CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-130, 21-131, 21-132 /S009
Submission date:	December 16, 2004
Product:	Linezolid (U-100766)
Sponsor:	Pfizer
Type of submission:	Labeling supplement
Reviewer:	Jenny J Zheng, Ph.D.

EXECUTIVE SUMMARY:

The sponsor submitted this application to request the Agency consider this supplement as a basis for granting the sponsor the additional marketing exclusivity based on pediatric data. Five studies were requested in the written request and this supplement consists of final study reports for Studies 4 and 5. The reports for Studies 1, 2, and 3 were included in supplemental NDA(s) 21-130/S003, 21-131/S003, and 21-132/S003, filed June 24, 2002, which were the basis for approval of pediatric use of the drug. The two studies in this application are as follows:

Study 4: Linezolid IV/PO for the Treatment of Vancomycin-Resistant Enterococcus Infections in Children.
Study 5: Ventricular Fluid and Plasma Levels in Pediatric Patients Receiving Multiple Doses (10 mg/kg) of Linezolid 3 Times Daily.

This review includes the evaluation of Study 5.

The results of the study showed that the steady-state Cmax in ventricular fluid was 5.84 ± 2.77 µg/mL (47% CV; range 1.8 to 9.3 µg/mL), and the steady-state trough concentrations were 1.94 ±1.72 µg/mL (84% CV; range (b)(4) µg/mL) after repeated doses of 10 mg/kg q8h. The dose regimen of 10 mg/kg q8h was used in this study because it was approved regimen in pediatric patients (<12 years old). The mean ratio of area under the curve of plasma-time profile to that of ventricular fluid (VF) concentration-time profile (AUC_{plasma}/AUC_{vf}) at steady state is about 95.3% with CV of 27%, (n=7), indicating a good penetration of linezolid into cerebrospinal fluid. However, these exposures are not believed to be adequate for gram-positive susceptible organism with MIC_{90} of 1-4 µg/mL for treatment of CNS shunt infections, for the following reasons:

1. The required exposure for treatment of CNS shunt infection and meningitis is higher than required exposures for other approved infections. The effective treatment of CNS shunt infections likely requires that the drug concentration in CSF are:
    - several fold higher than the MIC of the target pathogen
    - above the MIC throughout the dosing interval.

2. The variability of linezolid exposure in CSF is high. Concentration of linezolid above MIC90 are not consistently achieved and maintained in CSF.

Based on the required exposures and pharmacokinetic data of linezolid in VF, the study results indicated that the linezolid at 10 mg/kg q8h would not provide adequate exposures for treatment of CNS infections caused by gram-positive susceptible organism with MIC of 4 μg/mL. Therefore, the following information was proposed by the sponsor to be added in the label:
Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended.

COMMENTS:
Linezolid exposure in ventricular fluid might not be adequate to reach the required level that the concentration should be above MIC during the entire dose interval for treatment of CNS infection caused by organism with MIC of about 4 μg/mL but appeared reasonable for the organism with MIC of about1 μg/mL based on the time above MIC value.

RECOMMENDATION:
The supplemental application has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of pharmaceutical evaluation III. The application and proposed labeling changes are found to be acceptable.

STUDY #: OXAA-0026-147

TITLE: Linezolid: Ventricular Fluid and Plasma Levels in Pediatric Patients Receiving Multiple Doses (10 mg/kg) of Linezolid 3 Times Daily

OBJECTIVE:

- To assess the penetration of linezolid in the ventricular fluid (VF) of pediatric patients with an extra-ventricular drainage catheter, with or without acute inflammation, who were receiving multiple doses (10 mg/kg) of linezolid every 8 hours (q8h).
- To assess the relationship between ventricular inflammation and linezolid penetration into the ventricular fluid.

STUDY DESIGN:

This open-label, multiple-dose, single-treatment study was planned to enroll 16 pediatric male or female hydrocephalic patients, between the ages of birth through 11 years (inclusive; less than 12 years of age), with an existing extra-ventricular drainage catheter, with or without acute inflammation. Patients being treated for a suspected and/or culture proven bacterial infection were eligible for enrollment in the study. The 16 patients were to stratified into 4 groups: 1) birth through 2 years; 2) 3 through 5 years; 3) 6 through 8 years; and 9 through 11years.

Each subject was to be administered 10 mg/kg (up to a maximum of 600 mg) linezolid sterile solution given as a 30-minute infusion every 8 hours (q8h) for a total of 6 doses.

Blood and VF samples were obtained prior to and at 2, 4 6, and 8 hours after the first and last dose. The following pharmacokinetic (PK) parameters were assessed: area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin). The ratios (VF/plasma) for AUC, Cmax, and Cmin were also calculated. As markers of inflammation, WBC, protein and glucose concentrations in the VF were also measured.

BIOASSAY:

Six runs were performed to report the linezolid concentrations found in the plasma and VF specimens. Correlation coefficients were all (b)(4). Relative standard deviations (RSD%) were used to express the precision of the back-calculated calibration standard. The (b)(4) calibration standard points had RSDs that were (b)(4) with mean accuracies between (b)(4) . Interday accuracy and precision was further monitored by analysis of 3 levels of linezolid quality control (QC) standards with target concentrations of (b)(4) ng/mL. Interday precision (RSD%) for the 3 levels of QC standards was (b)(4) with mean accuracies between (b)(4) . Dilution quality control (DQC) standard was also monitored at 100-fold dilution, with interday precision (RSD%) of (b)(4) and accuracy of (b)(4) .

RESULTS:

Due to the enrollment difficulties, only 8 patients were enrolled and completed the study. One subject was receiving linezolid prior to the first study dose, therefore, all pharmacokinetic data (including plasma and VF concentration values and PK parameter

values) for the first dose was excluded from descriptive statistics. Among the 8 subjects, age ranged from 0.2 to 11.6 years. The demographic characteristics of patients and the summary of pharmacokinetic parameters in plasma and VF are shown in Table 1 and Table 2, respectively. The individual plasma or VF concentration vs time profiles are presented in Figure 1. The results of this study show that steady-state Cmax in VF was 5.84 ±2.77 µg/mL (47% CV; range (b)(4) µg/mL), and the steady-state trough concentrations were 1.94 ±1.72 µg/mL (84% CV; range (b)(4)). The concentrations in the VF from these patients are highly variable.

CONCLUSION:

The mean penetration of linezolid into CSF, represented as AUC ratio of plasma and VF, is about 95.3% after repeated doses of 10 mg/kg q8h, indicating a good penetration of the drug into CSF. However, the variability among patients is high.

In general, effective treatment of CNS shunt infections likely requires drug concentrations in VF several fold higher than the MIC of the target pathogen and concentrations above the MIC throughout the dosing interval. It is thought that for efficacy of serious CNS infections that concentrations need to be maintained above the MIC_{90} for the entire dosing interval, and some believe the levels should be as much as 3- to 10-fold higher than the MIC_{90} for the entire dosing interval. The MIC_{90} of gram-positive susceptible organisms for linezolid is about between 1 and 4 µg/mL.

The time when concentrations was above 4 µg/mL and 1 µg/mL at steady state in both ventricular fluid and plasma are shown in the following table:

	Ventricular Fluid			Plasma		
MIC (µg/mL)	# of subject with TMIC* > 8 (h)	# of subject with TMIC*=0	Mean TMIC (n=8) (h)	# of subject with TMIC* > 8 (h)	# of subject with TMIC=0	Mean TMIC (n=8) (h)
4	1	2	3.04	0	1	3.02
1	5	0	7.40	2	0	5.66

* TMIC: time when steady state concentration are above MIC (4 or 1 µg/mL)

The results indicated that linezolid exposure in ventricular fluid might not be adequate to reach the required level mentioned above for treatment of CNS infection caused by organisms with higher MICs of about 4 µg/mL but appeared reasonable for the organisms with lower MICs of about 1 µg/mL based on the time above MIC value. The linezolid exposure in plasma was not any better than linezolid exposure in ventricular fluid. However, the plasma level might be acceptable as demonstrated by clinical studies. The explanation might be that a higher exposure might be needed for CNS infection as compared with other approved indications.

Table 1. Demographic Characteristic of Patients

Subject	Sex	Race	Age (years)	Weight (kg)	Height (cm)	Body Mass Index (kg/m sq)
1101	Female	White	0.2	5.0	54.0	17.2
2102	Male	Asian	1.3	9.7	ND	ND
2201	Male	White	3.9	13.6	102.0	13.1
2401	Male	Black	9.6	16.5	135.0	9.1
4101	Male	Black	0.7	7.5	67.0	16.7
4401	Female	White	10.4	44.0	ND	ND
5101	Male	White	1.3	7.5	77.0	12.6
5401	Female	White	11.6	38.0	132.0	21.8
N			8	8	6	6
Mean ±SD			4.9 ±4.8	17.7 ±14.9	94.5 ±34.1	15.1 ±4.4

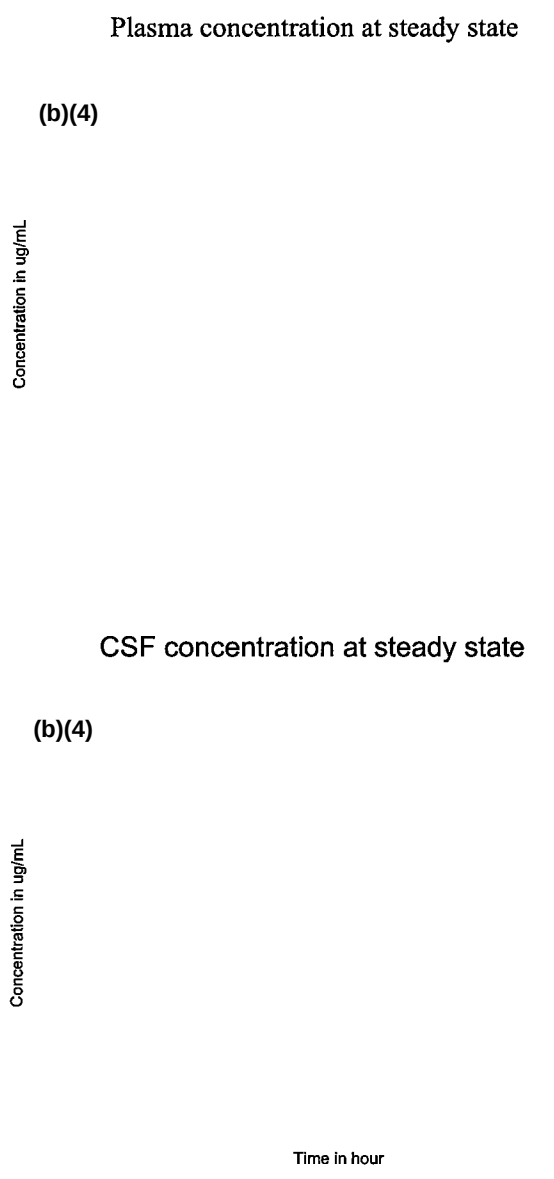
Table 2. Summary of Linezolid Plasma and Ventricular Fluid (VF) Pharmacokinetic Parameters

	Mean (%CV) Parameter Values					
	First Dose			Last Dose		
	Plasma	VF	Ratio (Plasma/VF)	Plasma	VF	Ratio (Plasma/VF)
N	7	7	7	8	8	8
tmax, hr	2.00 (9)	3.38 (65)	NA	1.77 (41)	2.78 (53)	NA
Cmax, µg/mL	8.32 (45)	3.31 (39)	0.480 (69)	9.83 (50)	5.84 (48)	0.647 (46)
AUC(0-8), µg hr/mL	25.7 (58)	15.2 (27)	0.732 (47)	33.3 (66)[a]	28.7 (56)	0.953 (27)[a]
Cmin, µg/mL	0.510 (146)	1.30 (88)	5.04 (108)	1.12 (116)	1.94 (84)	3.56 (90)

NA = Not Applicable

[a] N=7

Figure 1. Linezolid Concentration in Ventricular or Plasma vs Time profiles at Steady State and After a Single Dose of 10 mg/kg



Plasma Concentration after Single Dose

(b)(4)

Concentration in ug/mL

8

CSF Concentration after Single Dose

(b)(4)

Concentration in ug/mL

8

Time in hour

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/s/

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