SYNOPSIS

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

Title of study: Linezolid Versus Oxacillin Sodium/Dicloxacillin Sodium for the Treatment of Complicated Skin and Soft Tissue Infections

Protocol number: M/1260/0055 **Document number:** a0052357

Investigator(s): A total of 200 investigator sites; a list of all participating investigators is presented in Appendix 4 of the clinical study report.

Study centers: Multicenter/multinational (U.S., Canada, Europe, Australia, South Africa, Latin America, and Asia)

Publication (reference): None

Studied period (years): 19 November 1998 – 21 June 1999 **Phase of development:** III

Objectives: To assess the comparative efficacy (clinical and microbiological) of linezolid versus oxacillin sodium (oxacillin)/dicloxacillin sodium (dicloxacillin) in the treatment of adults with complicated skin and soft tissue infections and to assess safety and tolerance.

Methodology: This Phase III, randomized, double-blind, double-dummy, multicenter, multinational, comparator-controlled study was conducted in adult patients hospitalized with complicated skin and soft tissue infections. Patients were randomized in a 1:1 ratio to receive either of the following regimens:

Intravenous (IV) or oral linezolid 600 mg, alternated with placebo dummy every 6 hours
Intravenous oxacillin 2 g every 6 hours or oral dicloxacillin 500 mg every 6 hours

All treated patients received at least their first dose intravenously. The study consisted of: a Baseline/Screening visit, hospitalization phase (1 dose minimum), outpatient treatment with a Patient Treatment Evaluation visit every 6 days after discharge, 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 the final dose of study medication. Clinical and microbiological assessments were performed at Baseline, during patient hospitalization, at the switch from intravenous to oral treatment, after discharge while on treatment, and at the EOT and F-U visits. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and reporting of adverse events.

Number of patients (planned and analyzed): Approximately 632 (316 per treatment group) patients were to be enrolled to have 142 fully evaluable patients per treatment arm. A total of 826 patients were enrolled; 403 patients were randomized to linezolid and 423 patients were randomized to oxacillin/dicloxacillin.

Diagnosis and main criteria for inclusion: Hospitalized adults with suspected gram-positive complicated skin and soft tissue infection that involved deeper soft tissue or may have required significant surgical intervention (such as a major abscess, infected ulcer, major burn, or deep and extensive cellulitis) were eligible for enrollment in the study if they had an accessible infection site for Gram's stain and culture and at least 2 of the following symptoms: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, or swelling/induration; at least one of the following conditions considered to be pathogen related: fever, defined as >37.5°C/99.5°F (>38°C/100.4°F (orally); >38.5°C/101.3°F (tympanically); or >39°C/102.2°F (rectally), elevated total peripheral white blood cell count >10,000/mm^3, or >15% immature neutrophils (bands) regardless of total peripheral white count; was at least 18 years of age; able to take intravenous and oral medications; and willing to return for the EOT and F-U visits.

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Exclusion criteria: Patients were excluded from participation in the study if they met any of the following criteria: previous antibiotic treatment received for more than 24 hours within 7 days of study entry unless the pathogen showed drug resistance or the treatment failed (defined as no clinical improvement after 3 days of treatment); uncomplicated skin and superficial skin structure infection such as a simple abscess, impetiginous lesion, furuncle, or superficial cellulitis; abscesses that only needed surgical draining at the time of patient enrollment; self-limited infections such as isolated folliculitis or other infection that has a high surgical incision cure rate or furunculosis or carbunculosis that was not associated with a cellulitis at least 1 cm in radius; diabetic foot, decubitus, and ischemic ulcers, necrotizing fasciitis, gas gangrene, or burns on greater than 20% of total body surface; superinfected eczema or other chronic medical conditions (ie, atopic dermatitis) where inflammation may have been prominent for an extended period even after successful bacterial eradication; infections or conditions requiring concomitant antimicrobial (with the exception of aztreonam) or systemic corticosteroid treatment; infections complicated by the presence of prosthetic materials such as central venous catheters, permanent cardiac pacemaker battery packs, or those involving joint replacement prostheses, etc.; known to have osteomyelitis; females of childbearing potential who were unable to take adequate contraceptive precautions, had a positive serum pregnancy test result within 24 hours prior to study entry, were otherwise known to be pregnant, or were breastfeeding; known to have liver disease, with total bilirubin > 5 times the Upper Limit of Normal (ULN); known to have neutropenia (absolute neutrophil count <500 cells/mm^3); known to have pheochromocytoma, carcinoid syndrome, or uncontrolled hypertension; untreated hyperthyroidism; unlikely to survive through the treatment period and evaluation (<60 days); hypersensitivity to linezolid or its formulation excipients; hypersensitivity to penicillins or their formulation excipients; received another investigational medication within the past 30 days; or previously enrolled in this or another linezolid protocol.

Test product, dose and mode of administration, batch numbers: 600 mg intravenous linezolid every 12 hours [batch numbers: 98F16Z07, 98H25Z13, 98H28Z16, 98F15Z06, 98H27Z15]; 600 mg oral linezolid tablets, one tablet every 12 hours [batch number: 38195]

Reference therapy, dose and mode of administration, batch numbers: 2 g intravenous oxacillin sodium every 6 hours [batch numbers: 8E12442, 7L02197, 8E12428]; 500 mg oral dicloxacillin sodium tablets every 6 hours [batch number: C8V44A]

Duration of treatment: 10 to 21 consecutive days

Criteria for evaluation: The primary efficacy evaluations were based on the resolution or improvement in clinical and microbiologic signs and symptoms of infection on the Test-of-Cure (TOC) visit. Safety was evaluated by the collection and analysis of data on adverse events, clinical laboratory assays, physical examinations, vital signs, and concomitant medications.

Intent-to-Treat (ITT) Analyses: The ITT population included all randomized patients who received at least 1 dose of study medication.

Clinically Evaluable Analyses: All of the following criteria were to be satisfied for a patient to be considered clinically evaluable: the patient fulfilled the study entry criteria; the patient received at least 80% of the total prescribed study medication without missing 2 consecutive doses during the first 7 days of treatment; the patient returned for a F-U visit; and the patient did not receive a potentially effective concomitant antibiotic prior to or during the study.

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Microbiologically Evaluable Analyses: To be microbiologically evaluable, in addition to the clinically evaluable criteria listed above, patients were required to have a confirmed pathogen from the infection site and/or a blood culture at Baseline, and the confirmed pathogen must not have been resistant to either study medication.

Efficacy: Primary efficacy was assessed by evaluating patient clinical outcome, patient microbiological outcome, and patient overall (combined clinical/microbiological) outcome; secondary efficacy was assessed by evaluating follow-up clinical signs and symptoms, body temperature, white blood cell (WBC) counts, and individual organism/pathogen eradication rates.

Safety: Safety was evaluated 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 in this study were patient clinical outcome, patient microbiological outcome, and patient overall (combined clinical/microbiological) outcome. For each of these, the proportions of patients in each outcome category were compared between treatment groups at F-U using a chi-square test for homogeneity of proportions. In addition, for all 3 primary efficacy variables, 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. Other endpoints, including secondary efficacy variables, safety, and Baseline demographics, were analyzed for treatment differences via chi-square tests and one-way analysis of variance F-tests. Safety laboratories and vital signs were analyzed for statistical changes from Baseline to each post-Baseline visit using a paired t-test and for treatment group comparisons of mean changes from Baseline using a 2-sample t-test. Details of the statistical methods are presented in Section 9.8 of the clinical study report.

Results:

Demographic and other Baseline characteristics: The treatment groups were comparable at Baseline with respect to age, vital signs (temperature, systolic and diastolic blood pressure, mean arterial pressure [MAP] [calculated], pulse, and respiration rate), weight, lesion size (length, width, and area), duration of infection, sex, race, medical history, physical examination data, diagnosis, primary site of infection, degree of involvement, clinical signs and symptoms, and safety laboratory parameters.

Disposition of patients:

	Linezolid	Oxacillin/Dicloxacillin
ITT Patients	400	419
MITT Patients	212	219
Clinically Evaluable Patients	298	302
Microbiologically Evaluable Patients	143	151

Efficacy results: Linezolid was at least as effective as oxacillin/dicloxacillin in treating complicated skin and soft tissue infections. 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 Overall Outcome, and Microbiological Outcome. For the Investigator's Assessment of Clinical Outcome in Clinically Evaluable patients at the F-U visit, the cure rate was 96.1% for both the linezolid group and the oxacillin/dicloxacillin group. For the Sponsor's Assessment of Clinical Outcome in Clinically Evaluable patients at the TOC visit, the cure rate was 90.7% for the linezolid group and 86.3% for the oxacillin/dicloxacillin group. For the Patient Overall Outcome in Microbiologically Evaluable patients at the TOC visit, the cure rate was 87.9% for the linezolid group and 84.8% for the oxacillin/dicloxacillin group.

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Efficacy results (continued): In the Microbiologically Evaluable population, the microbiological success rate at the TOC visit was 88.7% (126/142) for the linezolid group and 85.4% (129/151) for the oxacillin/dicloxacillin group. The Patient Microbiological Outcome was not influenced by Baseline diagnosis, pathogen, gender, age, or race.

Linezolid was as effective as oxacillin/dicloxacillin in eradicating *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*.

For patients with bacteremia, the cure rate at the TOC visit was 85.7% (6/7) for patients in the linezolid group and 77.8% (7/9) for patients in the oxacillin/dicloxacillin group.

Safety results: There were no significant differences between treatment groups for the percentage of patients with one or more study-emergent adverse events (47.3% of the linezolid group and 41.3% of the oxacillin/dicloxacillin group) or in the percentage of patients with drug-related adverse events (16.8% of the linezolid group and 17.2% of the oxacillin/dicloxacillin group). There was a significantly ($p=0.0142$) higher percentage of patients who discontinued treatment due to a drug-related adverse event in the oxacillin/dicloxacillin group (3.6%) as compared to the linezolid group (1.0%).

There were only a small number of adverse events experienced by ≥ 2% of either treatment group, and most adverse events were of mild or moderate intensity. The most common adverse events occurred at similar frequencies between treatment groups, and included events such as diarrhea, nausea, and headache, which are often experienced during antibiotic treatment. Both nausea and headache were the most commonly-reported drug-related adverse events, with 3.5% of the linezolid group and 2.9% of the oxacillin/dicloxacillin group reporting nausea, and 2.5% of the linezolid group and 1.4% of the oxacillin/dicloxacillin group reporting headache.

Similar percentages of patients experienced serious adverse events in each treatment group: 5.5% (22/400) of patients in the linezolid group and 4.5% (19/419) in the oxacillin/dicloxacillin group. Serious adverse events related to the digestive system were experienced in 1.2% of the oxacillin/dicloxacillin group, but none of the patients in the linezolid group.

There were 4 deaths in the study, 3 in the linezolid group and 1 in the oxacillin/dicloxacillin group. There was no evidence of a monoamine oxidase inhibitor (MAOI) interaction between linezolid and any concomitant noninvestigational medications (NIMs). The clinical laboratory data, physical examination observations, vital sign results, and NIM use were unremarkable and typical of a patient population under treatment for complicated skin and soft tissue infections.

Conclusion: Linezolid is well tolerated, safe, and as effective as oxacillin/dicloxacillin in the treatment of adult complicated skin and soft tissue infections.

Date of the report: 10 September 1999

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

COSTART Body System /MET	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
	n	%†	n	%†
Patients With None	211	52.8	246	58.7
Patients With at Least One	189	47.3	173	41.3
BODY				
Abdominal Pain Localized	8	2.0	5	1.2
Fever	5	1.3	11	2.6
Headache	22	5.5	16	3.8
Localized Pain	11	2.8	3	0.7
CARDIOVASCULAR				
Hypertension	12	3.0	1	0.2
DIGESTIVE				
Constipation	7	1.8	13	3.1
Diarrhea	11	2.8	12	2.9
Dyspepsia	10	2.5	7	1.7
Nausea	23	5.8	24	5.7
Vomiting	13	3.3	8	1.9
NERVOUS				
Dizziness	9	2.3	3	0.7
Insomnia	10	2.5	9	2.1
SKIN				
Pruritus Non-application Site	6	1.5	9	2.1

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

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

COSTART Body System/MET	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
	n	%†	n	%†
Patients With None	333	83.3	347	82.8
Patients With at Least One	67	16.8	72	17.2
BODY				
Headache	10	2.5	6	1.4
DIGESTIVE				
Nausea	14	3.5	12	2.9

† 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.
Note: 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-4

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

Laboratory Assay	Criteria*	Linezolid			Oxacillin/Dicloxacillin		
		n	N	%	n	N	%
WBC (x 1000/cu mm)	<75% of LLN	11	399	2.76	1	416	0.24
Neutrophils (x 1000/cu mm)	<0.5 LLN	3	369	0.81	2	385	0.52
Platelet Count (x 1000/cu mm)	<75% of LLN	6	397	1.51	2	415	0.48
RBC (x million/cu mm)	<75% of LLN	11	399	2.76	17	416	4.09
Hemoglobin (g/dL)	<75% of LLN	20	399	5.01	26	416	6.25
Hematocrit (%)	<75% of LLN	14	398	3.52	14	416	3.37
ALT (U/L)	>2 x ULN	37	369	10.03	36	386	9.33
AST (U/L)	>2 x ULN	15	369	4.07	29	387	7.49
Amylase (U/L)	>2 x ULN	6	399	1.50	6	416	1.44

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