was trapped in linezolid suspension due to vigorous mixing. Therefore, linezolid dose in the bioequivalence study might have been under-dosed, which may explain why the confidence intervals of AUC and C_{max} were at the low end of the criterion. Although possibly under-dosed, the study still demonstrated that the suspension was bioequivalent with the tablet. The further "use-test" studies demonstrated that changing the way of mixing from vigorous shaking to gently inverting the bottle could decrease the air trapped in the suspension.

The bioequivalence study was acceptable from a clinical pharmacology and biopharmaceutical point of view. The chemist should evaluate the sponsor's manufacturing and controls program for linezolid powder for oral suspension to ensure the product delivers consistent dose to the patient by gently shaking the bottle prior to administration. The final product label should include directions to gently shake the bottle of suspension prior to use.

4 page(s) of revised draft labeling has been redacted from this portion of the review.

/S/ 4/17/00

Jenny Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT initiated by F. PELSOR, Pharm.D., Team Leader /S/ 4/18/00

cc: Original NDA 21-130, 21-131, 21-132
Division File: NDA 21-130, 21-131, 21-132
HFD-520 (D. Ross, Medical Officer, J. Alexander, Medical Officer)
HFD-880 (Division File; F. Pelsor, TL)
CDR (attn: B. Murphy)