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 Versus Clarithromycin for the Treatment of Uncomplicated Skin and Superficial Skin Structure Infections

Protocol number: M/1260/0039 **Document number:** ***Study Report Number***

Investigator(s): 47 investigators; a list of all participating investigators is presented in Appendix 6 of the clinical study report.

Study center(s): Multicenter, multinational (Argentina, Australia, Austria, France, Greece, Hungary, Indonesia, Italy, Netherlands, Pakistan, Peru, Philippines, Portugal, Slovenia, South Africa, Spain, Switzerland, United Kingdom, Venezuela

Publication (reference): None

Studied period (years): 05 August 1998 to 08 April 1999 **Phase of development:** III

Objectives: To assess the comparative efficacy (clinical and microbiologic), safety, and tolerance of linezolid versus clarithromycin in the treatment of adult uncomplicated skin and superficial skin structure infections

Methodology: This Phase III, randomized, double-blind, comparator-controlled, multicenter, multinational study was conducted in adult patients with uncomplicated skin and superficial skin structure infections. Patients were randomized in a 1:1 ratio to receive one of the following administered regimens:

400 mg linezolid twice daily (BID) for 7 to 14 consecutive days
250 mg clarithromycin BID for 7 to 14 consecutive days

The study consisted of 4 visits: a Baseline/Screening visit, a Patient treatment evaluation visit on Day 3 after treatment initiation, an End of Treatment (EOT) visit within 72 hours of the last dose of study medication, and a Follow-Up (F-U) visit 7 to 21 days after the EOT visit. Clinical and microbiologic assessments were performed at each visit; the Test-of-Cure assessments were completed at the Follow-Up visit. Patients who returned between 7 and 28 days after the last dose were included in the test-of-cure analysis. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, record of use of concomitant (non-investigational) medications, and reporting of adverse events (AEs).

Number of patients (planned and analyzed): Six hundred thirty-two (632) patients ($\geq$300 per treatment group) were to be enrolled. A total of 341 patients were enrolled; 170 patients were randomized to linezolid, and 171 patients were randomized to clarithromycin. A total of 332 patients received study medication; 166 patients received linezolid, and 166 patients received clarithromycin.

Diagnosis and main criteria for inclusion: Adult patients with suspected gram-positive (eg, *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, Enterococcus faecalis,* or *Enterococcus faecium*) uncomplicated skin and superficial skin structure infections, such as simple abscesses, impetiginous lesions, furuncles, carbuncles, cellulitis, erysipelas infections of intact skin, and mild burns, 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.

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Exclusion criteria: Patients were to be excluded for previous antibiotic treatment >24 hr within 7 days of study entry (unless pathogen showed drug resistance, documented persistence of infection, and treatment failure); abscesses that only needed surgical draining at the time of enrollment; a complicated skin and soft tissue infection that involved deeper soft tissue and/or may have required significant surgical intervention; diabetic foot ulcers, decubitus and ischemic ulcers, necrotizing fasciitis, gas gangrene, or burns on >10% of total body surface; an infection that had a high surgical incision cure rate; chronic medical conditions where inflammation could have been prominent for an extended period even after successful bacterial eradication; infections or conditions requiring concomitant antimicrobial or systemic corticosteroid therapy; infections of prosthetic materials; osteomyelitis; liver disease; neutropenia; pheochromocytoma, carcinoid syndrome, or uncontrolled hypertension; untreated hyperthyroidism; hypersensitivity to linezolid or its formulation excipients; hypersensitivity to clarithromycin or its formulation excipients; receipt of another investigational drug within the past 30 days; previous enrollment in this or another linezolid protocol; being female of childbearing potential and unable to take adequate contraceptive precautions, pregnant, or breastfeeding.
Test product, dose and mode of administration, batch numbers: 400 mg oral linezolid tablets, one tablet BID, administered orally, Batch No. 30,088

Reference therapy, dose and mode of administration, batch numbers: 250 mg oral clarithromycin tablets, one tablet BID, administered orally, Batch No. 34-123-AA-21 for Patients No. 3912037 to No. 3913188 and Batch No. 35-208-AA-21 for Patients No. 3950001 to No. 3950348.

Duration of treatment: 7 to 14 consecutive days for both treatments

Criteria for evaluation: The primary efficacy evaluations were based on the resolution of clinical and microbiologic signs and symptoms of infection at the Test-of-Cure visit. Adverse events and changes in vital signs, physical examinations, laboratory test results, and concomitant medication therapy were used to evaluate safety.

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 or more consecutive doses during the first 7 days of treatment
- The patient returned for a follow-up visit (unless the patient failed at EOT or took another antibiotic due to lack of efficacy)
- The patient did not receive a concomitant antibiotic during the study (unless the antibiotic was given due to lack of efficacy)

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

Intent to Treat (ITT) and Modified Intent to Treat (MITT) Analyses: The ITT population included all randomized patients who received at least one dose of study medication, and 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 microbiologic outcome, and patient overall outcome; secondary efficacy was assessed by evaluating clinical signs and symptoms, individual pathogen eradication rates, body temperature, 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.

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Statistical methods: The primary efficacy variables in this study were patient clinical outcome, patient microbiologic outcome, and patient overall (combined clinical/microbiologic) 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 Clinically Evaluable, Microbiologically Evaluable, ITT, and MITT 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 changes from Baseline at each post-Baseline visit using a paired t-test. For treatment group comparisons, mean changes from Baseline were compared 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:

In general, patients in both 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	Clarithromycin
ITT Patients	166	166
MITT Patients	85	96
Clinically Evaluable Patients	127	124
Microbiologically Evaluable Patients	55	68

Efficacy results:

Linezolid and clarithromycin were equally effective in treating uncomplicated skin/soft tissue infections. This effect was consistent across all primary and secondary efficacy assessments, including the Investigator's Assessment of Clinical Outcome, Sponsor's Assessment of Clinical Outcome, and Patient Overall Outcome. The cure rate for the Investigator's Assessment of Clinical Outcome was 93.4% in both treatment groups in the Clinically Evaluable population. For the Sponsor's Assessment of Clinical Outcome, the cure rate for Clinically Evaluable patients at F-U was 91.1% for the linezolid group and 92.7% for the clarithromycin group. The cure rate for Patient Overall Outcome was 84.1% for linezolid-treated patients and 86.1% for clarithromycin-treated patients.

In the Microbiologically Evaluable population, the microbiologic success rate was 98.1% (53/55) for linezolid-treated patients and 97.1% (66/68) for clarithromycin-treated patients. Clinical and microbiologic results were not influenced by the Baseline diagnosis or pathogen. In general, the effectiveness of the two treatments was similar among subgroups and comparable to that observed in the overall analyses.

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Efficacy results (Continued):
Linezolid was as effective as clarithromycin in eradicating *E faecalis*, *S aureus*, *S epidermidis*, *S lugdunensis*, *S agalactiae*, and *S pyogenes*. At the Test-of-Cure visit, the cure rate for patients with infection due to methicillin-resistant *S aureus* was 100% for both treatment groups. No patients had vancomycin- resistant *E faecium* cultures identified at Baseline.

Safety results:
There were no treatment-group differences in the percentage of patients with one or more treatment-emergent adverse event (31.9% of the linezolid group and 30.7% of the clarithromycin group) or in the percentage of patients with drug-related adverse events (15.7% of the linezolid group and 15.1% of the clarithromycin group). A total of 3.0% of linezolid group and 1.8% of clarithromycin group experienced adverse events resulting in the discontinuation of study medication. 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 events such as diarrhea and nausea were often experienced during antibiotic treatment. Only a small percentage of patients in either treatment group experienced serious adverse events (1.8% in the linezolid group and 2.4% in the clarithromycin group), and none of the events were considered to be related to study drug. There were no deaths reported in this study. The clinical laboratory data, physical examination observations, vital sign results, and noninvestigational medications use were similar between treatment groups and typical for a patient population undergoing treatment for uncomplicated skin and soft tissue infections. There did not appear to be any clinically significant treatment-group differences in these parameters.

Conclusion:
Linezolid is as safe and effective as clarithromycin in the treatment of adult uncomplicated skin and superficial skin structure infections.

Date of the report: 26 August 1999

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

COSTART Body System /MET	Linezolid N = 166		Clarithromycin N = 166	
	n	%†	n	%†
Total Number of Patients Reporting	166	100.0	166	100.0
Patients With None	113	68.1	115	69.3
Patients With at Least One	53	31.9	51	30.7
BODY				
Abdominal Pain Localized	5	3.0	-	-
Headache	5	3.0	7	4.2
DIGESTIVE				
Constipation	4	2.4	-	-
Diarrhea	7	4.2	5	3.0
Nausea	6	3.6	2	1.2
NERVOUS				
Dizziness	3	1.8	6	3.6

† Percentages are based on the number of patients reporting.
Note: MET (Medically Equivalent Term) is grammatically synthesized version of the adverse event.
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 = 166		Clarithromycin N = 166	
	n	%†	n	%†
Total Number of Patients Reporting	166	100.0	166	100.0
Patients With None	140	84.3	141	84.9
Patients With at Least One	26	15.7	25	15.1
DIGESTIVE				
Nausea	5	3.0	2	1.2
Diarrhea	2	1.2	4	2.4

† Percentages are based on the number of patients reporting.
Notes: Drug-related is defined as events specified as related to or with relatedness not reported.
MET (Medically Equivalent Term) is grammatically synthesized version of the adverse event verbatim.
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			Clarithromycin		
		n	N	%	n	N	%
WBC (x 1000/cu mm)	<75% of LLN	0	162	0.00	2	166	1.20
Neutrophils (x 1000/cu mm)	<0.5 LLN	0	152	0.00	1	156	0.64
Platelet Count (x 1000/cu mm)	<75% of LLN	3	162	1.85	1	165	0.61
RBC (x million/cu mm)	<75% of LLN	--	--	--	--	--	--
Hemoglobin (g/dL)	<75% of LLN	2	162	1.23	0	166	0.00
Hematocrit (%)	<75% of LLN	1	162	0.62	0	166	0.00
ALT (U/L)	>2 x ULN	5	153	3.27	4	155	2.58
AST (U/L)	>2 x ULN	2	153	1.31	2	155	1.29
Amylase (U/L)	>2 x ULN	1	163	0.61	0	165	0.00

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