

Study 54A, Vancomycin-Resistant *Enterococcus* (VRE)

<p>Name of Company: Pharmacia & Upjohn</p> <p>Name of Finished Product:</p> <p>Name of Active Ingredient: Linezolid (PNU-100766)</p>	<p>Individual study table</p>	<p>(For national authority use only)</p>
<p>Exclusion criteria: Patients were to be excluded from the study if they met any of the following criteria: females of child-bearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy test result within 24 hours prior to study entry, were otherwise known to be pregnant, or were currently breastfeeding an infant; had endocarditis, osteomyelitis, or central nervous system (CNS) infections; had infected devices that were not to be removed; had gas gangrene or necrotizing fasciitis; had known pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled or untreated hypertension; had previously enrolled in this or another linezolid study; were hypersensitive to linezolid or one of its excipients; were currently using another investigational medication; had received more than 24 hours of a potentially effective antibiotic in the last 7 days prior to entry or since the last positive blood culture.</p> <p>Test product, dose and mode of administration, batch numbers: 600 mg IV (batch number 98I23Z14 and 98I08Z04) or oral linezolid every 12 hours (batch number 38,228) and 200 mg IV (batch number 98I23Z14) or oral linezolid every 12 hours (batch number 38,228).</p> <p>Reference therapy, dose and mode of administration, batch numbers: None</p> <p>Duration of treatment: 7 to 28 consecutive days</p>		
<p>Criteria for evaluation: The primary efficacy evaluations were based on the resolution of clinical and microbiological signs and symptoms of VRE infection when compared with Baseline. Adverse events, changes in physical findings, vital signs, and laboratory values were used to assess safety.</p> <p>Clinically Evaluable Analyses: All patients who met any of the following criteria were considered clinically nonevaluable: use of a potentially effective concomitant antibiotic, insufficient therapy (<7 days or <13 doses), noncompliance with study medication regimen (ie, <80% taken or missed 2 or more consecutive doses through Day 7), primary source of VRE infection of endocarditis, meningitis, osteomyelitis or infected device, or no post-Baseline assessment (unless the patient was classified as a failure at EOT or was given an antibiotic due to lack of efficacy).</p> <p>Microbiologically Evaluable Analyses: To be Microbiologically Evaluable, in addition to the criteria listed above, patients were required to have confirmed VRE from the infection site or blood culture in the evaluable window at Baseline; and the pathogen must not have been resistant to study medication.</p> <p>Intent-to-Treat (ITT) Analyses: The ITT population included all randomized patients who received at least one dose of study medication.</p> <p>Modified-Intent-to-Treat (MITT) Analyses: The MITT population included all patients in the ITT population who also had a pathogen isolated at Baseline.</p> <p>Efficacy: Primary efficacy was assessed by evaluating patient clinical outcome (sponsor and investigator). Secondary efficacy was assessed by evaluating patient microbiological outcome, patient overall outcome, clinical signs and symptoms, individual pathogen eradication rates, body temperature, and white blood cell counts.</p> <p>Safety: Safety was assessed by the collection and analysis of data on adverse events, clinical laboratory assays, physical examinations, vital signs, and concomitant medications.</p>		

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<p>Statistical methods: The primary efficacy variables in this study were Sponsor-Defined Patient Clinical Outcome and Investigator-Defined Patient Clinical Outcome. The proportions of patients in each group were compared between treatment groups at F-U using a chi-square test for homogeneity of proportions. In addition, 95% confidence intervals (CI) for the differences in success rates between the treatment groups were calculated. These analyses were done separately for ITT, MITT, Clinically Evaluable, and Microbiologically Evaluable patients for the Sponsor-Defined Patient Clinical Outcome. These analyses were also done for the MITT and Clinically Evaluable populations for the Investigator-Defined Patient Clinical Outcome. The secondary efficacy variables of Sponsor's Patient Microbiological Outcome and Patient Overall Outcome were analyzed similarly to that performed for the Sponsor-Defined Clinical Outcome.</p> <p>Additional endpoints, including other secondary efficacy variables, safety, and Baseline demographics, were analyzed for treatment differences via chi-square tests and one-way analysis of variance F tests (ANOVA). Safety laboratory assays and vital signs were analyzed for statistical changes from Baseline to each post-Baseline visit within treatment groups using a paired t-test and for treatment group comparisons of mean changes from Baseline using one-way analysis of variance F-tests. Details of the statistical methods are presented in Section 9.8 of the clinical study report.</p> <p>Results:</p> <p>Demographic and other Baseline characteristics: There were no significant differences in age, weight, sex, and race between groups. Both treatment groups were comparable with respect to Baseline characteristics.</p> <p>Disposition of patients: Of the 145 patients who enrolled in the study, 79 were randomized to the high dose treatment group, and 66 were randomized to the low dose treatment group. A total of 110 patients completed treatment. Of these, 60 patients received high dose linezolid and 50 patients received low dose linezolid. Comparable percentages of patients between treatment groups completed follow-up.</p> <p>Efficacy results: The 600 mg dose was consistently more effective in the treatment of VRE infections than the 200 mg dose. This dose effect was manifested both clinically and microbiologically with more clinical cures and fewer microbiological failures in the high dose group. The 600 mg dose demonstrated statistical superiority over the 200 mg dose for patient microbiological outcome and patient overall outcome, including supplementary analysis in which indeterminates were classified at failures. <i>Enterococcus faecium</i> was the predominant pathogen realized in the study. The eradication rates for the <i>E faecium</i> were statistically higher in the 600 mg dose group. Furthermore, clinical and microbiological outcome could not be explained by concomitant use of aminoglycosides.</p>		
<p>Safety results: There does not appear to be a dose relationship associated with the occurrence of adverse events. Overall, there were significantly more adverse events in the low-dose treatment group and a greater number of patients died in the low-dose treatment group. The low-dose treatment group also had significantly more adverse events in the nervous system than in the high-dose treatment group (in spite of the latter having more nervous system abnormalities at Baseline). The number of serious adverse events was similar between high-dose and low-dose treatment groups. There were no clinically relevant differences between treatment groups for any laboratory assay, however more substantially low platelets were observed in the high-dose treatment group.</p> <p>Conclusion: Although our enrollment target was not reached (nor was the desired statistical power under study assumptions), significant differences were still seen between treatment groups. This is most evident in the patient microbiological outcome and patient overall outcome where in all general populations the 600 mg dose was statistically superior to the 200 mg dose. The addition of an aminoglycoside did not improve outcomes. Thus, linezolid alone is effective in treating vancomycin-resistant enterococcal infections, including <i>E faecium</i>. Except for reversible thrombocytopenia, there were no adverse events that appeared to be dose-related.</p> <p>Date of the report: 21 September 1999</p>		

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Table 1. Study-Emergent Adverse Events $\geq 10\%$ Within Body Systems: ITT

COSTART Body System /MET	600 mg BID N = 79		200 mg BID N = 66	
	n	%†	n	%†
Patients With None	8	10.1	1	1.5
Patients With at Least One	71	89.9	65	98.5
BODY				
Fever	11	13.9	11	16.7
Sepsis	9	11.4	9	13.6
Localized Pain	3	3.8	8	12.1
CARDIOVASCULAR				
Hypertension	5	6.3	7	10.6
Hypotension	7	8.9	13	19.7
DIGESTIVE				
Diarrhea	9	11.4	13	19.7
Nausea	7	8.9	12	18.2
Vomiting	11	13.9	10	15.2
HEMIC AND LYMPHATIC				
Anemia	8	10.1	8	12.1
Thrombocytopenia	8	10.1	1	1.5
METABOLIC AND NUTRITIONAL				
Peripheral Edema	8	10.1	2	3.0
NERVOUS				
Somnolence	3	3.8	7	10.6
SKIN				
Erythema	1	1.3	7	10.6
Rash	6	7.6	7	10.6
UROGENITAL				
Infection Urinary Tract	8	10.1	5	7.6

† Percentages are based on the number of patients reporting. Patients are only counted once for each MET. MET (Medically Equivalent Term) is a standardized version of the adverse event verbatim based on COSTART conventions.

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; BID = Twice daily

Reference: Section 14, Table 7.3; Appendix 15, Table S-4

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Table 2. Study-Emergent Drug-Related Adverse Events $\geq 2\%$ Within Body System: ITT

COSTART Body System/MET	600 mg BID N = 79		200 mg BID N = 66	
	n	%†	n	%†
Patients With None	59	74.7	52	78.8
Patients With at Least One	20	25.3	14	21.2
CARDIOVASCULAR				
Hypertension	1	1.3	2	3.0
DIGESTIVE				
Diarrhea	0	-	3	4.5
Incontinence Fecal	2	2.5	0	-
Vomiting	2	2.5	0	-
HEMIC AND LYMPHATIC				
Thrombocytopenia	3	3.8	1	1.5
SKIN				
Rash	2	2.5	2	3.0

† Percentages are based on the number of patients reporting.

MET (Medically Equivalent Term) is a standardized version of the adverse event verbatim based on COSTART conventions.

Drug-related is defined as events specified as related to or with relatedness not reported.

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; BID = Twice daily

Reference: Section 14, Table 7.6; Appendix 15, Table S-4

Table 3. Frequency Table for Selected Substantially Abnormal Laboratory Values (Corrected for Baseline Abnormalities): ITT

Laboratory Assay	Criteria*	Linezolid 600 mg BID			Linezolid 200 mg BID		
		n	N	%	n	N	%
WBC (x 1000/cu mm)	<75% of LLN	2	78	2.56	1	66	1.52
Neutrophils (x 1000/cu mm)	<0.5 LLN	2	78	2.56	0	66	0.00
Platelet Count (x 1000/cu mm)	<75% of LLN	13	77	16.88	4	64	6.25
RBC (x million/cu mm)	<75% of LLN	12	78	15.38	13	66	19.70
Hemoglobin (g/dL)	<75% of LLN	15	78	19.23	15	66	22.73
Hematocrit (%)	<75% of LLN	14	78	17.95	11	66	16.67
ALT (U/L)	>2 x ULN	9	76	11.84	12	65	18.46
AST (U/L)	>2 x ULN	5	77	6.49	9	65	13.85
Amylase (U/L)	>2 x ULN	3	76	3.95	4	65	6.15

N = Total number of patients with at least one observation of the given laboratory parameter while on study.

n = Total number of patients with a substantially abnormal value.

* Criteria 1 is displayed. For patients with an abnormality at baseline, Criteria 1 plus Criteria 2 must be met.

LLN = lower limit of normal

ULN = upper limit of normal

Study Report Source: Section 14, Table 8.4