



## Study 39A, Uncomplicated Skin/Soft Tissue Infection (USST)

<p><b>Name of Company:</b> Pharmacia &amp; Upjohn</p> <p><b>Name of Finished Product:</b></p> <p><b>Name of Active Ingredient:</b> Linezolid (PNU-100766)</p>	<p><b>Individual study table</b></p>	<p>(For national authority use only)</p>
<p><b>Exclusion criteria:</b> Patients were to be excluded for the following reasons: previous antibiotic treatment &gt;24 hr within 7 days of study entry (unless pathogen showed drug resistance, positive infection site culture was obtained, and treatment failed); 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 &gt;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; concomitant use of terfenadine or astemizole (Canada only; See Amendment E of the clinical protocol); being female of childbearing potential and unable to take adequate contraceptive precautions, pregnant, or breastfeeding.</p> <p><b>Test product, dose and mode of administration, batch numbers:</b> Linezolid 400-mg tablets; one tablet administered orally BID. Batch number: 38,088</p> <p><b>Reference therapy, dose and mode of administration, batch numbers:</b> Clarithromycin 250-mg tablets, one tablet administered orally BID. Batch numbers: 34,123-AA and 34,861-AA-21</p> <p><b>Duration of treatment:</b> 7 to 14 consecutive days for both treatments</p> <p><b>Criteria for evaluation:</b> The primary efficacy evaluations were based on the resolution of clinical and microbiological 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.</p> <p><b>Clinically Evaluable Analyses:</b> All patients who met any of the following criteria were considered clinically nonevaluable: prior antibiotic usage (with the exception of antibiotics stopped on the study medication start day), insufficient therapy (&lt;7 days or &lt;14 doses), noncompliance with study medication regimen (ie, &lt;80% taken or missed 2 or more consecutive doses through Day 7), concomitant antibiotics given for intercurrent illness, or no post-baseline assessment (unless the patients was classified as a failure at EOT or was given antibiotic due to lack of efficacy).</p> <p><b>Microbiologically Evaluable Analyses:</b> 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 in the evaluable window at Baseline; and at least one of the confirmed pathogen(s) must not have been resistant to either study medication.</p> <p><b>Intent-to-Treat (ITT) and Modified-Intent-to-Treat (MITT) Analyses:</b> 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 in the ITT window at Baseline.</p> <p><b>Efficacy:</b> Primary efficacy was assessed by evaluating patient clinical outcome, patient microbiological 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.</p> <p><b>Safety:</b> 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><b>Statistical methods:</b> The primary efficacy variables in this study were patient clinical outcome, patient microbiological 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 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 9.7 of the clinical study report.</p> <p><b>Results:</b></p> <p><b><u>Demographic and other baseline characteristics:</u></b> 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.</p> <p><b><u>Disposition of patients:</u></b></p> <table data-bbox="248 982 1107 1129"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Linezolid</u></th> <th style="text-align: center;"><u>Clarithromycin</u></th> </tr> </thead> <tbody> <tr> <td>ITT Patients</td> <td style="text-align: center;">382</td> <td style="text-align: center;">371</td> </tr> <tr> <td>MITT Patients</td> <td style="text-align: center;">210</td> <td style="text-align: center;">215</td> </tr> <tr> <td>Clinically Evaluable Patients</td> <td style="text-align: center;">314</td> <td style="text-align: center;">309</td> </tr> <tr> <td>Microbiologically Evaluable Patients</td> <td style="text-align: center;">144</td> <td style="text-align: center;">146</td> </tr> </tbody> </table> <p><b><u>Efficacy results:</u></b> Linezolid and clarithromycin were both 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. In the linezolid group, the cure rate for the Investigator's Assessment of Clinical Outcome was 93.8% in the MITT population (versus 91.8% for clarithromycin-treated patients) and 95.4% in the Clinically Evaluable population (versus 93.1% for clarithromycin-treated patients). For the Sponsor's Assessment of Clinical Outcome, the cure rate at the F-U was 83.7% for patients in the linezolid treatment group and 80.9% for patients in the clarithromycin treatment group; in the Clinically Evaluable population, over 91% of the patients in both treatment groups were considered to be a success at the EOT visit, and at least 87% of the patients in both treatment groups were considered to be cured at the F-U visit. The cure rate for Patient Overall Outcome was 85.2% for linezolid-treated patients and 77.6% for clarithromycin-treated patients.</p> <p>Linezolid-treated patients tended to have a better microbiological outcome than did clarithromycin-treated patients, but there was not a significant treatment-group difference in the Microbiologically Evaluable patient subset. In the Microbiologically Evaluable population, the microbiological success rate was 90.9% (130/143) for linezolid-treated patients and 84.1% (122/145) for clarithromycin-treated patients. Clinical and microbiological results were similar across the Baseline diagnoses and pathogens. If patients who returned for the F-U visit within the 7- to 14-day window were considered, the overall rates of treatment success and cure were similar to those observed in the primary analyses based on 7 to 28 days. In general, the effectiveness of the two treatments was similar among subgroups and comparable to that observed in the overall analyses.</p>				<u>Linezolid</u>	<u>Clarithromycin</u>	ITT Patients	382	371	MITT Patients	210	215	Clinically Evaluable Patients	314	309	Microbiologically Evaluable Patients	144	146
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<p><b><u>Efficacy results (Continued):</u></b> Linezolid was as effective as clarithromycin in eradicating <i>E faecalis</i>, <i>S aureus</i>, <i>S epidermidis</i>, <i>Staphylococcus lugdunensis</i>, <i>S agalactiae</i>, and <i>S pyogenes</i>. For penicillin-resistant pathogens, the eradication rates at the Test-of-Cure visit were similar between treatment groups and ranged between 72.7% and 100.0% for <i>Staphylococcus cohnii</i>, <i>S epidermidis</i>, <i>Staphylococcus hemolyticus</i>, <i>S lugdunensis</i>, <i>Staphylococcus simulans</i>, <i>Staphylococcus warneri</i>, and <i>S agalactiae</i>. Vancomycin-resistant <i>E faecium</i> was isolated at Baseline from one patient in the linezolid treatment group; at the Test-of-Cure visit, this patient was evaluated as clinically cured with presumed eradication (no follow-up culture information was reported).</p> <p><b><u>Safety results:</u></b> The percentage of patients with one or more drug-related adverse events was statistically greater (<math>p = 0.0118</math>) in linezolid-treated patients (29.6%) compared with clarithromycin-treated patients (21.6%). This was not caused by a difference in the frequencies of adverse events in any one particular body system. A total of 7.3% of linezolid-treated and 4.9% of clarithromycin-treated patients experienced adverse events resulting in the discontinuation of study medication (<math>p=0.1557</math>). Only a small number of adverse events were experienced by <math>\geq 2\%</math> of either treatment group; most were of mild or moderate intensity. The most common adverse events occurred at similar frequencies between treatment groups; the most frequently reported drug-related events in this study, diarrhea and nausea, are often experienced during antibiotic treatment. Although the percentage of patients who experienced a serious adverse event or discontinued due to an adverse event was slightly higher in the linezolid group than in the clarithromycin group, there did not appear to be a treatment-related pattern in the nature of these events. Two deaths, both in the linezolid treatment group, were reported in the study; neither was deemed related to the study medication. The clinical laboratory data, physical examination observations, vital sign results, and noninvestigational medications use were typical of this patient population being treated for skin and skin structure infections. There did not appear to be any clinically significant treatment group differences in these parameters.</p> <p><b><u>Conclusion:</u></b> Linezolid is well tolerated, safe, and effective as clarithromycin in the treatment of adult uncomplicated skin and superficial skin structure infections.</p> <p><b><u>Date of the report:</u></b> 19 August 1999</p>		

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**Table 1. Study-Emergent Adverse Events Within Body Systems Which Occurred in  $\geq 2\%$  of All Patients: ITT**

COSTART Body System /MET	Linezolid N=382		Clarithromycin N=371	
	n	%†	n	%†
Total Number of Patients Reporting	382	100.0	371	100.0
Patients With None	176	46.1	201	54.2
Patients With at Least One	206	53.9	170	45.8
<b>BODY</b>				
Headache	43	11.3	38	10.2
Infection Fungal NOS‡	8	2.1	1	0.3
Trauma	10	2.6	9	2.4
<b>DIGESTIVE</b>				
Diarrhea	38	9.9	28	7.5
Dyspepsia	8	2.1	4	1.1
Nausea	22	5.8	22	5.9
Vomiting	8	2.1	7	1.9
<b>NERVOUS</b>				
Dizziness	11	2.9	10	2.7
<b>SPECIAL SENSES</b>				
Taste Perversion	8	2.1	9	2.4
<b>UROGENITAL</b>				
Moniliasis Vaginal	10	2.6	7	1.9

† Percentages are based on the number of patients reporting.

‡ Not otherwise specified.

MET (Medically Equivalent Term) is a grammatically synthesized version of the adverse event verbatim.

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

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**Table 2. Study-Emergent Drug-Related Adverse Events Within Body System Which Occurred in  $\geq 2\%$  of All Patients: ITT**

COSTART Body System/MET	Linezolid N=382		Clarithromycin N=382	
	n	%†	n	%†
Total Number of Patients Reporting	382	100.0	371	100.0
Patients With None	269	70.4	291	78.4
Patients With at Least One	113	29.6	80	21.6
<b>BODY</b>				
Headache	13	3.4	11	3.0
Infection Fungal NOS	8	2.1	1	0.3
<b>DIGESTIVE</b>				
Diarrhea	27	7.1	22	5.9
Nausea	14	3.7	17	4.6
<b>SPECIAL SENSES</b>				
Taste Perversion	8	2.1	9	2.4
<b>UROGENITAL</b>				
Moniliasis Vaginal	9	2.4	7	1.9

† Percentages are based on the number of patients reporting.

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

MET (Medically Equivalent Term) is a grammatically synthesized version of the adverse event verbatim.

NOS = Not otherwise specified.

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	1	382	0.26	1	371	0.27
Neutrophils (x 1000/cu mm)	<0.5 LLN	0	382	0.00	1	371	0.27
Platelet Count (x 1000/cu mm)	<75% of LLN	1	380	0.26	3	370	0.81
RBC (x million/cu mm)	<75% of LLN	1	382	0.26	0	371	0.00
Hemoglobin (g/dL)	<75% of LLN	3	382	0.79	0	371	0.00
Hematocrit (%)	<75% of LLN	3	381	0.79	0	371	0.00
ALT (U/L)	>2 x ULN	4	382	1.05	5	371	1.35
AST (U/L)	>2 x ULN	7	382	1.83	5	371	1.35
Amylase (U/L)	>2 x ULN	0	382	0.00	1	371	0.27

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