SYNOPSIS

Name of Company: Pharmacia & Upjohn **Name of Finished Product:** **Name of Active Ingredient:** Linezolid (PNU-100766)	**Individual study table**	(For national authority use only)

Title of study: Linezolid (PNU-100766) in the Treatment of Patients with Nosocomial Pneumonia: A Double-Blind, Randomized, Comparator-Controlled Study

CTN: M/1260/0048A **Document number:** a0052355

Investigators: 90 investigator sites; a list of all participating investigators is presented in Appendix 5 of the clinical study report.

Study centers: Multinational (North America, Europe [including Israel, South Africa, Australia], and Latin America)

Publication (reference): None

Studied period (years): 13 October 1998 to 16 July 1999 **Phase of development:** III

Objectives: To assess the comparative efficacy (clinical and microbiological) of linezolid plus aztreonam therapy versus vancomycin plus aztreonam therapy in the treatment of nosocomial pneumonia in hospitalized adults, to assess safety and tolerance, and to assess the prevalence of vancomycin-resistant enterococci (VRE) in patients receiving broad-spectrum antibiotic therapy.

Methodology: This Phase III, randomized, double-blind, multicenter study was designed to compare the efficacy, safety, and tolerance of linezolid and vancomycin in the treatment of nosocomial pneumonia.

Patients were randomized in a 1:1 ratio to receive intravenously (IV) either of the following regimens:

- linezolid IV 600 mg every 12 hours plus aztreonam IV 1-2 g every 8 hours. Aztreonam use was optional if no gram-negative pathogens were identified.
- vancomycin IV 1 g every 12 hours plus aztreonam IV 1-2 g every 8 hours. Aztreonam use was optional if no gram-negative pathogens were identified.

The study consisted of a Baseline/Screening visit, Patient Treatment Evaluation visits every 3 days while on study medication, an End of Treatment (EOT) visit within 72 hours of the last dose of study medication, and a Follow-Up (F-U) visit 15 to 21 days after completion of treatment. Clinical and/or microbiological assessments were performed at each visit; the test-of-cure (TOC) assessments were completed at the F-U visit. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and adverse events (AEs) monitoring.

Number of patients (planned and analyzed): Approximately 476 (238 per treatment group) patients were to be enrolled. A total of 402 patients were enrolled; 203 patients were treated with linezolid and 193 patients were treated with vancomycin.

Main criteria for inclusion: Adult patients with a clinical picture compatible with pneumonia (acquired in an in-patient health care facility or chronic care facility) were required to satisfy at least 2 of the following criteria: cough; production of purulent sputum or a change (worsening) in character of the sputum; auscultatory findings on pulmonary exam of rales and/or pulmonary consolidation; dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; and an organism consistent with a respiratory pathogen isolated from respiratory, sputum, or blood cultures; the patient was also expected to survive at least 7 days.

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Main criteria for inclusion (continued): Each patient should also have had at least 2 of the following: fever; respiratory rate >30 breaths per minute; systolic hypotension; pulse rate ≥120 beats per minute; altered mental status; requirement for mechanical ventilation; elevated total peripheral white blood cell (WBC) count >10,000/mm^3; >15% immature neutrophils (bands) regardless of total peripheral WBC; leukopenia with total WBC < 4,500/mm^3; the patient had a chest radiograph at Baseline/Screening or within 48 hours of initiation of treatment consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion); provided a suitable invasive respiratory specimen and a sputum specimen for Gram's stain and culture; venous access available for intravenous dosing; and was willing to complete all study-related activities and F-U visit.

Primary Exclusion criteria: Patients were to be excluded for the following reasons: infection due to organisms known to be resistant to either of the study medication regimens before study entry; known or suspected meningitis, endocarditis, or osteomyelitis; CD4 cell count < 200 cells/mm^3 secondary to Human Immunodeficiency Virus (HIV) infection; previous antibiotic treatment received for more than 24 hours, unless documented to be a treatment failure (72 hours treatment and not responding) or if the isolated pathogen for the current pneumonia was resistant in vitro to previous nonstudy antibiotic therapy; known liver disease and total bilirubin > 5 X the upper limit of normal (ULN); severe neutropenia (< 500 cells/mm^3).

Test product, dose and mode of administration, manufacturing lot number: linezolid 600 mg, IV, every 12 hours, supplied as 2 mg/mL solutions in prefilled IV bags from the following manufacturing lot numbers: 97F11M98, 97E21M91, 98F18Z09, 98K27Z18, 98F17Z08, 98H21Z11, and 98H27Z15.

Reference therapy, dose and mode of administration, manufacturing lot number: vancomycin, 1 g, IV, every 12 hours, supplied in 1 g vials from the following manufacturing lot numbers: 2MH80M and 2ML80M.

Duration of treatment: 7 to 21 consecutive days for both treatments

Criteria for evaluation: The primary efficacy evaluations were based on the resolution or improvement in clinical and microbiologic signs and symptoms of infection at the TOC visit. Safety was evaluated by analyzing adverse events and changes in vital signs, physical examinations, and laboratory test results.

Clinically Evaluable Analyses: Patients were considered Clinically Evaluable if the following criteria were met:

- The patient had a positive chest radiograph at Baseline (within 48 hours of study entry) consistent with the diagnosis of pneumonia.
- The patient did not start taking a potentially effective antibiotic before taking the first dose of study medication that continued during treatment.
- The patient did not discontinue study medication, for any reason other than lack of efficacy, before 7 days and 14 doses.
- The patient received at least 80% of the prescribed study medications without missing 2 or more consecutive doses through the first 7 days of treatment.
- The patient did not receive a potentially effective concomitant noninvestigational antibiotic for an adverse event or intercurrent illness (unless the antibiotic was given due to lack of efficacy).
- The patient had a post-Baseline assessment in the F-U analysis window (15-21 days after end of treatment) unless the Investigator's Clinical Outcome was a failure at the EOT, or the patient was given an antibiotic for lack of efficacy any time during study.

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Microbiologically Evaluable Analyses: To be microbiologically evaluable, in addition to the criteria listed above, patients were required to have a confirmed pathogen from a respiratory specimen or blood culture at Baseline and the confirmed pathogen must not have been resistant to either study drug (ie, linezolid or vancomycin).

Intent-to-Treat (ITT) and Modified-Intent-to-Treat (MITT) Analyses: The ITT population included all randomized patients who received at least 1 dose of study drug. The MITT population included all patients in the ITT population who also had a pathogen isolated at Baseline.

Efficacy: Primary efficacy was assessed by evaluating patient clinical outcome, patient microbiological outcome, and patient overall outcome at TOC; secondary efficacy was assessed by evaluating clinical signs and symptoms, chest radiographs, body temperature, respiratory rate, and white blood cell counts.

Safety: Safety was assessed by the collection and analysis of data on adverse events, clinical laboratory assays, physical examinations, vital signs, and concomitant medications.

Statistical Methods: The primary efficacy variables were Patient Clinical Outcome (Investigator's and Sponsor's assessments), Patient Microbiological Outcome, and Patient Overall Outcome and the secondary efficacy variables were clinical signs and symptoms, chest radiograph results, VRE prevalence, intubation status, mortality status by APACHE II score, body temperature, respiration rate, WBC counts, and individual pathogen eradication rates. For Patient Clinical Outcome, Patient Microbiological Outcome, and Patient Overall Outcome, the proportions of patients in each category were compared between treatment groups at F-U using a chi-square test for homogenity of proportions. In addition, 95% confidence intervals (CI) for the difference in success rates between treatment groups were calculated. These analyses were done separately for the Clinically Evaluable, Microbiologically Evaluable, ITT, and MITT patients. Other endpoints, including safety and Baseline demographics, were analyzed for treatment differences using a chi-square test or a one-way analysis of variance model. Laboratory safety results and vital signs were analyzed for 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 a one-way analysis of variance model. Details of the statistical methods are presented in Section 9.8 of the clinical study report.

RESULTS:

Demographic and other baseline characteristics: Patients in both treatment groups were comparable at Baseline with respect to age, vital signs (temperature, blood pressure, calculated mean arterial pressure [MAP], pulse, and respiration), Baseline APACHE II score, intubation status at Baseline, pretreatment ventilator status, weight, sex, race, medical history, physical examination data, diagnosis, clinical signs and symptoms, and safety laboratory parameters.

Disposition of patients:

	Linezolid	Vancomycin
ITT Patients	203	193
MITT Patients	94	83
Clinically Evaluable Patients	108	96
Microbiologically Evaluable Patients	54	40

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Efficacy results:
Linezolid and vancomycin were equally effective in treating nosocomial pneumonia. This effect was consistent across all primary and secondary efficacy assessments, including Investigator's Assessment of Clinical Outcome, Sponsor's Assessment of Clinical Outcome, Patient Microbiological Outcome, and Patient Overall Outcome. In general, the effectiveness of the 2 treatments was similar among subgroups and comparable to that observed in the overall analyses. However, the cure rates for both treatment groups were lower in certain subgroups such as those patients who were intubated and those patients with the highest APACHE II scores. The microbiological eradication rates for linezolid and vancomycin were comparable for the primary pathogens (*S pneumoniae* and *S aureus* including oxacillin-resistant *S aureus*).

Safety results:
The percentages of patients who experienced study-emergent adverse events and drug-related adverse events were similar between treatment groups. Most adverse events were of mild or moderate intensity and were of limited duration, and most adverse events did not require study medication discontinuation. The most common adverse events occurred at similar frequencies between treatment groups and included events such as diarrhea and pneumonia. The percentage of patients who discontinued due to an adverse event was slightly higher in the vancomycin group than in the linezolid group and similar percentages of patients in each group discontinued due to serious adverse events. A greater percentage of patients died (25.4%, 49/193) in the vancomycin group than in the linezolid group (17.7%, 36/203). These deaths were deemed unrelated to the study medication by the investigators. There does not appear to be a substantial risk of drug interactions. The clinical laboratory data, physical examination observations, vital sign results, and noninvestigational medications use were unremarkable and typical of patients under treatment for nosocomial pneumonia. There did not appear to be any clinically significant treatment group differences in these parameters.

Conclusion:
Linezolid was well-tolerated, safe, and effective in the treatment of nosocomial pneumonia. Linezolid and vancomycin were equally effective in treating HAP. In general, the effectiveness of the 2 treatments was similar among subgroups and comparable to that observed in the overall analyses. The cure rates and microbiological eradication rates for linezolid and vancomycin were comparable for the treatment of the primary pathogens, *S aureus* and *S pneumoniae*. In general, the frequencies of study-emergent adverse events, adverse events resulting in discontinuation of study medication, and serious adverse events were comparable between the linezolid and vancomycin treatment groups. The most common adverse events occurred at similar frequencies between treatment groups and included events such as diarrhea and pneumonia. The percentage of patients who discontinued due to an adverse event was slightly higher in the vancomycin group than in the linezolid group and similar percentages of patients in each group discontinued due to serious adverse events. A greater percentage of patients died (25.4%, 49/193) in the vancomycin group than in the linezolid group (17.7%, 36/203). No deaths were attributed to either study medication. Most adverse events were of mild or moderate intensity and were of limited duration, and most adverse events did not require study medication discontinuation. The analysis of adverse events, along with the evaluation of clinical laboratory data and other safety data, does not suggest a substantial difference in clinical risk to patients on intravenous administration of linezolid compared to vancomycin.

Date of the report: 24 September 1999

Table 1. Frequencies of Study-Emergent Adverse Events ≥2% Within Body Systems: ITT

COSTART Body System /MET	Linezolid N = 203		Vancomycin N = 193		
	n	%†	n	%†	P-Value‡
Patients With None	60	29.6	50	25.9	
Patients With at Least One	143	70.4	143	74.1	0.4176
BODY					
Chest Pain	1	0.5	4	2.1	0.1593
Fever	8	3.9	7	3.6	0.8701
Generalized Edema	6	3.0	3	1.6	0.3497
Infection Bacterial NOS	1	0.5	4	2.1	0.1593
Inject./Vascular Catheter Site Infect.	4	2.0	1	0.5	0.1957
Localized Pain	4	2.0	2	1.0	0.4469
Microbiological Test Abnormal NOS	6	3.0	6	3.1	0.9292
Reaction Unevaluable	4	2.0	1	0.5	0.1957
Sepsis	11	5.4	8	4.1	0.5533
Septic Shock	5	2.5	5	2.6	0.9355
Trauma	8	3.9	4	2.1	0.2783
CARDIOVASCULAR					
Atrial Fibrillation	3	1.5	4	2.1	0.6535
Bradycardia NOS	5	2.5	3	1.6	0.5206
Cardiac Arrest NEC	3	1.5	5	2.6	0.4314
Congestive Heart Failure	9	4.4	2	1.0	0.0398*
Deep Vein Thrombosis	4	2.0	4	2.1	0.9425
Hypertension	7	3.4	0	-	0.0092*
Hypotension	5	2.5	5	2.6	0.9355
Myocardial Infarction	4	2.0	4	2.1	0.9425
DIGESTIVE					
Constipation	8	3.9	9	4.7	0.7230
Diarrhea	19	9.4	15	7.8	0.5730
Gastrointestinal Bleeding	4	2.0	6	3.1	0.4705
Ileus	5	2.5	1	0.5	0.1133
Monilia Oral	4	2.0	5	2.6	0.6789
Multiple Organ Failure	5	2.5	2	1.0	0.2815
Nausea	7	3.4	4	2.1	0.4050
Vomiting	6	3.0	4	2.1	0.5756
HEMIC AND LYMPHATIC					
Anemia	10	4.9	7	3.6	0.5238
Thrombocytopenia	2	1.0	4	2.1	0.3760
METABOLIC AND NUTRITIONAL					
Hyperglycemia	5	2.5	3	1.6	0.5206
Hypokalemia	4	2.0	2	1.0	0.4469

Continued

Table 1. Frequencies of Study-Emergent Adverse Events ≥2% Within Body Systems: ITT (continued)

COSTART Body System /MET	Linezolid N = 203		Vancomycin N = 193		
	n	%†	n	%†	P-Value‡
NERVOUS					
Agitation	6	3.0	6	3.1	0.9292
Anxiety	4	2.0	4	2.1	0.9425
Confusion	4	2.0	2	1.0	0.4469
Convulsion	6	3.0	1	0.5	0.0658
Depressive Symptoms	4	2.0	3	1.6	0.7535
Encephalopathy	6	3.0	2	1.0	0.1748
Insomnia	7	3.4	2	1.0	0.1074
RESPIRATORY					
Dyspnea	6	3.0	5	2.6	0.8252
Effusion Pleural	3	1.5	4	2.1	0.6535
Pneumonia	13	6.4	11	5.7	0.7690
Respiratory Distress Syndrome	3	1.5	5	2.6	0.4314
Respiratory Failure	14	6.9	8	4.1	0.2322
SKIN					
Dermatitis Fungal	2	1.0	4	2.1	0.3760
Erythema	1	0.5	5	2.6	0.0876
Pressure Sore	6	3.0	5	2.6	0.8252
Rash	4	2.0	11	5.7	0.0520
Skin Erosion NEC	4	2.0	2	1.0	0.4469
UROGENITAL					
Failure Kidney Acute	6	3.0	1	0.5	0.0658
Infection Urinary Tract	12	5.9	6	3.1	0.1808
Kidney Failure	0	-	4	2.1	0.0392*

† Percentages are based on the number of patients reporting. Patients are only counted once for each MET.

‡ Chi-square test is based on the number of patients reporting.

* P-value ≤0.05 indicates statistical significance.

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; ITT = Intent-to-Treat; NEC = Not elsewhere classified; NOS = Not otherwise specified

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

Table 2. Frequencies of Study-Emergent Drug-Related Adverse Events ≥2% Within Body System: ITT

COSTART Body System/MET	Linezolid N = 203		Vancomycin N = 193		P-Value†
	n	%‡	n	%‡	
Patients With None	176	86.7	163	84.5	
Patients With at Least One	27	13.3	30	15.5	0.5250
DIGESTIVE					
Diarrhea	9	4.4	5	2.6	0.3209

† Chi-square test is based on the number of patients reporting.
‡ Percentages are based on the number of patients reporting. Patients were counted only once for each MET.
MET (Medically Equivalent Term) is a standardized version of the adverse event verbatim based on COSTART conventions.
ITT = Intent-to-Treat; COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms
Drug-related is defined as events specified as related to or with relatedness not reported.
Study Report Reference: Section 14, Table 7.6; Appendix 15, Table S-6

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

Laboratory Assay	Criteria*	Linezolid			Vancomycin		
		n	N	%	n	N	%
WBC (x 1000/cu mm)	<75% of LLN	0	201	0.00	4	187	2.14
Neutrophils (x 1000/cu mm)	<0.5 LLN	0	199	0.00	3	186	1.61
Platelet Count (x 1000/cu mm)	<75% of LLN	5	200	2.50	13	186	6.99
RBC (x million/cu mm)	<75% of LLN	30	201	14.93	27	187	14.44
Hemoglobin (g/dL)	<75% of LLN	33	201	16.42	35	187	18.72
Hematocrit (%)	<75% of LLN	25	200	12.50	28	186	15.05
ALT (U/L)	>2 x ULN	37	200	18.50	32	188	17.02
AST (U/L)	>2 x ULN	20	200	10.00	21	188	11.17
Amylase (U/L)	>2 x ULN	10	199	5.03	6	188	3.19

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