

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-130/S-003

21-131/S-003

21-132/S-003

MEDICAL REVIEW

Clinical Review Cover Sheet

CLINICAL REVIEW

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Executive Summary Section

Clinical Review for NDA 21-130 SE-003, 21-131 SE-003 and 21-132 SE-003

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The sponsor has submitted two phase 3 studies in this supplement for the use of linezolid in pediatric patients. One study compared the use of linezolid with cefadroxil for the treatment of uncomplicated skin and skin structure infections in children from ages 5-17 years. The second study compared the use of linezolid with vancomycin in the treatment of Gram positive infections in children from birth through 11 years of age. Additionally data from phase 1 and 2 studies and pharmacokinetic data from a study in adolescents are provided in support of this application.

Linezolid is an oxazolidinone antibiotic that has activity against resistant Gram positive organisms such as methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus faecium*. It thus has an important role in the treatment of such infections, as only limited treatment options are currently available. Linezolid (Zyvox™) tablets, IV formulation and oral suspension was approved on April 18, 2000 for use in adults with vancomycin resistant *Enterococcus faecium* infections, community and nosocomial pneumonia, complicated and uncomplicated skin and skin structure infections.

Myelosuppression is a significant side effect of linezolid evidenced in adult and juvenile animal studies. A sufficient number of cases were also detected during post marketing surveillance resulting in the addition of a warning in the linezolid label. Data from phase 3 studies in adult patients suggested that use of linezolid was associated with thrombocytopenia. In all the pediatric studies submitted in this application no statistically significant difference in the incidence of myelosuppression was seen in the linezolid treated patients. However, interpretation of these pediatric studies is limited by the small number of patients enrolled and by the different dosing regimens used in these studies.

Linezolid is effective in infections due to Gram positive organisms including resistant organisms like MRSA and vancomycin resistant *Enterococcus faecium*. However, it has the potential for myelosuppression and its pharmacokinetics in pediatric patients,

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primarily clearance and hence systemic exposure are variable. Therefore, consideration should be given to the potential risks of linezolid (including myelosuppression) before its use in a situation where linezolid's medical need is established. Variable linezolid pharmacokinetics in the pediatric population requires careful dose selection and close follow up for clinical response.

From a clinical perspective, based on the evidence from a comparator controlled clinical trial provided by the sponsor, there is adequate efficacy and safety data to recommend approval of linezolid in children with uncomplicated skin and skin structure infections. There is also adequate efficacy and safety data provided in the comparator controlled study in hospitalized pediatric patients with suspected or proven Gram positive infections, efficacy data from adult studies and pharmacokinetic data in pediatric patients to recommend approval of linezolid in children with the following Gram positive infections:

- Nosocomial pneumonia
- Community acquired pneumonia
- Complicated skin and skin structure infections
- Vancomycin resistant *Enterococcus faecium* infections

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There were no new Phase 4 commitments required as part of the approval process for this supplemental NDA. Reports from post marketing surveillance will be monitored for evidence of increased incidence of myelosuppression and or lymphoid depletion in pediatric patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Linezolid is the first drug in the oxazolidinone class of drugs that has been studied for use in children. It can be dosed both intravenously and orally. Linezolid has been shown to be effective in adults with infections due to resistant Gram positive pathogens such as MRSA and vancomycin resistant *E. faecium*.

This submission includes studies in pediatric patients from birth through 17 years including the two phase 2 studies submitted in the original linezolid NDA.

Phase I

The safety, tolerability, and pharmacokinetics of linezolid was assessed in four Phase I studies that enrolled 177 patients. These studies were conducted in pediatric patients and not healthy volunteers.

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Phase 2

Two uncontrolled Phase 2 trials of linezolid in pediatric patients in the treatment of community acquired pneumonia (M/1260/0045) and acute otitis media (M/1260/0049) were submitted in the original linezolid NDA and also included in this supplement. Data for pediatric patients in an uncontrolled compassionate use study (M/1260/0025) are also included in this submission.

Phase 3

Results of two phase 3 studies, one in children with uncomplicated skin and skin structure infection (M/1260/0065) and the second in children with suspected or proven resistant Gram-positive bacterial infections (M/1260/0082) were included in this supplement.

Study 0065 was a comparator controlled study using cefadroxil as the comparator that enrolled pediatric patients from 5-17 years of age. A total of 248 patients were enrolled in the linezolid arm and 251 in the cefadroxil arm. Patients in both arms received oral therapy. Patients aged 5 through 11 years received either linezolid suspension 10 mg/kg (up to 600 mg/dose) every 12 hours or cefadroxil suspension 15 mg/kg (up to 1 g/day) every 12 hours. Patients aged 12 through 17 years received either linezolid tablets 600 mg every 12 hours or cefadroxil capsules 500 mg every 12 hours. Duration of treatment was from 10-21 days.

Study 0082 enrolled hospitalized children from birth to 11 years of age with hospital acquired pneumonia (HAP), complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unidentified source, or other infections. Vancomycin was the comparator drug. All patients with vancomycin resistant Enterococcal infections were treated with linezolid. A total of 215 pediatric patients were treated with linezolid and 101 with vancomycin. Patients in both arms could be switched to appropriate oral therapy after initial intravenous therapy if they were ≥ 91 days of age. In the linezolid arm, patients were treated with linezolid 10 mg/kg every 8 hours intravenously followed by oral linezolid at the same dose. In the vancomycin arm dosing was based on age and renal function and choice of the oral step down medication was based on susceptibility of the baseline pathogen. Patients could receive up to 24 hours of a potentially effective antibiotic for the current infection prior to enrollment. During the study, additional antibiotic coverage for Gram-negative and anaerobic bacterial pathogens could be given as long as it had no activity against the primary Gram-positive pathogen (per recommended, labeled dosing guidelines).

Results of these two phase 3, comparator-controlled clinical trials and pharmacokinetic data in pediatric patients are intended to support efficacy in children with the following infections:

- Nosocomial pneumonia
- Community-acquired pneumonia
- Vancomycin-resistant *Enterococcus faecium* infections

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- Complicated skin and skin structure infections
- Uncomplicated skin and skin structure infections

B. Efficacy

Study 0065: Uncomplicated skin and skin structure infections

The sponsor has provided sufficient data to support granting the indication of uncomplicated skin and skin structure infections in children. Oral linezolid in a dose of 10 mg/kg (maximum 600 mg) in children ages 5-11 years and 600 mg in children 12-17 years twice a day (BID) was demonstrated to be non-inferior to cefadroxil which has FDA approval for this indication. The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. This was evidenced by the lower bound of the confidence interval being less than the pre-determined value of 10 %, the confidence intervals crossing zero and the p values exceeding 0.05.

Pediatric patients with uncomplicated skin infections in children including impetigo, cellulitis, minor abscesses and folliculitis were enrolled. The primary efficacy endpoints were investigator and sponsor defined clinical outcomes at the follow up visit (test of cure) 10-21 days after end of therapy. The sponsor defined clinical outcomes were more stringent than the investigator defined clinical outcomes as in addition to clinical response, it took into account the length of therapy. The patient must have received at least 5 days (10 doses) of study medication to be classified as a cure or improved and at least 2 days (4 doses) to be classified as a failure. The sponsor defined clinical outcome superseded the investigator defined outcomes.

In the sponsor's analysis patients with missing or indeterminate outcomes were excluded from the ITT and MITT populations. Additional analyses classifying patients with missing or indeterminate outcomes as failures were also performed in the ITT population.

In the ITT population (excluding missing and indeterminate outcomes), the difference in the clinical response was 2.5% (95% CI, -3.5, 8.7, p = 0.405).

Sponsor results: Clinical outcome (ITT) excluding missing/indeterminate

Assessment	Treatment Group		Statistical Test	
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)	P-Value	95% CI
No. assessed	231 (100)	224 (100)	0.405	-3.5, 8.7
Cured	205 (88.7)	193 (86.2)		
Failed	26 (11.3)	31 (13.8)		
Indeterminate	15	22		
Missing	2	5		

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A supplementary analysis of the sponsor's assessment of clinical outcome at follow up in which indeterminate and missing outcomes were classified as failures showed that the difference in the clinical response was 5.8 % (95% CI, -1.3, 12.8, $p = 0.109$). Results for the ITT population at the follow up visit classifying missing and indeterminate outcomes as failures are summarized in the following table.

The modified intent to treat (MITT) population included all ITT patients who had a pathogen isolated at baseline. In the MITT population (excluding missing and indeterminate outcomes), the difference in the clinical response was 2.5% (95% CI, -4.5, 9.6, $p = 0.479$).

Results for the MITT population at the follow up visit, excluding missing and indeterminate outcomes are summarized in the following table:

Sponsor results: Clinical outcome (MITT) excluding missing/indeterminate

Assessment	Treatment Group		Statistical Test	
	Linezolid N = 171 n (%)	Cefadroxil N = 166 n (%)	P-Value	95% CI
No. assessed	164 (100)	155 (100)	0.479	-4.5, 9.6
Cured	147(89.6)	135 (87.1)		
Failed	17 (10.4)	20 (12.9)		
Indeterminate	7	11		

The FDA statistical reviewer, Dr. Nancy Silliman Ph.D. performed an additional analysis using an algorithm in which patients were analyzed by the treatment group to which they were randomized and not taking into account the length of treatment. Patients were considered cures if they were assessed as cures at F-U by the investigator.

They were assessed as failures if any of the following applied:

- They were assessed as failures by the investigator at either the EOT or F-U visit
- They had died by the F-U visit and were not assessed as a cure by the investigator at the F-U visit (note: no patients died in this study)
- They were prescribed an additional antibiotic for lack of efficacy at any time during the study up to and including the F-U visit;

All other patients were assessed as missing.

No differences in the clinical outcomes between the two treatment groups were seen using this approach. The difference in cure rates between the two groups in the ITT population using this approach was 1.1% (90% in the linezolid arm versus 88.9% in the cefadroxil arm, 95% CI -5.1, 7.2).

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Study 0082: Suspected or Proven Resistant Gram Positive Infections

The sponsor has provided sufficient efficacy and safety data for the use of linezolid at a dose of 10 mg/kg every eight hours in hospitalized children with Gram positive infections from birth through 11 years of age. Pediatric patients with a variety of clinical diagnoses were enrolled in this study and hence no direct conclusions about the efficacy of linezolid in pediatric patients with a specific clinical indication can be drawn. Based on efficacy and safety data from this study, efficacy data from adult studies and pharmacokinetic data in pediatric patients the efficacy of linezolid in pediatric patients with community or nosocomial pneumonia, complicated skin and skin structure infections due to gram positive pathogens and vancomycin resistant *Enterococcus faecium* infections can be inferred.

This phase 3 comparator controlled open-label study was done to compare the safety, tolerability, and clinical efficacy of intravenously and orally administered linezolid with intravenously administered vancomycin in the treatment of resistant Gram-positive bacterial infections, including MRSA, methicillin-resistant *Staphylococcus* species, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin resistant Enterococcus (VRE) in children from birth through 11 years of age. Hospitalized children with suspected or known infections due to resistant Gram-positive bacteria, including hospital acquired pneumonia, complicated skin and skin structure infections, catheter-related bacteremia, bacteremia of unidentified source, and other infections were enrolled. Though the protocol was intended to enrich enrollment of pediatric patients with resistant Gram positive infections, patients with both sensitive and resistant Gram positive pathogens and patients with no baseline pathogen were enrolled. The latter could be enrolled if the patient fit clinical criteria for a given clinical syndrome despite negative cultures.

No formal sample size calculations were done for this study and the protocol did not specify the confidence limits to determine equivalence. The primary efficacy variables were patient clinical outcome at the EOT and F-U visits. The follow up visit was 12-28 days after the end of therapy and was considered the test of cure. The sponsor-defined patient clinical outcome was based on the investigator's evaluation of clinical outcome and on the number of days and doses of study medication received. The patient must have received at least 5 days and 15 doses of study medication for a cure or improvement and at least 2 days and 6 doses of study medication for treatment failure. The sponsor-defined patient clinical outcome superseded the investigator's assessments and only sponsor defined outcomes will be discussed.

The following table shows the baseline diagnosis of patients enrolled in this study:

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Sponsor results: Baseline diagnosis

Baseline Diagnosis	Treatment Group	
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)
Hospital-Acquired Pneumonia	23 (10.7)	16 (15.8)
Skin / Skin Structure Infection	80 (37.2)	40 (39.6)
Bacteremia, catheter-associated	48 (22.3)	13 (12.9)
Bacteremia , unknown source	33 (15.3)	19 (18.8)
Other infection	31 (14.4)	13 (12.9)

Sponsor's analysis of the ITT population (excluding missing and indeterminate outcomes) showed that the difference in the clinical response was 5.0% (95% CI, -6.0, 15.9). Results for the ITT population at the follow up visit, excluding missing and indeterminate outcomes are summarized in the following table:

Sponsor results: Clinical outcome (ITT) excluding missing and indeterminate outcomes

Assessment	Treatment Group		Statistical Test	
	Linezolid N= 215 n (%)	Vancomycin N= 101 n (%)	P value	95% CI
Cured	155 (79.1)	63 (74.1)	0.359	-6.0, 15.9
Failed	41 (20.9)	22 (25.9)		
No. assessed	196	85		
Indeterminate	7	6		
Missing	12	10		

CI= Confidence interval

Sponsor's analysis of the MITT population (excluding missing and indeterminate outcomes) showed that the difference in clinical response was 5.0% (95% CI, -6.0, 15.9).

Results for the MITT population at the follow up visit, excluding missing and indeterminate outcomes are summarized in the following table:

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Sponsor results: Clinical outcome (MITT) excluding missing and indeterminate outcomes

Assessment	Treatment Group		Statistical Test	
	Linezolid N= 137 n (%)	Vancomycin N= 62 n (%)	P-Value	95% CI
Cured	101 (80.8)	43 (81.1)	0.959	-12.9, 12.3
Failed	24 (19.2)	10 (18.9)		
No. assessed	125 (100.0)	53 (100.0)		
Indeterminate	6	4		
Missing	6	5		

FDA analysis was done using a similar algorithm as described in study 0065. For FDA definitions of study populations and clinical end points the reader is referred to the statistical review by Dr. Erica Brittain Ph.D.

The following table provides analysis of FDA clinical endpoints using FDA defined primary analysis populations.

FDA results: FDA clinical endpoints in FDA primary analysis populations (Missing data excluded)

Population	Linezolid		Vancomycin		95% Confidence Interval	
	Cure Rate	N	Cure Rate	N	Lower	Upper
FDA ITT	0.806	186	0.831	83	-.132	0.082
FDA MITT	0.796	108	0.898	49	-.230	0.027
FDA CE	0.906	117	0.891	55	-.096	0.126
FDA ME	0.888	80	0.905	42	-.148	0.113

In the FDA analyses no statistically significant treatment differences were seen between the two arms in any of the study populations. However, the greatest difference in cure rates between the two groups was seen in the MITT population (79.6% versus 89.8%). The significance of this finding is difficult to ascertain. However, it is noteworthy as the MITT population represents patients who had an identified Gram positive pathogen.

No significant treatment differences were seen between the two arms in the various subgroups analyzed, either by age, underlying illness or baseline pathogen.

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A total of 27 patients had infections due to MRSA in the FDA defined MITT population (excluding missing values); 18 were in the linezolid arm and 9 were in the vancomycin arm. No difference in cure rate was seen between the two groups in patients with MRSA infections. Only three patients with vancomycin resistant *Enterococcus faecium* infection were enrolled in this study and all were treated with linezolid. Two of these patients were cures at follow up and one was a failure.

Phase 2 studies

Results of two phase 2 studies, one for community acquired pneumonia (CAP) and the other for acute otitis media (AOM) were submitted with the original NDA and have been reviewed by Dr. John Alexander. The following is excerpted from Dr. Alexander's review.

Study 0045 (CAP)

This was an open-label, non-comparative, multicenter study of linezolid in the treatment of CAP in pediatric patients from 12 months to 17 years of age. The intravenous and oral dosing regimens used were 10 mg/kg (up to 600 mg) approximately every 12 hours. A total of 79 pediatric patients were enrolled in this trial. Except for one infant all enrolled patients were between 1-12 years of age. Clinical cure rate in the ITT population (excluding missing or indeterminate outcomes) was 63/67 (94%). Only 6 patients were microbiologically evaluable: in five *Streptococcus pneumoniae* was isolated and in one *Streptococcus pyogenes*.

Study 0049 (AOM)

This was an open-label, non-comparative, multicenter study of linezolid (10 mg/kg q 12 h) in the treatment of otitis media in pediatric patients from 12 months to 6 years of age. A total of 65 pediatric patients were enrolled in this trial. Fifty-five (84.6%) subjects completed the study. The success rate at follow-up was 39/60 (65%) in the ITT population (excluding missing or indeterminate outcomes). The sponsor is not seeking an indication for otitis media, hence efficacy results from this study will not be discussed further.

Study 0025 (Compassionate use)

In this compassionate use protocol patients were severely ill and had few other treatment options. Results pertaining to pediatric patients only will be discussed in this review.

In order to be eligible, a patient had to be either infected with an organism that was resistant to conventional therapy, yet susceptible to linezolid or intolerant of or allergic to all other conventional therapies. Patients were treated with linezolid 600 mg BID, using any combination of the IV solution, tablets, or oral suspension. Patients younger than 13 years old or who weighed less than 40 kg were treated with a dose of 10 mg/kg oral suspension twice daily (up to 600 mg BID). A small number of patients were also eligible for enrollment because they

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required intravenous (IV) vancomycin but lacked an IV access. The recommended duration of therapy was 10 to 21 days; however, patients could receive therapy for up to 3 months with the P&U medical monitor's approval.

There were 22 pediatric patients in this study, 12 of whom received linezolid 10 mg/kg BID and 10 received linezolid 600 mg BID. Of the 22 patients, 11 (50%) patients completed the course of treatment, 6 (27.3%) patients died, 3 (13.6%) patients withdrew due to serious adverse events, 1 (4.5%) withdrew due to a non serious adverse event, and 1 (4.5%) withdrew due to other reasons. Based on investigator-assessed clinical outcome, 5 patients had a clinical outcome of cure. The following table summarizes the investigator's assessment of clinical outcome at the FU visit pediatric patients in study 0025.

Sponsor: Clinical outcomes

Assessment	n (%)
Total Number of Patients	22
Cured	5 (71.4)
Failed	2 (28.6)
Indeterminate	7
Missing	8

In this study, 12 patients with VRE infection were identified. One of the isolates was *Enterococcus faecalis* and the remainder were *Enterococcus faecium*.

The following table summarizes clinical/microbiologic information in patients with VRE:

Sponsor: Patients with VRE infections

Age (years)	Clinical Outcome	Diagnosis
1	Cured	Peritonitis
< 1	Cured	CRBSI
15	Cured	Intra-abdominal infection
2	Cured	UTI
17	Failed	SSSI
5	Failed	Peritonitis
14	Failed	Infected device
12	Missing	Bacteremia, unknown source
14	Missing	Bacteremia, unknown source
5	Missing	Peritonitis
17	Indeterminate	Intra-abdominal infection
16	Indeterminate	Infected device

SSSI = Skin and skin structure infection

CRBSI = Catheter related bacteremia

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C. Safety

Overall, in the linezolid treated pediatric patients, no unexpected major toxicity was noted. However, dosing regimens varied among the different studies. Results for two phase 2 studies (0045 and 0049) will be combined since both used a BID dosing regimen and were not comparator controlled. Results of the compassionate use study will be discussed separately. Combined results from all three studies using a BID dosing regimen (0045, 0049 and 0065) will not be discussed in the executive summary. Results of the two phase 3 studies will be presented separately as one study used a BID regimen and the other used a TID regimen.

Adverse events in Phase 1 studies

A total of 177 patients received linezolid intravenously in the four phase 1 studies. The phase 1 studies were conducted in hospitalized patients rather than healthy volunteers. Of these patients, 43 received a single 1.5 mg/kg dose, 126 received a single 10 mg/kg dose, and 8 received multiple doses of linezolid, 10 mg/kg/dose (up to a maximum of 600 mg) every 12 hours for 4-5 doses. Four patients discontinued treatment, 1 due to an adverse event (AE) and 3 due to withdrawal of consent. AEs occurred more often in patients who received multiple doses of linezolid. Overall, 13% (23/177) of the patients experienced an adverse event. AEs that occurred in > 1% were injection/vascular catheter site pain/reaction (4%), rash (2.3%), nausea (1.1%), vomiting (1.1%), and hypokalemia (1.1%).

In the single-dose (1.5 mg/kg) group, 9.3% of patients experienced one or more AEs including rash (4.7%), disorder tongue (2.3%), and injection/vascular catheter site inflammation (2.3%). In the single-dose (10 mg/kg) group, 11.9% experienced one or more AEs. AEs occurring in more than 1% of patients were injection/vascular catheter site pain/reaction (4.7%), nausea (1.6%), and hypokalemia (1.6%).

In the multiple-dose (10 mg/kg) group, 4/8 patients experienced 1 or more AEs. These included fatigue, edema (generalized and local), ventricular bigeminy, ventricular extrasystoles, vasodilatation, vomiting, hemiplegia, pleural effusion, pneumothorax, and hydronephrosis; none were reported for more than 1 patient. Five of the 11 events, including fatigue, ventricular bigeminy, ventricular extrasystoles, vasodilatation, and hemiplegia, were reported in 1 patient in study 0059 who had a history of congenital heart defect, bigeminy, and hydrocephalus at baseline.

The frequency of drug-related AEs was 7.0% in the single-dose (1.5 mg/kg) group, 7.9% in the single-dose (10 mg/kg) group, and 12.5% in the multiple-dose (10 mg/kg) group. Two serious adverse events (SAE) were reported and neither was considered related to study medication. One (bone pain localized) occurred in the single-dose (10 mg/kg) group, and the other (pneumothorax) occurred in the

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multiple-dose (10 mg/kg) group. One patient discontinued treatment due to an injection/vascular catheter site reaction.

Adverse events in Phase 2 studies

Studies 0045 and 0049

Both phase 2 studies used the same dosing regimen of 10 mg/kg (maximum 600 mg) twice a day. In study 0045, IV linezolid was followed by oral linezolid and in 0049 only oral linezolid was used.

A total of 143 patients received at least one dose of linezolid. In study 0045, the mean duration of IV treatment was 4.4 ± 4.1 days and of oral treatment was 8.3 ± 3.0 days; the mean total duration of treatment (IV and oral) was 11.2 ± 6.4 days. In study 0049, the mean duration of oral treatment was 7.5 ± 2.0 days. Overall, 56% (80/143) of patients experienced one or more AEs. AEs occurring in $\geq 5\%$ were diarrhea (16.8%), vomiting (11.9%), rash (9.8%), and loose stools not elsewhere classified (5.6%). Three patients developed neutropenia as an AE and it was considered to be drug related in all three. The neutropenia resolved in all three patients. The most common drug related AE was diarrhea /loose stools, reported by 12.6% of patients. Five patients experienced a SAE including vomiting, neutropenia, seizures and pneumothorax and bronchiolitis. The SAE of neutropenia was considered drug related. There were no deaths in either of these studies.

Substantially abnormal hemoglobin or platelet values ($<75\%$ of LLN) were seen in 3.6% of patients and for neutrophils (<0.5 of LLN) in 1.5 % of patients. Substantially abnormal values ($>2 \times$ ULN) for ALT was seen in 3.6% and for lipase in 2.2 % of patients in study 0045. None of the patients in study 0049 had abnormal values for chemistry assays.

Study 0025

In this study only data on SAEs was collected and therefore discussion on AEs pertain only to SAEs. Of the 22 patients, 15 (68.2%) experienced one or more SAEs. Sepsis, reported by three patients, was the most common SAE, followed by anemia, intestinal perforation, and multiple organ failure, each reported by two patients. Four (18.2%) patients experienced SAEs that were thought to be related to linezolid; two developed anemia and one each developed thrombocytopenia and bone marrow depression.

Six of the 22 patients (27.3%) died during the treatment period. Three patients died of sepsis or septic shock and 1 patient each died of cardiac arrest, acute lymphoblastic leukemia, and multiple organ failure. All deaths were considered to be unrelated to study drug.

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Adverse events in Phase 3 studies

Study 0065

The mean length of treatment with linezolid for patients enrolled in this study was 12.0 ± 3.6 days compared to 11.9 ± 3.9 with cefadroxil. The mean number of doses in the linezolid group was 22.3 ± 7.2 and in the cefadroxil group was 22.1 ± 7.5 . No statistically significant differences were observed between treatment groups in the percentages of patients with any AEs, SAEs, drug-related adverse events, or discontinuations due to adverse events. In the linezolid arm, 111 (45.3%) reported one or more AE compared to 117 (47.0%) in the vancomycin arm. There were no deaths in this study. No statistically significant differences were observed between treatment groups in either age subgroup in the overall incidence of AEs.

The most frequently reported (incidence $\geq 5\%$) AEs in the linezolid group were diarrhea (7.8%) and headache (6.5%) and in the cefadroxil group were diarrhea (8.0%), vomiting (6.4%), and upper respiratory infection (5.2%). One patient in the linezolid arm had neutropenia and one patient in cefadroxil arm had leukopenia. There were no reports of thrombocytopenia in either treatment arm.

The most frequently reported drug-related AE was diarrhea. There were no statistically significant differences between the groups in the incidence of any drug-related AE. In the linezolid arm, 2.0% (5/245) of patients discontinued study medication due to an adverse event compared to 3.6% (9/249) in the cefadroxil arm. Adverse events that led to the discontinuation of study were generally considered moderate or severe. There were no statistically significant differences between the groups in frequencies of events leading to discontinuation.

SAEs were reported in 0.8% (2/245) of patients in the linezolid group and in 1.6% (4/249) of patients in the cefadroxil group. All patients recovered from their SAEs. One patient (6500436) had an elevated lipase value (7390 IU/L) on day 8 of the study, which had resolved within 3 days. The AE was considered drug related by the investigator and the drug was permanently withdrawn. One patient who developed diabetic ketoacidosis was a known diabetic and the event occurred almost a month after stopping study medication.

Study 0082

Relative to the linezolid group, the vancomycin group on average was treated for approximately 1 more day (mean duration 11.3 ± 5.0 days versus 12.2 ± 6.4 days) and received approximately 1 more dose (mean number of doses 30.3 ± 14.7 versus 31.5 ± 17.2).

Overall, toxicities were more common in this study compared to all other studies. Most patients enrolled in this study were more severely ill and often had other significant underlying medical conditions. Adverse events were more common in the vancomycin arm and were mainly related to skin rash/anaphylaxis. Though

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there was no statistically significant difference in the overall incidence of thrombocytopenia between the two groups, the incidence of study emergent and drug related thrombocytopenia was higher in linezolid arm. No difference in the incidence of neutropenia or anemia was seen between the two treatment arms. Mortality was also higher in the linezolid arm (6 % in the linezolid arm compared to 2.9% in the vancomycin arm). No age specific differences in the incidence of adverse events were seen. No significant differences were observed between treatment groups in the percentages of patients with any AEs. Drug-related AEs were reported more frequently in the vancomycin group than in the linezolid group.

Overall, study-emergent AEs were similar in the two groups. Rash and anaphylaxis were significantly more common in the vancomycin group. All reported events coded to the COSTART term "anaphylaxis" were described by investigators as "red man syndrome." AEs reported by $\geq 5\%$ of patients in the linezolid group were fever (14.1%), diarrhea (10.8), vomiting (9.4%), sepsis (8%), anemia (5.6%), and rash (7%); in the vancomycin group they were rash (15.2%), fever (14.1%), diarrhea (12.1%), anaphylaxis (10.1%), vomiting (9.1%), sepsis (7.1%), oral moniliasis (7.1%), and anemia (7.1%).

The most common drug-related AE was diarrhea in the linezolid group and anaphylaxis in the vancomycin group. Statistically significant differences between treatment groups in frequency of drug-related AEs were seen for anaphylaxis (linezolid 0.0%, vancomycin 10.1%; $p < 0.0001$), non-application-site pruritus (linezolid 0.0%, vancomycin 2.0%; $p = 0.0374$), and rash (linezolid 1.4%, vancomycin 7.1%; $p = 0.0082$). Drug-related thrombocytopenia was reported more frequently in linezolid-treated patients (1.9%) than in vancomycin-treated patients (0.0%), but the difference was not statistically significant ($p = 0.17$).

No statistically significant differences between treatment groups were observed in frequencies of SAEs. SAEs were reported in 19.7% (42/213) of patients in the linezolid group and 16.2% (16/99) of patients in the vancomycin group. Four hematologic SAEs occurred in 3 patients in the linezolid arm, two of whom had hematologic malignancies and one had bone marrow transplant for Wilm's tumor. The AEs were anemia and neutropenia (1 patient each), and thrombocytopenia (2 patients). In one patient anemia and thrombocytopenia was considered drug related. No patients in the vancomycin arm had hematologic SAE.

A total of 13 deaths (6%) were reported in the linezolid arm and 3 (2.9%) in the vancomycin arm. The medical reviewer reviewed case report forms of all deaths. There were four deaths each in the 0-90 days and 5-11 year age group and 5 deaths in the 1-4 year age groups. Causes of death included cardiac arrest ($n=3$), cardiac failure ($n=3$), gastrointestinal bleeding ($n=3$) and others ($n=4$). Deaths occurred at varying periods of time relative to start of treatment and given the nature and severity of underlying illnesses in these children no causality with drug

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administration could be inferred. However it merits caution and close monitoring once the use of linezolid in children is more widespread.

Adverse events by age

Among patients treated with linezolid, 76.7% (33/43) of patients aged 0 to 90 days, 88.2% (30/34) of patients aged 91 days to <1 year, 70.9% (61/86) of patients aged 1 to 4 years, and 62% (31/50) of patients aged 5 to 11 years reported one or more study-emergent AEs. In the vancomycin group, 73.7% (14/19) of patients aged 0 to 90 days, 87.5% (14/16) of patients aged 91 days to <1 year, 76.2% (32/42) of patients aged 1 to 4 years, and 81.8 % (18/22) of patients aged 5 to 11 years reported one or more study-emergent AEs. No specific adverse events were more common in any one particular age group.

Overall, diarrhea, fever, vomiting, headache and skin rash were the most common adverse events reported in patients treated with linezolid. Reduction in hemoglobin, platelet counts, white blood cell counts, and elevation of alanine aminotransferase (ALT) levels were the most common laboratory abnormalities noted in patients treated with linezolid. No age specific differences in the incidence of adverse events were seen. No significant adverse events were more common in patients treated with linezolid compared to the comparator drugs. The incidence of thrombocytopenia was slightly higher in the linezolid group in study 0082 though the difference was not statistically significant. Supportive evidence from the uncontrolled studies also showed no specific areas of concern. However, the dosing regimens and hence the systemic exposure to the drug varied between studies. Also, the patient populations enrolled in various studies were very different. Pediatric patients less than 12 years of age were treated with an eight-hourly (q 8h) dosing regimen only in study 0082. Patients in all other studies received 12-hourly dosing. The recommended frequency of administration in children less than 12 years of age is q 8h except for children ages 5-11 years with uncomplicated skin and skin structure infections. Thus the frequency of adverse events observed in all clinical studies combined may not truly represent the likelihood of adverse events in pediatric patients at the recommended dosing regimens.

D. Dosing

Linezolid dosing regimens in the various clinical studies were as follows:

Phase 1 studies

Single dose 1.5 mg/kg intravenous
Single dose 10 mg/kg intravenous
Multiple dose 10 mg/kg intravenous

Phase 2 studies

10 mg/ kg every 12 hours intravenous/oral

Phase 3 studies

Study 0065

10 mg/kg every 12 hours in children 5-11 years of age oral

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600 mg BID in children 12-17 years of age oral

Study 0082

10 mg/kg every 8 hours intravenous followed by oral step down at same dose

Pharmacokinetic data in pediatric patients and in healthy adolescents have shown that clearance of linezolid and hence systemic exposure to linezolid varies as a function of age. Clearance of linezolid is most rapid in the youngest age groups ranging from >1 week old to 11 years resulting in lower systemic exposure (AUC) and shorter half-life compared to adults and hence they require eight hourly dosing. Adolescents have mean clearance values approaching those observed in the adult population and hence require 12 hourly dosing. Neonates less than 34 weeks gestation and less than 7 days post natal age also have reduced clearance and hence need 12 hourly dosing. Due to the wide variability in clearance of linezolid in pediatric patients, including preterm neonates, it is possible that some patients could have subtherapeutic levels with the recommended dosing regimens. One specific area of concern is in the treatment of infections where the MIC of the infecting organisms is high ($= 4\mu\text{g/mL}$), especially in the context of severe life threatening infections. Thus the recommended dose of linezolid depends on the age of the pediatric patient and the clinical indication.

The following dosage and administration table is included in the label:

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Dosage Guidelines for ZYVOX

Infection*	Dosage and Route of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections Community-acquired pneumonia, including concurrent bacteremia Nosocomial pneumonia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	10 to 14
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	14 to 28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral‡ q8h 5-11 yrs: 10 mg/kg oral‡ q12h	Adults: 400 mg oral‡ q12h, Adolescents: 600 mg oral‡ q12h	10 to 14

* Due to the designated pathogens (see INDICATIONS AND USAGE)

† Neonates <7 days: Most pre-term neonates < 7 days of age (gestational age < 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric).

‡ Oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension

E. Special Populations

The following discussion pertains only to pediatric patients exposed to linezolid in the clinical studies submitted in this application. Males and females were both well represented in the clinical studies database. Race of the patients were predominantly white and mixed/multiracial in most studies except the compassionate use protocol and all phase 1 studies combined where they were predominantly white. The various pediatric studies submitted in this application enrolled patients in different age categories. Hence age distribution will be discussed by study and an aggregate for all studies combined will also be provided.

Phase 1 studies

Distribution of patients in the four age group categories were as follows: 64 in the < 1 year, 41 in the 1- 4 years, 43 in the 5-11 years, and 29 in the 12-17 years age group.

Phase 2 studies

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Studies 0045 and 0049 combined

Distribution of patients in the four age group categories were as follows: 1 in the < 1 year, 109 in the 1- 4 years, 32 in the 5-11 years, and 1 in the 12-17 years age group.

Study 0025

Distribution of patients in the four age group categories were as follows: 2 in the < 1 year, 6 in the 1- 4 years, 4 in the 5-11 years, and 10 in the 12-17 years age group.

Phase 3 studies

Study 0065

Patients from 5 to 17 years were included in this study. The mean age was 10.86 years and the range was 4.9-17.9 years. There were 146 children aged 5-11 years and 102 children aged 12-17 years.

Study 0082

Patients from birth to 11 years were enrolled in this study. The mean age was 2.92 years and the range was 0-11.7 years. Distribution of patients in the four age group categories in the linezolid arm were as follows: 43 in the 0-90 days, 34 in the 91-<1 year, 88 in the 1- 4 years and 50 in the 5-11 years age group. Only 2 neonates in each group were < 7 days old. Twenty-six infants in the 8-90 days age group had a gestational age at delivery of < 34 weeks.

All studies combined

Distribution of patients in the four age group categories were as follows: 80 in the < 1 year, 203 in the 1- 4 years, 232 in the 5-11 years, and 113 in the 12-17 years age group.

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I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Applicant: Pharmacia & Upjohn Company
Kalamazoo, Michigan

Drug Product Information

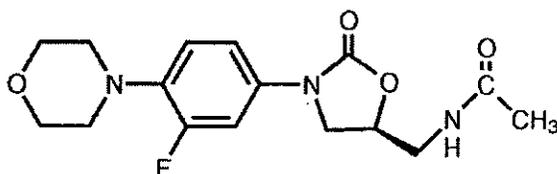
Generic name: Linezolid

Trade Name: Zyvox™

Chemical Name: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]- 2-oxo-5-oxazo-lidinyl] methyl]-acetamide

Chemical formula: C₁₆ H₂₀ FN₃ O₄

Chemical structure



Drug Category: Oxazolidinone antibiotic

Sponsor's proposed indication: Nosocomial pneumonia, community acquired pneumonia, complicated skin and skin structure infections, uncomplicated skin and skin structure infections and infections due to vancomycin resistant *Enterococcus faecium*.

Dosage forms: Intravenous solution, oral suspension

Age groups: Neonates-17 years

Dose:

Neonates (gestational age < 34 weeks and postnatal age < 7 days): 10 mg/kg every 12 hours

Children up to 11 years: 10 mg/kg every 8 hours

Children ≥12 years and adolescents: 600 mg every 12 hours

B. State of Armamentarium for Indication(s)

Linezolid and vancomycin are the only two drugs currently approved for the treatment of infections due to methicillin resistant *Staphylococcus aureus*.

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Vancomycin resistant *Enterococcus* infections

Zyvox™ (Linezolid) and Synercid® (quinupristin/dalfopristin) are the only two drugs currently approved for the treatment of infections due to vancomycin resistant *Enterococcus faecium*. Synercid® is not approved for use in pediatric patients.

Uncomplicated and complicated skin and skin structure infections

Several antibiotics are approved for uncomplicated skin and skin structure infections in pediatrics including Biaxin® (clarithromycin), Ceftin® (cefuroxime axetil), and Maxipime® (cefepime).

The package insert for Primaxin® (imipenem and cilastatin), Duricef® (cefadroxil), and Timentin® (ticarcillin and clavulanate) list skin and skin structure infections in the indication section without differentiating complicated from uncomplicated. None of the above antibiotics are approved for use in patients with infections due to MRSA.

Timentin® is approved for use in pediatric patients, 3 months-16 years, imipenem for neonates - 16 years and cefepime for patients from 2-16 years.

Community acquired pneumonia and Nosocomial pneumonia

Cefepime is approved for use in patients with pneumonia and Timentin® is approved for use in lower respiratory tract infections. Biaxin® (clarithromycin) is approved for pediatric patients > 6 months with community acquired pneumonia.

C. Important Milestones in Product Development

Linezolid (Zyvox™) tablets, IV formulation and oral suspension was approved on April 18, 2000. It was approved for use in adults for the following indications:

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains only).

Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

Some of the important time points in the pediatric development program for linezolid are as follows:

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March 15, 1999: P&U submitted their initial proposed pediatric study request. FDA issued written comments on this submission in a letter to P&U dated May 21, 1999. A revised proposed pediatric study request was submitted by P&U on July 12, 1999.

December 22, 1999: FDA issued a written request (WR) letter to P&U outlining the pediatric studies need for pediatric exclusivity. The written request was subsequently amended on February 28, 2002 and May 14, 2002. The final WR dated May 14, 2002, recommends that the following studies be performed. A copy of the WR is provided in Appendix 1.

1. Study # 1; Assessment of linezolid pharmacokinetics in full term and pre-term neonates
2. Study # 2: A randomized, blinded comparison of the safety and efficacy of linezolid versus a cephalosporin for treatment of skin and skin structure infections in pediatric patients ages 3 months to 18 years.
3. Study # 3: A randomized open label comparison of IV linezolid/oral linezolid and IV vancomycin (with other IV/oral switch, if appropriate) in suspected resistant gram positive infections in pediatric patients, and a prospective study of vancomycin resistant enterococcal infections in pediatric patients
4. Study # 4: A randomized, comparative trial of linezolid versus vancomycin in pediatric patients with CSF shunt infections.

February 28, 2002:

Pre sNDA meeting

The following agreements were reached at this meeting:

- P&U agreed to submit side by side comparisons of BID versus TID safety (serious adverse events) data as well as pediatric versus adult safety data.
- P&U agreed to submit a timeline for conducting and submitting results from a toxicity study in juvenile dogs.
- FDA confirmed that the pediatric sNDA would receive a priority review (i.e., 6-month clock) under the legislation of the Better Pharmaceuticals for Children Act.

The unresolved issues were as follows:

- Issue of adolescent dosing
- Integrated safety data from studies 0045, 0049 and 0065.

March 20, 2002:

Teleconference regarding dosing regimen for adolescents

FDA had expressed concerns about BID dosing regimen in this population, as there was a high degree of variability and recommended performing an additional pharmacokinetic (PK) study in adolescents with data collection extended to 24 hours. P&U agreed to perform another study and submit the data.

June 14, 2002:

Teleconference regarding juvenile toxicity studies

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The FDA had requested comparison of pharmacokinetic/toxicokinetic data between animals and humans of two rat studies (97-151 and 2001-0476) to which P&U had responded. The following points were discussed:

Toxicity in juvenile rats

Findings of two recent neonatal rat studies that showed endocardial thrombosis and lipid degeneration in the liver were summarized. P&U suggested that there was a difference in the susceptibility to toxicity of linezolid in the Sprague-Dawley rat stock used between earlier juvenile rat studies and these studies as they had not been noted previously in juvenile rats studies at the same exposure levels or in a different stock of adult rats.

Toxicity in juvenile dogs

P&U confirmed that the definitive GLP 4-week dog study would start on July 1, 2002, with an interim report by August 7, 2002 and a peer reviewed histopathology report by September 15, 2002. P&U agreed to provide FDA with histopathology results from liver and heart samples in addition to marrow, testes, and spleen.

October 15, 2002:

Teleconference regarding enrollment of adolescents in study 0082

P&U had amended protocol for study 0082 on August 23, 2002 to enroll adolescents in the extended vancomycin resistant Enterococcus (VRE) study. FDA reiterated their concerns over inclusion of adolescents until information from the pending pharmacokinetic study was evaluated to determine an appropriate dosing regimen in adolescents.

D. Other Relevant Information

Study 0082 was amended to keep the VRE arm open and closing the comparative arm with vancomycin. This is an open label multicenter study entitled linezolid IV/PO for the treatment of VRE infections in children. Results of this study have not yet been submitted to the Agency.

E. Important Issues with Pharmacologically Related Agents

No other oxazolidinone antibiotic is currently approved for use in humans.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

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Statistics

The following is excerpted from the review by Dr. Erica Brittain Ph.D. For details of the analytical methods and review please refer to the review by Dr. Brittain.

FDA analyses differed from that of the sponsor in some respects. The main differences were in the algorithm used to define clinical outcomes and in the classification of patients into treatment groups based on randomization and not by treatment received. This approach suggested that there might possibly be an advantage with vancomycin compared to linezolid among patients with documented Gram-positive infections. In the FDA Microbiological Intent to Treat (MITT) analysis, the reviewer's clinical success rate in the linezolid arm was about .80 versus about .90 for the vancomycin arm, with a corresponding 95% confidence interval for the treatment difference of (-.230, .027). The protocol did not appear to pre-specify a non-inferiority margin, and thus it is not straightforward to assess this result. Nonetheless, the confidence interval indicates that the difference may be as great as -.23, and that the difference approached, but did not reach statistical significance at the .05 level. This potential advantage also was observed in a number of key subgroups. In contrast, corresponding analyses among patients that met pre-specified "per-protocol" criteria, showed little difference between the arms.

Animal Pharmacology and Toxicology

The following is excerpted from the review by Dr. Amy Ellis Ph.D. For details please refer to the review by Dr. Ellis.

Target organs of toxicity for linezolid include the bone marrow, lymphoid tissues (thymus, lymph nodes, spleen, etc.), and liver. Extramedullary hematopoiesis in the spleen and liver was significantly reduced following linezolid exposure. Lymphoid depletion and reduction of extramedullary hematopoiesis were especially striking in juvenile animals. The margin of safety for linezolid toxicity between animals and humans is not large. Due to the variable human pharmacokinetics of this drug, C_{max} and AUC values observed in the clinic (especially in pediatric subjects) are similar to values obtained in animals that showed signs of linezolid toxicity. Additionally, spermatogenesis in rats was adversely affected by this drug, but this effect appeared reversible. Fertility in adult female rats was not reduced by linezolid treatment. Linezolid did not appear to be teratogenic in mice or rats at exposure levels approximately 10-fold or equivalent to human exposure, respectively, but it was fetotoxic in these species. Linezolid was neither mutagenic nor clastogenic in a battery of in vitro and in vivo assays. In general, the severity of linezolid toxicity appeared greater in young animals than adults; this is a potential concern for pediatric patients as well, particularly because lymphoid depletion is of special concern in the young and the human pediatric NDA database is small.

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Biopharmaceutics

The supplement was jointly reviewed by Jenny J. Zheng, Ph.D. and Philip M. Colangelo, Pharm.D., Ph.D. Review of the clinical pharmacology studies in children from 3 months to 18 years was performed by Dr. Jenny Zheng Ph.D. Review of the clinical pharmacology study in children from birth to 3 months was performed by Dr. Philip M. Colangelo, Pharm.D., Ph.D.

The following is excerpted from the review by Dr. Jenny J. Zheng Ph.D. For details please refer to the review by Dr. Zheng.

Pharmacokinetic studies in pediatric subjects aged from 3 months to 18 years old (Study 111 and 148) showed that after a single IV dose of 10 mg/kg linezolid, subjects from 3 months to 12 years of age, had lower area under the concentration versus time curve (AUC) as compared with the adults, because they had higher body weight-normalized clearance (CL_{bw}). It appears that from age 3 months to 5 years, the AUC remains relatively unchanged. However, after 5 years and up to 18 years of age, the CL_{bw} decreases and AUC increases. The mean AUC value is similar in adolescents (13 – 18 years old) compared to adults. To achieve a comparable daily exposure to adults receiving the clinical regimen of 600 mg q12h, a 10 mg/kg q8h regimen for pediatric subjects from 3 months to 12 years of age and 600 mg q12h regimen for adolescents is needed. Even though the mean daily exposure is similar at suggested regimens, it was found that the variability in clearance is higher in pediatric subjects than in the adults, which could result in potential sub-therapeutic exposure in some pediatric patients.

The following is excerpted from the review by Dr. Philip M. Colangelo Pharm.D., Ph.D. For details please refer to the review by Dr. Colangelo.

The pharmacokinetics of linezolid were determined following single IV doses of 10 mg/kg (infused over 1-hour) to full-term (gestational age ≥ 34 weeks / postnatal age ≤ 7 days or > 7 days to 12 weeks) and pre-term (gestational age < 34 weeks / postnatal age ≤ 7 days or > 7 days to 12 weeks) neonates (study 0064).

Of all neonate age groups studied, the clearance of linezolid was the slowest and the resulting systemic exposure (AUC(0- ∞)) was the highest in pre-term infants of gestational age < 34 weeks / postnatal age ≤ 7 days. In these pre-term neonates linezolid clearance and AUC(0- ∞) estimates were similar to those reported in adults receiving the recommended dose of 600mg. Thus, the dosage regimen in these patients should be 10 mg/kg q 12 hr.

As postnatal age increases beyond 7 days and up to approximately 12 weeks (~3 months) in both full-term infants and pre-term neonates, linezolid clearance increased and exceeded that of adult values. Consequently, the systemic exposure (AUC(0- ∞)) in this group of pediatric patients was significantly less than that in adults receiving 600mg. Thus, the dosage regimen for this group of pediatric

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patients should be 10 mg/kg q 8 hr. The volume of distribution and C_{max} estimates of linezolid were similar among all the neonate age groups studied, and were also similar to that of older pediatric patients from 3 months to 11 years, adolescents from 12 to 17 years, and adults.

The bioavailability/bioequivalence (BA / BE) studies performed to assess the comparative bioavailability between the _____ linezolid powder for oral suspension formulations used in the two pivotal Phase 3 trials for this NDA supplement and the marketed Zyvox™ film-coated tablet and oral suspension, demonstrated an adequate BA / BE comparison. However, at a dose of 600mg, the experimental _____ suspension formulation is not bioequivalent to the 600mg dose of the marketed Zyvox™ film-coated tablet.

Microbiology

No new microbiology issues were associated with this supplement. For details regarding the microbiology review please refer to the review by Dr. Frederic Marsik Ph.D.

Chemistry

No significant chemistry issues were associated with this supplement.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The pharmacokinetics of linezolid following single IV doses were studied in healthy adolescent subjects from 12-17 years, and pediatric patients ranging in age from birth through 17 years, including premature neonates. The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar in all pediatric patients regardless of age. However, clearance of linezolid is most rapid in pediatric patients ranging from >1 week old to 11 years. This results in lower systemic exposure (AUC) and shorter half-life compared to adults. As age of the children increases the clearance of linezolid gradually decreases. By adolescence the mean clearance values approach those observed for the adult population. Neonates < 34 weeks gestation and postnatal age less than a week showed decreased clearance compared to other pediatric age groups.

The inter-subject variability in linezolid clearance and hence variability in systemic drug exposure (AUC) is high across all pediatric age groups compared to adults. Due to this wide inter-subject variability in linezolid clearance and systemic drug exposure in pediatric patients it is possible that decreased efficacy may be observed in some pediatric patients especially when the pathogens have high MIC (= 4 µg/mL)

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B. Pharmacodynamics

The following is excerpted from the review by Dr. Jenny Zheng Ph.D.

A population pharmacokinetic/pharmacodynamic (PK/PD) study was included as part of Study 0082. All linezolid-treated patients were eligible to participate in the population PK component of the trial if they had taken at least six doses of linezolid. Each patient in the linezolid treatment arm was to have had a maximum of four blood samples collected one each on Days 3, 10, 17, and 24. One hundred ninety five patients and 376 concentrations were available for the pharmacokinetic analysis.

The relationship of exposure with efficacy and safety was explored. The exposure measures were AUC (0-24 hr) and the time above MIC₉₀ (4 µg/mL). The efficacy measures were clinical outcome and microbiological outcome. The safety measures were the peak changes of hemoglobin concentration, platelet count, neutrophil count, and adverse events such as convulsion and cardiac events. The findings were as follows:

- There was no apparent correlation between either clinical or microbiological failure and linezolid exposure levels.
- There was no association between changes in hemoglobin concentration or platelet count and linezolid plasma exposure.
- Changes observed with neutrophil counts reflect clinical improvement over time in patients with systemic infections rather than an association with plasma exposure to linezolid.
- There was no association between the infrequently reported adverse events of cardiovascular events and plasma exposure to linezolid.

IV. Description of Clinical Data and Sources

A. Overall Data:

All data in this supplemental NDA were submitted electronically and are available in the electronic document room.

Study 0082:

\\CDSESUB1\N21130\S_003\2002-06-21\clinstat\resistantgram-positiveinfections\0082.pdf

Study 0065:

\\CDSESUB1\N21130\S_003\2002-06-21\clinstat\skinandskin structure infections\0065.pdf

Study 0045:

\\CDSESUB1\N21130\S_003\2002-06-21\clinstat\communityacquired pneumonia\0045.pdf

Study 0049:

\\CDSESUB1\N21130\S_003\2002-06-21\clinstat\otitis media\0049.pdf

Study 0025

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\\CDSESUB1\N21130\S_003\2002-06-21\clinstat\compassionate use\0025.pdf

Integrated safety summary

\\CDSESUB1\N21130\S_003\2002-06-21\clinstat\iss.pdf

B. Tables Listing the Clinical Trials

Study	Indication	Design	Number treated	Linezolid Dosage
0045	Community Acquired Pneumonia	Multicenter Non comparator controlled	Linezolid:78	10 mg/kg, up to 600 mg every 12 hours
0049	Acute Otitis Media	Multicenter Non Comparator Controlled	Linezolid:65	10 mg/kg, up to 600 mg every 12 hours
0065	Uncomplicated Skin and Skin Structure	Multicenter Linezolid versus Cefadroxil	Linezolid:248 Cefadroxil:251	5-11 years:10 mg/kg q12 hours 12-17 years: 600 mg every 12 hours
0082	Resistant Gram-positive Infections	Multicenter Linezolid versus Vancomycin	Linezolid:215 Vancomycin:101	10 mg/kg every 8 hours
0025	Compassionate Use	Multicenter Non Comparator Controlled	Linezolid:22	≤ 13 yrs /< 40 kg:10 mg/kg every 12 hours >13 yrs/>40kg: 600 mg every 12 hours

C. Postmarketing Experience

Pediatrics

The sponsor has provided the following information on post marketing experience with linezolid in children. As of 08 May 2002, there have been spontaneous reports of 24 adverse events in 13 pediatric patients treated with linezolid, 5 of which were reported as serious adverse events. The most frequently reported events were myelosuppression (8%, 2/24) and drug interaction (8%, 2/24). All other events were reported only once each. A total of three patients had four hematologic adverse events, one each had myelosuppression and pancytopenia and the third patient had anemia and myelosuppression.

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Of the 5 SAEs, the following 2 have not been previously described:
The first report refers to a 2-year-old male who sustained severe burns (#2000029557US). Cultures were positive for vancomycin-resistant *Enterococcus faecium*. The patient received 1 or 2 doses of linezolid (10 mg/kg intravenously). According to the report, the patient tolerated the dose and infusion well. He died the following day. The reporter did not associate death with linezolid.

The second report concerns an 8-year-old patient who received linezolid suspension for a skin infection (#2000032699US). The patient developed an itchy vasculitis-type rash on hands, feet, buttocks and back (a measles-type rash with pustules) after 1 day of linezolid therapy. He subsequently was restarted on linezolid and his rash subsided.

Adults

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of linezolid. Neuropathy (peripheral, optic) has been reported in adult patients treated with linezolid. Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, it has also been reported in patients receiving shorter courses of therapy. Reports of myelosuppression resulted in the addition of a warning in the linezolid label. Reports of neuropathy associated with linezolid use were submitted as a labeling supplement [NDA 21130, 21131, 21132 (SLR 002)] and changes have been made to the package insert in the Postmarketing Experience section to include this adverse event.

D. Literature Review

The sponsor has provided a comprehensive literature review. The medical reviewer consulted the following additional references.

1. Diekema DJ Jones RN. Oxazolidinone antibiotics. *Lancet*. 2001;358:1975-82
2. Tsiodras S et al. Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet* 2001;358: 207-208.
3. Gonzales DR et al. Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid. *The Lancet* 2001;357:179
4. Attassi K et al. Thrombocytopenia associated with linezolid therapy. *Clin Infect Dis* 2002;34:695-8.

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V. Clinical Review Methods

A. How the Review was Conducted

The two phase 3 studies submitted in this application, Study M/1260/0065 (uncomplicated skin and skin structure infections) and Study M/1260/0082 (suspected or proven resistant Gram positive infections) were reviewed in detail. Two phase 2 studies, M/1260/0045 and M/1260/0049 had been submitted in the original linezolid NDA and have been reviewed by Dr. John Alexander. Dr. Alexander's review was consulted during the review of this supplement. Additionally, data from these two studies were evaluated for the integrated safety summary. Study 0025 was not reviewed in detail for efficacy, as it was a compassionate use study. Safety data from study 0025 and from the four phase 1 studies were included in the integrated safety summary.

Case report forms of 20% of the study population in study 0082 and 10% in study 0065 were reviewed in a blinded manner by the medical officer. Additionally, case report forms of all 39 children in study 0082 with hospital acquired pneumonia were reviewed. Case report forms of all children who died in study 0082 were also evaluated. Overall, no major inconsistencies were seen in the evaluability or outcome assessments. Hence, this sample was considered to be adequately representative of the quality of data and the sponsor's data were used for FDA analyses.

In addition to the sponsor's analyses of data, FDA analyses were performed using FDA defined patient populations and FDA defined clinical end points for both the phase 3 studies.

B. Overview of Materials Consulted in Review

The following materials were consulted during the review process

- Electronically submitted final study reports
- Case report forms
- Data sets submitted by sponsor and some additional data sets requested by FDA.
- Medical officer review of the original linezolid NDA
- Medical officer review of the phase 2 studies (0045 and 0049)
- Current and proposed package insert
- Literature review

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C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits were performed at four clinical trial sites and did not reveal any significant deficiencies or discrepancies that would invalidate the studies. A summary of audited sites is displayed in the following table.

Investigator (number)	Location	Study number	Number of patients enrolled
Oca (46234)	Fountain Valley CA	0065	27
Qaqundah (46637)	Huntington CA	0065	27
Deville (48850)	Los Angeles CA	0082	14
Adler (48066)	Richmond VA	0082	13

The medical officer reviewed a random sample of 20% of the case report forms, for study 0082 and 10% for study 0065 for concurrence with the sponsor's evaluability and outcome assessments. Also, case report forms for all patients with hospital acquired pneumonia and for all patients who died in study 0082 were reviewed. The sponsor's results were reviewed and confirmed by the FDA statistical reviewers (Nancy Silliman Ph.D. for study 0065, and Erica Brittain Ph.D. for study 0082).

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The protocols for both trials were reviewed by Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) of all the study sites. Amendments were reviewed by the IECs and IRBs if applicable to the site. The investigators were responsible for reporting any serious adverse events to their IECs/IRBs.

According to the sponsor, with three minor exceptions in study 0065 and four minor exceptions in study 0082 none of which jeopardized the safety or welfare of the patients, this trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Prior to enrolling patients in the study, the investigator was responsible for providing the patients' parents or legal guardians with full and adequate written and oral information regarding the objectives and procedures of the study and the possible risks involved and about their right to withdraw their child from the study at any time. The investigator was responsible for obtaining a signed informed consent from each patient's parent or legal guardian (or witnessing verbal consent according to applicable regulations) prior to inclusion in the study.

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Assent of the children participating in the study was obtained as per the IEC/IRB requirements of each site.

E. Evaluation of Financial Disclosure

Study 0065

The sponsor has submitted form FDA 3454, Certification: Financial interests and arrangements of clinical investigators. The sponsor certifies that they have not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation will be affected by the outcome of the studies as defined in CFR 54.2(a).

Study 0082

The sponsor has submitted form FDA 3454, Certification: Financial interests and arrangements of clinical investigators. The certificate states that as the applicant who is submitting a study by a firm or party other than the applicant, they certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators have not entered into any financial arrangement with the sponsor whereby the value of the compensation will be affected by the outcome of the studies as defined in CFR 54.2(a).

Form FDA 3455, Disclosure: Financial interests and arrangements of clinical investigators have been submitted for the following three investigators in this study: _____

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Linezolid has a role in treatment of infections due to Gram positive cocci such as methicillin resistant *Staphylococcus aureus* and vancomycin resistant Enterococcus where only few other treatment options exist. It also has the advantage of oral dosing and hence provides for step down to oral therapy after initial intravenous therapy. However, given its pharmacokinetic characteristics in pediatric patients, evidence of myelosuppression in juvenile and adult animals, the post marketing evidence of myelosuppression in adults and the reports of linezolid resistance after clinical use among Enterococci and *Staphylococcus aureus*, it will be prudent to use linezolid only in selected patients and under close supervision.

In study 0065, linezolid showed equal efficacy compared to cefadroxil in the treatment of uncomplicated skin and skin structure infections. However, the role of linezolid for this indication is limited, as several other treatment options are currently available. The comparator controlled study (0082) in hospitalized pediatric patients with suspected or proven Gram positive infections, showed that the efficacy of linezolid was comparable to vancomycin. In patients with

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documented Gram positive pathogens, there was a suggestion of vancomycin efficacy advantage though these differences were not statistically significant. Mortality was higher in the linezolid arm.

B. General Approach to Review of the Efficacy of the Drug

For both the phase 3 studies, study 0082 and study 0065 data from the final study reports were reviewed for safety and efficacy by the medical reviewer. Additionally FDA analyses were performed using a slightly different definition of patient populations and clinical endpoints for both the phase 3 studies. Medical officer review of the study 0045 (community acquired pneumonia) submitted with the original NDA were also consulted for efficacy analysis. Results of two uncontrolled studies, study 0025 (compassionate use) and study 0049 (Acute otitis media) were not reviewed in detail for efficacy, but were reviewed for safety.

C. Detailed Review of Trials by Indication

Study 0065 (Uncomplicated skin and skin structure infections)

Objectives

Primary objective

The primary objective was to compare the clinical efficacy, safety, and tolerability of orally administered linezolid with orally administered cefadroxil for the treatment of skin and skin structure infections in children aged 5 through 17 years.

Secondary Objective

The secondary objective was to obtain steady-state linezolid pharmacokinetic (PK) data at 4 centers for children aged 5 through 11 years and 12 through 17 years.

Overall Study Design and Plan

The following description of the study design and study procedures is excerpted from the sponsor's final study report for study 0065.

Study period: June 12, 2000 to February 8, 2001.

Study sites: United States (68), Canada (8), Argentina (5), Brazil (3), Chile (3), Mexico (2) and Peru (2).

Investigators: 91 investigators enrolled patients. CV's of investigators have been provided by the sponsor and reviewed by the medical officer.

Study design: Phase III, blinded, randomized, comparator-controlled, multinational study comparing the efficacy, safety, and tolerability of linezolid and cefadroxil for the treatment of skin and skin structure infections in children

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aged 5 through 17 years. The sponsor chose cefadroxil as a comparator instead of cephalexin as cephalexin suspension was not commercially available. Cefadroxil is approved for the treatment of skin and skin structure infections caused by staphylococci and/or streptococci.

Comments

Choice of cefadroxil as a comparator is acceptable as it is effective in treating skin and skin structure infections and can be administered orally twice a day.

Study procedures

After informed consent was obtained, a medical history was taken, a physical examination performed, vital sign measurements obtained, blood drawn for laboratory assays, and a pregnancy test performed for females with childbearing potential. A negative pregnancy test was required before administration of study medication. Infection site specimens for Gram stain and culture were required before the administration of study medication. Patients were allowed to receive 48 hours of study medication while the results of the safety laboratories, microbiological cultures, and susceptibility tests were completed. In order to continue treatment beyond the first 48 hours, laboratory assay results and other enrollment tests must have satisfied the inclusion/exclusion criteria. Patients whose laboratory results did not meet the protocol-specified requirements were to be withdrawn from the study.

Patients whose cultures grew organisms other than Gram-positive pathogens were allowed to remain in the study if they showed clinical improvement and did not require concomitant antibiotic therapy. Patients whose cultures were negative but who were clinically improving were also allowed to remain in the study. The sponsor has provided a list of organisms that were defined as pathogens for this study and is reproduced in Appendix 2.

Comments

In the list of pathogens acceptable for microbiologic availability the sponsor has included pathogens that would otherwise not be considered pathogens for uncomplicated skin infections. This includes species of coagulase negative staphylococci (CONS), and viridans group streptococci. CONS and viridans group streptococci are common inhabitants of skin and mucus membrane and are uncommon causes of skin infections in otherwise well children. Abscesses due to CONS have been reported in neonates, but are less likely in older children. S.lugdunensis can cause abscesses, which are more commonly seen in patients with underlying medical conditions. Streptococcus dysgalactiae can colonize the skin and gain access to subcutaneous tissue following a break in skin integrity. It is not unusual to have negative baseline cultures from the site in patients with skin infections like cellulitis.

Study visits: Patients were to return for an outpatient evaluation seven days after beginning treatment. During this visit, clinical observations, vital sign assessments, laboratory assays, infection site culture if indicated, and adverse

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event monitoring were performed and blood samples for PK analysis were obtained from the patients enrolled in the PK substudy. Within 72 hours after completing treatment patients returned for an end of therapy (EOT) visit. At this visit, clinical evaluation, vital sign assessments, laboratory assays (if this visit was > than 72 hours after the day seven visit), infection site culture if indicated, and adverse event monitoring were performed. A F-U evaluation (10 to 21 days after EOT) was considered the TOC evaluation. At this visit, clinical observations, vital sign assessments, laboratory assays (including a repeat pregnancy test), infection site culture if indicated, adverse event monitoring, and a clinical response evaluation were completed.

Inclusion Criteria

- Expected to survive with effective antibiotic therapy and appropriate supportive care throughout the study.
- Willing to complete all study-related activities
- Ability to swallow the suspension or tablets.
- Clinical presentation compatible with a diagnosis of skin or skin structure infection due to a suspected gram-positive pathogen, with at least 2 of the following signs and symptoms: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/ tenderness to palpation, or swelling/induration.
- An infection site accessible for specimen collection for Gram stain and culture.
- If the primary site of infection was an abscess, in addition to surgical draining, systemic antibiotic therapy must have been required to effect a cure.
- Treatment with the comparator was considered appropriate.
- Willingness of the patient's parent or legal guardian to review and sign an informed consent form.

Exclusion Criteria

- Previous antibiotic treatment for more than 24 hours with a potentially effective systemic antibiotic within 48 hours of study entry unless the treatment failed (defined as no clinical improvement after 3 days of treatment) or the pathogen showed drug resistance.
- Presence of any of the following:
- Infection(s) with a high surgical incision cure rate, e.g., isolated furunculosis, and folliculitis.
- Medical conditions in which inflammation could have been prominent for an extended period even after successful bacterial eradication, e.g., superinfected eczema or atopic dermatitis.
- Infection(s) requiring potentially effective concomitant antimicrobial therapy.

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- Decubitus, ischemic ulcers (unless an associated cellulitis), necrotizing fasciitis, gas gangrene, or burns on greater than 20% of total body surface.
- Orbital, buccal, or facial (unless related to traumatic injury or other obvious insult to the skin) cellulitis suspected to be due to *Haemophilus influenzae* type b or other gram-negative pathogens.
- Infection due to organisms known to be resistant to the study medications.
- An infected device that would not be removed.
- Endocarditis, osteomyelitis/septic arthritis, or central nervous system (CNS) infections.
- Known pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension.
- Known or suspected leukemia.
- Known or suspected human immunodeficiency virus (HIV) infection in Argentina, Brazil, Chile, Mexico, or Peru; otherwise, if HIV infected, CD4 cell count ≤ 200 cells/mm³.
- Hypersensitivity to linezolid or cefadroxil or one of the excipients.
- Previous enrollment in this or another study of linezolid.
- Concurrent use of another investigational medication.
- Pregnant or breastfeeding females and females of childbearing age unable to take adequate contraceptive precautions.

Comments

Overall, the inclusion and exclusion criteria are acceptable. Presence of at least two signs and symptoms makes it more likely that true bacterial infections of the skin are included. A requirement for baseline absolute neutrophil count (ANC) $\geq 500/\mu\text{L}$ was removed by amendment 3. It is likely that in neutropenic patients signs and symptoms of inflammation could be masked. Patients with HIV should be able to mount an adequate inflammatory response unless the ANC is low.

Removal of Patients from Therapy or Assessment

- A patient was to be withdrawn from the study if, in the investigator's opinion, it was medically necessary or if it was the wish of the patient or patient's parent or legal guardian.
- In addition, a patient was to be withdrawn from the study for the following reasons:
 - The isolated pathogen was not susceptible to any of the study medications

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- Presence of Gram-negative bacterial pathogen(s) that required Gram-negative coverage.
- Completion of the protocol-defined dosing period.
- Disease progression (e.g., septic shock, acute renal failure). After withdrawal, these patients were to begin therapy with other antimicrobials.
- Administrative reasons (e.g., patient noncompliance or a major protocol violation).
- Request of the sponsor or regulatory agency.
- Lack of clinical improvement within 72 hours.
- Lack of microbiological improvement.

Patients who were withdrawn from the study were to undergo a clinical assessment, including the appropriate EOT activities on the day that study medication was discontinued. A F-U visit was also to be completed. If a patient did not return for a scheduled visit, every effort was to be made to document the patient's response to the study medication. The investigator was to document the primary reason for the patient's discontinuation on the CRF.

Treatments

Both study medications were to be taken orally for 10 to 21 consecutive days and could be taken with or without food. Dosing through nasogastric, jejunostomy, or gastrostomy feeding tubes was allowed. Patients who could not swallow the tablets or capsules could receive suspension regardless of age. Patients were randomized in a 1:1 ratio to receive one of the following oral treatments:

Linezolid:

Suspension (children aged 5-11 years): 10 mg/kg (up to 600 mg/dose) q12 hours

Tablets (children aged 12-17 years): 600 mg every 12 hours.

Cefadroxil:

Suspension (children aged 5-11 years): 15 mg/kg (up to 1 g/day) every 12 hours

Capsules (children aged 12-17 years): 500 mg every 12 hours.

Comments

Most uncomplicated skin and skin structure infections in otherwise healthy children should be cured with 7-10 days of therapy. Dosage of cefadroxil used in this study is per the approved label. The label does not give a recommended length of treatment.

In this study, children from ages 5-11 years received 12 hourly dosing, subsequent pharmacokinetic data however showed that children < 12 years of age require 8 hourly dosing as they have increased clearance and hence lower systemic exposure.

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Blinding

Encapsulation of the oral solid dosage forms was not attempted as it would increase the size of the study medication and limit the number of children who were able to swallow the dosage form. Cefadroxil suspension was provided in the original manufacturer bottles and was labeled to hide the product name. Because of the limitations of blinding in this study, it was likely that some study coordinators and some patients/guardians knew the group assignment. Study coordinators, patients, and parents were instructed not to reveal the physical characteristics of the study medication or the medication name to the investigator. The field monitors of this study were unblinded in order to complete study medication accountability and compliance documentation. Unblinding was only to be used under circumstances where knowledge of the study treatment was necessary for the proper treatment of the patient. The investigator was to contact the Pharmacia medical monitor prior to breaking the blind. If the treatment blind was broken, the reason and the date were to be recorded on the CRF, which was to be signed by the investigator.

Prior and Concomitant Therapy

Patients were not to receive more than 24 hours of treatment with a potentially effective systemic antibiotic within 48 hours of study entry, unless the treatment failed (defined as no clinical improvement after 3 days of treatment) or the patient's pathogen showed drug resistance. Patients were not to receive a concomitant antibiotic during the treatment period or before the F-U visit, unless the study medication was not an effective treatment for the patient's pathogen(s). In the event that such treatment was provided, the patient was considered a treatment failure. All medications received seven days prior to the start of study medication and during the study were to be recorded on the appropriate CRF.

The use of antimicrobial topical solutions such as bacitracin, polymyxin, or pramoxine and daily debridement or dressing changes were acceptable adjunctive therapies that could be employed throughout the treatment period (including F-U), as long as they did not exceed the investigator's normal practice of therapy. Topical steroids could be used, provided they were not in direct contact with the site of infection. Adjunctive therapies and/or surgical interventions were to be recorded on the appropriate CRF.

Comments

In patients who have received prior antibiotics, presence of signs and symptoms may not truly reflect a failure because some skin and skin structure infections such as cellulitis may have slow resolution of inflammation. Enrolling such patients is likely to over estimate the efficacy of study medications.

Treatment Compliance

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Each site was to maintain an Investigational Medication Record Form itemizing all study medications administered to or taken by each patient during the study. The patient's parents/legal guardians were instructed to bring their unused study medication to each visit, to return any unused study medication at their final visit, and to describe their child's compliance with the oral therapy. The site was to account for all study medications and to explain any discrepancies.

Efficacy Evaluations

The clinical evaluation of uncomplicated skin and skin structure infection was based on the resolution or improvement in clinical and microbiological signs and symptoms of infection. Objective and subjective clinical observations were to be made by the investigator and recorded on the CRF; these assessments included:

- Anatomical site of infection at the baseline visit
- Infected site description including discharge, erythema, fluctuance, heat/localized
- warmth, pain, tenderness, swelling, and induration at each clinic visit
- Body temperature at each clinic visit
- Extent of infection (length, width) at the baseline and F-U visits
- Degree of involvement (superficial or deep) at the baseline and F-U visits

Safety Evaluations

A medical history, which included previous medical/surgical therapy for the infected site and an evaluation of previous antibiotic exposure, and a physical examination were performed at the baseline visit. Vital sign measurements, including blood pressure, pulse, and respiration, were obtained at the baseline visit and at each subsequent study visit. Laboratory assays (hematology and chemistry) were obtained at the baseline and day 7, EOT and F-U visits. All adverse events that occurred during the study were to be recorded.

Efficacy Variables

The primary efficacy variable was patient clinical outcome. The sponsor-defined patient clinical outcomes superseded the investigator's assessments. Secondary efficacy variables were patient microbiologic outcome, clinical signs and symptoms, individual pathogen outcomes, body temperature, WBC counts, and size of lesion.

Investigator-Defined Patient Clinical Outcome

At the EOT and F-U visits, the investigator assessed each patient and assigned a clinical outcome according to the following criteria:

- Cured - Resolution of the clinical signs and symptoms of infection, when compared to baseline.

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- Improved - Incomplete resolution of the clinical symptoms (only used at EOT).
- Failed - Persistence, incomplete resolution (at F-U) or worsening of the baseline clinical signs and symptoms of infection, or the development of new clinical signs and symptoms consistent with an active infection that required additional antimicrobial therapy. If a patient experienced an adverse event(s) and the discontinuation of study medication was required, the patient was to be considered a clinical failure. In addition, patients who withdrew from the study due to lack of clinical improvement after at least 48 hours of treatment were to be classified as clinical failures.
- Indeterminate - Extenuating circumstances precluded classification to one of the above outcomes. Patients whose infection required an incision and drainage more than 48 hours after the first dose of study medication were also to be classified as indeterminate.

Sponsor-Defined Patient Clinical Outcome

The sponsor-defined clinical outcome at the EOT and F-U visits was based on the global evaluations made by the investigator, the number of days and doses of study medication received, and whether a concomitant antibiotic had been administered. The patient must have received at least 5 days (10 doses) of study medication to be classified as a cure or improved and the patient must have received at least 2 days (4 doses) of study medication to be classified as a failure.

The algorithm used by the sponsor to classify outcomes is described below:

Failed

- If a patient was given an antibiotic for lack of efficacy any time between day 2 and the day after the investigator's clinical assessment, inclusive (if an assessment was made), then the outcome was classified as failed for that assessment and all assessments that followed. If no investigator's clinical assessment was made in the F-U window and the patient was given an antibiotic for lack of efficacy at any time between day 2 and the upper limit of the F-U window inclusive, then the outcome was classified as failed for the F-U visit.
- If a patient had no postbaseline assessment in the EOT and F-U window or the assessments were indeterminate in both, the patient was classified as a clinical failure at both visits.
- If a patient had no data or if the outcome was indeterminate at the F-U visit, an outcome of failed at the EOT visit was carried forward to the F-U visit.

Indeterminate - If a patient was assessed by the sponsor as clinically improved or cured at the EOT visit and had no assessment or was indeterminate at the F-U visit the outcome was indeterminate.

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Missing - If a patient received less than 2 days of treatment or received less than 4 doses, an outcome of Missing was assigned.

Comments

The sponsor defined clinical outcome was more stringent than the investigator defined clinical outcome as in addition to presence or absence of clinical features it took into consideration days of therapy/ or doses of medication received. For this review only the sponsor defined clinical outcomes will be presented and discussed.

Sponsor-Defined Patient Microbiologic Outcome

Each baseline pathogen was assigned a sponsor-defined microbiologic outcome. Multiple pathogens identified in culture samples from the same patient were assigned separate outcomes. Baseline pathogens were assigned an outcome for the F-U visit based on the results obtained from culture and sensitivity testing done at the central laboratory. Patients must have received at least 2 days and 4 doses of study medication to be evaluated as documented microbiologic persistence or as presumed microbiologic persistence.

The categories for sponsor-defined patient microbiologic outcome for patients who had one or more pathogens isolated at the baseline visit are described below:

Eradication:

- Documented Microbiologic Eradication - The absence of the original pathogen or pathogens from a culture at the F-U visit
- Presumed Microbiologic Eradication - The patient's outcome was classified as clinically Cured at the F-U visit, and no microbiological data were available.

Persistence:

- Documented Microbiologic Persistence - The presence of at least one of the original pathogens from a culture obtained at the F-U visit
- Presumed Microbiologic Persistence – The presence of either of the following:
 - The patient's outcome was classified as clinical Failure at the F-U visit, and no microbiological data were available.
 - A concomitant antibiotic therapy was used due to a lack of efficacy before the F-U culture, or in the absence of a culture, after the first dose of study medication and before the end of the F-U window.

Superinfection - The patient's outcome was classified as clinically Failed, Indeterminate, or Missing, and a pathogen was isolated from a culture at the F-U visit that was different from the original pathogen(s).

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Colonization - The patient's outcome was classified as clinically Cured at the F-U visit, and a pathogen other than the one isolated at the baseline visit was present in a culture at the F-U visit.

Indeterminate - The patient's outcome was classified as clinically Indeterminate at the F-U visit, and no microbiological data were available.

Missing - Any patient whose Sponsor-Defined Clinical Outcome at the F-U visit was missing, and no microbiological data were available at the F-U visit or the response was Documented or Presumed Microbiological Persistence, but the patient received less than 2 days or 6 doses of study medication.

The above microbiologic outcome categories were collapsed into the following categories:

- Microbiologic Success - Any patient who had a documented or presumed eradication or colonization
- Microbiologic Failure - Any patient who had a documented or presumed persistence or superinfection
- Indeterminate - Any patient who was classified as Indeterminate
- Missing - Any patient who was classified as Missing

Sponsor-Defined Pathogen Microbiologic Outcome

Each baseline pathogen was assigned a sponsor-defined microbiologic outcome at the F-U visit and collapsed as follows:

- Eradication: Documented or presumed eradication of the given pathogen
- Non-eradication: Documented or presumed persistence of the given pathogen
- Indeterminate: Any pathogen for which the outcome is indeterminate
- Missing: Any pathogen for which the outcome is missing

Safety Variables

Clinical

Throughout the study, changes in physical findings as well as clinical signs and symptoms that may have reflected adverse effects were documented. A physical examination was completed at the baseline visit and vital signs were recorded at all scheduled visits.

Laboratory

Laboratory assays (hematology and chemistry) for all sites were to be performed by _____ . However, if the sample could not be processed, or an extra sample was collected during the study, local laboratory data were used. Blood samples were obtained at the baseline, day 7, EOT (if more than 72 hours after the day 7 visit), and F-U visits for the following tests:

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Hematology: Complete blood count (CBC) with differential and platelet count

Chemistry: Aspartate transferase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine, and lipase.

Adverse Events

All adverse events that occurred between the first dose of study medication and the F-U visit were to be recorded in the CRF and reported to Pharmacia. In addition, any known untoward event that occurred subsequent to the adverse event reporting period that the investigator assessed as possibly related to the study medication was also to be reported as an adverse event.

Exposure in Utero

If a patient became pregnant while receiving study medication or within 30 days of discontinuing the study medication, the investigator was to submit a Serious Adverse Event Form—Exposure in utero that included the anticipated date of birth or pregnancy termination. If the pregnancy was discovered during the treatment period, the study medication was to be discontinued, and the patient was to be given an appropriate antibiotic that is labeled as safe for use during pregnancy. The patient was to be followed by the investigator until the completion of the pregnancy. If the pregnancy ended for any reason before the anticipated date provided, the investigator was to notify the Pharmacia monitor.

Statistical and Analytical Plans

General

All patients were to have microbiological assessments at the baseline visit, but the primary efficacy assessments were based on clinical outcome. The TOC evaluation was conducted at the F-U visit 10 to 21 days after EOT.

All data listings, summaries, and statistical analyses were generated using SAS® Version 6.12. All statistical tests were 2-sided. P-values less than or equal to 0.05 were considered statistically significant. All 95% confidence intervals were based on the normal approximation to the binomial distribution and were considered consistent with equivalence if the lower limit of the confidence interval exceeded -10%.

Patients who received the wrong study medication (i.e., the treatment other than the one they were randomized to receive) were included in their actual treatment group (i.e., the one representing the medication they actually received) for both safety and efficacy analyses.

Key efficacy results were presented by investigator/center. Due to the expected small number of evaluable patients at each center, terms for investigator effect and treatment group-by-investigator interaction were not included in the statistical models used for analysis. However, consistency of treatment effects across centers was investigated for those centers with appreciable numbers of evaluable patients.

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Determination of Sample Size

Using a 2-sided test level of 5% and a desired statistical power of 80% under the assumption that each treatment group would yield a 90% success rate, the number of evaluable patients required per treatment group for a determination of equivalence between the 2 treatment groups to within 10%, was 142. Assuming a 60% clinical evaluability rate, target enrollment was 237 patients per treatment group.

Comments

A delta of 10 % for determination of equivalence is acceptable. An evaluability rate of 60% seems low for this indication.

Patient Subsets

Analyses of efficacy variables were done separately for intent-to-treat (ITT), modified intent-to-treat (MITT), clinically evaluable (CE), and microbiologically evaluable (ME) populations. The subsets are described below.

ITT Patients - All patients who received one or more doses of study medication. This population of patients was used for analyses of safety and primary efficacy variables.

MITT Patients - All ITT patients who had a baseline pathogen isolated from a culture taken in the ITT window from the infected site or blood. This population was used for the analyses of primary and secondary efficacy variables.

CE Patients - This population was used for the analyses of primary and secondary efficacy variables. It included all patients in the ITT population unless they met 1 or more of the following criteria.

- Eligibility criteria not met.
- Prior antibiotic usage - if the antibiotic was started before the start of study medication and was potentially effective against the condition under study. Patients whose prior antibiotics were stopped on day 1 were not excluded.
- Insufficient therapy - a patient who discontinued study medication for any reason other than lack of efficacy before the minimum requirement of 7 days.
- Noncompliance with study medication regimen - a patient who did not take at least 80% of the prescribed study medication based on their study medication record or who had noncompliance documented elsewhere in the CRF.
- Concomitant antibiotics given for intercurrent illness - a patient who was prescribed an antibiotic for an adverse event or intercurrent illness after day 1 and before the F-U visit if the antibiotic was potentially effective against the condition under study. The use of concomitant antibiotic therapy due to a lack of efficacy in the treatment of baseline pathogens was not a reason for exclusion from the CE population.

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- No postbaseline assessment - a patient without an assessment (indeterminate is an assessment) in the F-U visit analysis window was not evaluable unless they met either of the following criteria:
 - The investigator's clinical outcome was a failure at EOT.
 - The patient was given an antibiotic due to lack of efficacy any time between day 2 and the last day of the F-U analysis window, inclusive.

ME Patients - This population was used for the analyses of primary and secondary efficacy variables. It included all CE patients unless they met either of the following criteria.

- No baseline pathogen was isolated from a culture taken in the evaluable window from the infected site or blood.
- All baseline pathogens in the evaluable window were resistant to linezolid or cephalothin.

Comments

The rationale for not excluding patients who received antibiotics that were stopped on day 1 from the CE population is unclear. Such patients could have potentially received > 24 hours of effective therapy prior to enrolling in the study, thus artificially increasing the cure rates in both arms of the study.

Visit Windows

Study days were numbered relative to the first day of dosing. The start of the study (day 1) was defined as the date on which a patient took the first dose of study medication, as recorded on the CRF. Relative to the study start, days were numbered (-2, -1, 1, 2) with day -1 being the day prior to the start of study medication. Relative to the EOT, post-study medication days were numbered 0P (last day of dosing), 1P, 2P, etc.

The protocol-specified F-U window was 10 to 21 days; however, a 7- to 28-day F-U analysis window was employed, as shown in the following table (Sponsor table 9, page 45 final study report).

Table 1 Sponsor: Visit windows

Visit	Nominal Day Relative to Treatment Start	Visit Window for Evaluable Analysis	Visit Window for ITT Analysis
Baseline	1	-2 to 1 (72hours)	≤1
End of Treatment	10 to 21	0P to 6P	0P to 6P
Follow-Up	10P to 21P	7P to 28P	7P to 28P

Comments

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The follow up window of 10-21 days seems appropriate. The draft FDA guideline for skin and skin structure infections (July 1998) recommends a follow up visit 7-14 days after therapy for most anti infectives and 14-21 days for drugs likely to have significant tissue levels for prolonged period of time. Seven days after stopping study medication, it is unlikely that therapeutic tissue levels will be present for either linezolid or cefadroxil. By extending the evaluable analysis window to 28 days there is a possibility of attributing recurrence to lack of drug efficacy, though recurrence of uncomplicated SSSI is usually not common in otherwise healthy children.

Changes in the Conduct of the Study

The protocol was amended 5 times. Amendments 1, 2, and 3 applied to all sites, and amendments A and B were country or site specific.

Amendment 1 was issued 28 April 2000 prior to the enrollment of patients.

This amendment clarified that children aged 5 through 17 years could be enrolled in the study and that the age subsets were 5 through 11 years and 12 through 17 years; allowed for the administration of study medication through feeding tubes; corrected the description of dosing of cefadroxil; eliminated the phlebotomy for safety laboratory assays at the EOT visit if that visit occurred within 72 hours of the day 7 visit; clarified that patients were not required to have an abscess for study entry; allowed the use of systemic corticosteroid therapy; allowed for a delay of the receipt of baseline safety laboratory data; incorporated an automated study medication randomization process; corrected statistical algorithms; and clarified wording in the informed consent that "your child" was the recipient of the study medication and procedures. This amendment applied to all study sites.

Amendment A (19 May 2000)

Amendment A was issued on 19 May 2000 prior to the enrollment of patients in Latin America. This amendment excluded patients with known or suspected HIV infection and applied to all study sites in Argentina, Brazil, Chile, Mexico, and Peru.

Amendment B (30 June 2000)

Amendment B was issued on 30 June 2000 after the enrollment of 14 patients. Since a new formulation of linezolid was used in this study, PK testing on up to 50 patients was added. The amendment described the manner in which the PK samples would be collected and analyzed. This amendment applied to 7 study sites in the United States.

Amendment 2 (3 October 2000)

Amendment 2 was issued on 3 October 2000 after the enrollment of 306 patients. This amendment eliminated the requirement to measure individual skin lesions of patients with impetigo; stated that the Data Safety Monitoring Committee (DSMC) would include both Pharmacia employees (not associated with study or site management teams) and independent members; and reiterated the role of the

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DSMC (to review only the safety variables in this study). This amendment applied to all study sites.

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Amendment 3 (23 January 2001)

Amendment 3 was issued on 23 January 2001 after the enrollment of all patients. This amendment added information that had been gained from other linezolid studies and, because of those results, allowed patients with a baseline absolute neutrophil count $<500/\mu\text{L}$ to enroll in the study. This amendment applied to all study sites.

Changes in the Planned Analyses

The analyses presented herein differ in some respects from those stated in the protocol and its amendments. At the request of the FDA, additional analyses were performed for the MITT population. All other deviations were approved by the sponsor before the study blind was broken. Major differences include the following items.

General

Subgroup analyses by geographic region and baseline pathogen were done for selected primary and secondary efficacy variables in selected patient subsets. Key efficacy and demographic results were presented by investigator/center. Analyses for the MITT population were added for selected baseline characteristics and primary and secondary efficacy variables.

Pretreatment Characteristics

Analyses of lesion size included patients with impetigo if their lesion measurements had been recorded on the CRF.

Primary and Secondary Efficacy

In addition to the overall frequency tables and analyses generated for patient microbiological outcome, corresponding frequency tables and analyses were produced for this variable by age, gender, race, baseline diagnosis, geographic region, and pathogen. Frequency tables for sponsor-defined patient clinical outcome and pathogen microbiologic outcome by baseline linezolid MIC values were produced. As supplementary analyses, results for investigator-defined patient clinical outcome, sponsor-defined patient clinical outcome, and patient microbiological outcome were presented considering indeterminate and missing outcomes as failures.

Monoamine Oxidase Interaction (MAOI) Analyses

Study-emergent adverse event frequency tables were generated for selected adverse events for patients taking/not taking selected concomitant medications (i.e., potent MAOIs and MAOI-interacting drugs). Frequency tables were generated for MAOI-associated adverse events considered drug-related for patients taking/not taking selected concomitant medications.

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Pharmacokinetic Analysis

Overall, only 10 patients were enrolled in the PK portion of the study, and PK samples were obtained in only eight of these patients. The low enrollment in the PK portion of the study was due in part to the rapid enrollment as the rest of the study quickly completed soon after the Amendment B was approved at the sites. The blinded randomization resulted in 6 cefadroxil-treated patients and two linezolid-treated patients, hence PK analysis was not done.

RESULTS

Disposition of Patients

A total of 508 patients enrolled by 91 investigators, were randomized in a 1:1 ratio to receive either linezolid or cefadroxil. Nine patients were randomized but were withdrawn from the study before receiving study medications. A total of 499 patients received study medication and were included in the ITT population. Of these patients, 232 (93.5%) in the linezolid group and 229 (91.2%) in the cefadroxil group completed the study.

The most common reasons for discontinuation from the study were loss to follow-up, adverse events, protocol specific withdrawal criteria and protocol violations. The reasons for study discontinuation were similar between the treatment groups.

The following table (Sponsor table 11, page 55 final study report) shows the distribution of patients into categories by arm based on the investigator's assessment of the primary reason for study discontinuation.

Table 2 Sponsor: Reasons for study discontinuation

Reasons for Discontinuation	Treatment Group	
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)
Discontinued Patients	16 (6.5)	22 (8.8)
Lost to follow-up	5 (2.0)	8 (3.2)
Adverse event	3 (1.2)	4 (1.6)
Protocol specific withdrawal criteria	3 (1.2)	3 (1.2)
Protocol violation	3 (1.2)	2 (0.8)
Progression of disease	1 (0.4)	2 (0.8)
Withdrawn consent	1 (0.4)	2 (0.8)
Lack of efficacy	0 (0.0)	1 (0.4)

Comments

A similar number of patients in both treatment arms discontinued from the study. The reasons for discontinuation were also similar in the two arms.

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Protocol Deviations

Protocol deviations that occurred during the study are listed in the following table (Sponsor table 12, page 56 final study report).

Table 3. Sponsor: Protocol deviations

Protocol Deviation/Data Issues	Number of patients
Laboratory	104
Baseline ANC results not available	103
Local laboratory discarded baseline isolate	1
Protocol	12
Received concomitant antimicrobials for elective surgery	1
Follow-up serum pregnancy test not done	2
Site did not contact medical monitor prior to breaking blind	2
Investigator aware of study medication assignment	5
Patient <5 years old when enrolled	1
Follow-up visit completed <10 days after last dose	3
Study medications not kept in a locked cabinet	1
EOT visit completed prior to receiving last dose	3
Study Medication	12
Patient received/took incorrect dose	12
Randomization	3
Informed consent	2
Data Issues	5

Comments

Amendment 3 allowed enrollment of patients with a baseline ANC of <500/ μ L. Most other protocol violations were minor and probably had no bearing on the efficacy of study medications. The investigators were aware of the study medication assignment in five patients, four of whom were in the cefadroxil arm and one in the linezolid arm, thereby potentially introducing some bias. Most patients who received or took incorrect dose only had minor deviations from the protocol.

Data Sets Analyzed

The percentages of patients in the ITT, MITT, CE, and ME populations were similar between the two treatment arms.

The following table (Sponsor table 13, page 58 final study report) shows the patient groups used in the analyses and the reasons patients were excluded from these groups.

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Table 4. Sponsor: Study evaluation groups

Reasons for Exclusion*	Treatment Group	
	Linezolid N = 252 n (%)	Cefadroxil N = 256 N (%)
All randomized patients	252 (100)	256 (100)
ITT Population	248 (98.4)	251 (98.0)
Never received study medication	4 (1.6)	5 (2.0)
MITT Population	171 (67.9)	166 (64.8)
No baseline pathogen (ITT window)	77 (31.0)	85 (33.9)
CE Population	224 (88.9)	216 (84.4)
Prior antibiotic usage	1 (0.4)	0 (0.0)
Insufficient therapy	5 (2.0)	12 (4.8)
Concomitant antibiotics for intercurrent illness	3 (1.2)	6 (2.4)
Noncompliant with therapy regimen	3 (1.2)	3 (1.2)
No postbaseline clinical outcome	15 (6.0)	22 (8.8)
ME Population	159 (63.1)	150 (58.6)
Not clinically evaluable	24 (9.7)	35 (13.9)
No baseline pathogen (evaluable window)	78 (31.5)	85 (33.9)

* Patients could have more than one reason for exclusion

Two patients were misrandomized in the study. The investigator was not aware that the randomization had to come from the central IVRS, and hence selected "Treatment B" for these patients. Subsequently, the patients were entered into the IVRS and were found to have received the incorrect treatment when the blind was broken. All patients are included in the analyses according to the medication that they actually received.

Comments

Lack of a post baseline assessment was the most common cause for exclusion from the clinically evaluable population and was slightly higher in the cefadroxil group. Almost one third of patients in both treatment arms had no baseline pathogen detected.

Demographic and other Baseline Characteristics

Demographic Characteristics

Overall, the mean patient age was 10.86 years and the range was 4.9 to 17.9 years. Most patients were white (71.5%, 357/499), and from North America (73.9%, 369/499).

In the ITT population, the treatment groups were comparable in demographic characteristics and in baseline measurements of age, weight, height, or geographic region. There were more females in the linezolid group than in the

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cefadroxil group 55.6%, (138/248) versus 44.2% (111/251) respectively (p = 0.011). The following table (Sponsor table 14, page 60 final study report) summarizes the pretreatment demographic characteristics of the patients in the ITT population by treatment group.

Table 5 Sponsor: Demographic Characteristics

Demographic Characteristic	Treatment Group		P-value
	Linezolid N = 248	Cefadroxil N = 251	
Age			
Mean, yr ± SD	10.75 ± 3.72	10.97 ± 3.74	0.5115
Range, yr	4.9 - 17.7	5.0 - 17.9	
5 - 11, n (%)	146 (58.9)	148 (59.0)	0.9831
12 - 17, n (%)	102 (41.1)	103 (41.0)	
Gender, (n, %)			
Male	110 (44.4)	140 (55.8)	0.011
Female	138 (55.6)	111 (44.2)	
Weight (kg)			
Mean ± SD	43.62 ± 20.45	44.78 ± 20.79	0.5329
Range	14.7 - 103.9	15.9 - 117.5	
Height (cm)			
Mean ± SD	141.9 ± 21.0	144.7 ± 21.0	0.1371
Range	92.0 - 192.5	101.0 - 188.0	
Race, n (%)			
White	170 (68.5)	187 (74.5)	0.246
Black	29 (11.7)	17 (6.8)	
Asian or Pacific Islander	5 (2.0)	3 (1.2)	
Mixed/Multiracial	43 (17.3)	44 (17.5)	
Not allowed to ask	1 (0.4)	0 (0.0)	
Geographic Region, n (%)			
North America	176 (71.0)	193 (76.9)	0.132
Latin America	72 (29.0)	58 (23.1)	

Comments

The linezolid group had more female patients and a slightly higher percentage of patients in the linezolid group were from Latin America. Neither of these factors will have a major bearing on the efficacy outcomes. Pathogens causing uSSSI and the care for such infections should not be significantly different in Latin America compared to the United States.

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Medical history

History of eczema and trauma involving the skin were more common in the cefadroxil group ($p = 0.026, 0.043$) respectively (Source: Section 10.1.4.2, table 15). No other statistically significant differences between groups in the clinically significant medical history findings were seen.

Comments

The two treatment arms were similar with respect to past and present medical history. Infected eczema was an exclusion criterion as inflammation can be prolonged even after resolution of infection. Minor trauma to skin in itself should not have any bearing on the final clinical outcome.

Physical Examination

The baseline physical examination findings unrelated to the skin infection were comparable between the treatment arms. The baseline mean temperature, systolic and diastolic blood pressure, and respiration rate were similar between treatment groups in both the ITT and CE populations. In the ITT population, the difference between the groups in baseline mean pulse rate was statistically significant (linezolid: $84.1 \pm 13.4/\text{min}$, cefadroxil: $81.6 \pm 13.0/\text{min}$, $p = 0.0322$). This is unlikely to be clinically relevant.

Clinical Signs and Symptoms

Erythema, tenderness, swelling, and heat/localized warmth were the most common signs/symptoms at the baseline visit. The percentages of patients experiencing each clinical sign and symptom of skin and skin structure infections were similar between treatment groups.

Clinical signs and symptoms of skin and skin structure infections at the baseline visit in the ITT population are shown in the following table (Sponsor table 16, page 64 final study report)

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Table 6 Sponsor: Clinical signs and Symptoms

Signs and Symptoms	Treatment Group		P-value
	Linezolid N = 248 n (%)	Cefadroxil N = 250 n (%)	
Pain	145 (58.5)	155 (62.0)	0.421
Tenderness	206 (83.1)	198 (79.2)	0.270
Erythema	241 (97.2)	243 (97.2)	0.988
Swelling	183 (73.8)	188 (75.2)	0.718
Induration	144 (58.1)	138 (55.2)	0.519
Fluctuance	59 (23.8)	69 (27.6)	0.344
Heat/Localized Warmth	177 (71.4)	184 (73.6)	0.578
Nonpurulent Discharge	83 (33.5)	84 (33.6)	0.999
Purulent Discharge	145 (58.5)	131 (52.4)	0.173

Laboratory Assays

Hematology

In the ITT population, statistically significant differences between the groups were found in the baseline mean hemoglobin values and platelet count. The mean hemoglobin values in the linezolid arm was 12.9 g/dl compared to 13.19 g/dl in the cefadroxil arm (p=0.015). The mean platelet count in the linezolid arm was 307 x 103/ μ L compared to 291 x 103/ μ L in the cefadroxil arm (p=0.022) (Source: Section 14, Tables 3.13).

Comments

The differences in both hemoglobin values and platelet count are unlikely to be clinically relevant.

Chemistry

The mean baseline chemistry assay values (ALT, AST, BUN creatinine, and lipase) were within normal ranges and similar between treatment groups for the ITT population (Source: Section 14, Tables 3.13 final study report).

Clinical Diagnosis

The most common diagnoses were impetigo, cellulitis, and paronychia. The treatment groups were similar with respect to baseline diagnosis. A summary of the primary diagnosis of the skin infections of patients in the ITT population is provided in the following table (Sponsor table 18, page 67 final study report)

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Table 7. Sponsor: Clinical Diagnosis

Diagnosis	Treatment Group	
	Linezolid n (%)	Cefadroxil n (%)
Number Reported	248 (100)	251 (100)
Infected Wound	11 (4.4)	10 (4.0)
Cellulitis	46 (18.5)	50 (19.9)
Folliculitis	9 (3.6)	10 (4.0)
Carbuncle	3 (1.2)	3 (1.2)
Furuncle	7 (2.8)	6 (2.4)
Skin Ulcer	1 (0.4)	0 (0.0)
Skin Abscess	18 (7.3)	20 (8.0)
Impetigo	95 (38.3)	85 (33.9)
Infected Bite	11 (4.4)	16 (6.4)
Infected Surgical Incision	4 (1.6)	0 (0.0)
Paronychia	23 (9.3)	34 (13.5)
Burn	1 (0.4)	0 (0.0)
Other	19 (7.7)	17 (6.8)

Comments

Isolated folliculitis and furunculosis were exclusion criteria since spontaneous resolution in these conditions is very likely. As the number of patients with these diagnoses were small and comparable between the two arms, the effect on overall efficacy comparisons should not be significant. The number of patients with impetigo was slightly higher in the linezolid arm and those with paronychia was higher in the cefadroxil arm.

Degree of Involvement

Slightly more than 20% of patients in both treatment groups had infections with deep involvement. Both treatment arms were similar with respect to degree of involvement. The following table (Sponsor table 19, page 68 final study report) provides a summary of the degree of involvement at the baseline visit for patients in the ITT population.

Table 8 Sponsor: Depth of involvement in ITT patients

Degree of Involvement	Treatment Group		P-value
	Linezolid n (%)	Cefadroxil n (%)	
Number Reported	248 (100)	251 (100)	0.889
Superficial	192 (77.4)	193 (76.9)	
Deep	56 (22.6)	58 (23.1)	

Duration of Infection

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In the ITT population, mean duration of infection recorded at the baseline visit was 11.8 ± 18.7 days in the linezolid arm and 14.9 ± 30.0 days in the cefadroxil arm ($p = 0.172$).

Size of Lesion

A summary of the size of the patient's primary lesion at the baseline visit for the ITT, population is provided in the following table (Sponsor table 20, page 69 final study report).

Table 9 Sponsor: Size of Lesions

Area of Lesion (cm ²)	Treatment Group		P-value
	Linezolid	Cefadroxil	
Number Reported	219	227	
Mean \pm SD	32.9 ± 111.6	18.5 ± 43.9	0.072
Median	4.00	3.75	
Range			

In the ITT population, the mean area of the primary lesion at the baseline visit was 32.9 ± 111.63 cm² for the patients in the linezolid arm and 18.52 ± 43.88 cm² for the patients in the cefadroxil arm, ($p = 0.072$). Though the mean lesion size was higher in the linezolid arm, the median baseline lesion area for the treatment groups was similar.

Comments

No specific parameters were defined to classify a lesion as being deep or superficial. It is likely that most patients with deep infections had complicated skin infections. Though the mean duration of infection in both arms was similar it is fairly long for uncomplicated skin infection. Mean lesion size was higher in the linezolid arm due to the presence of outliers.

Concomitant Use of Antibiotics

In the ITT population, similar percentages of patients in both treatment groups took non investigational antibiotics (linezolid: 16.1% [40/248], cefadroxil: 17.1% [43/251]) prior to or on the first day of study medication. In the linezolid group, 18 (7.3%) patients used topical antibiotics, 6 (2.4%) used penicillins, and 10 (4.0%) used cephalosporins. In the cefadroxil group, 16 (6.4%) patients used topical antibiotics, 13 (5.1 %) used penicillins, and 8 (3.2%) used cephalosporins. (Source: Final study report, Section 14, table 4.1)

In the ITT population, similar percentages of patients in both treatment groups received non-investigational antibiotics after the first day of study medication (linezolid: 9.7% [24/248], cefadroxil: 9.6% [24/251]). The use of individual topical and systemic antibiotics was similar between treatment groups. In the linezolid group, 5 (2%) used topical antibiotics, 6 (2.4%) used penicillins, and 6

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(2.4%) used cephalosporins. In the cefadroxil group, 5 (2.0%) used topical antibiotics, 5 (2.0%) used penicillins, and 10 (4.0%) used cephalosporins. (Source: Final study report, Section 14, Table 4.2)

Incision and Drainage

If a patient's infection was treated with an incision and drainage it was to be recorded on the CRF. In the ITT population, 4.8% (12/248) of patients in the linezolid group and 6.0% (15/251) of patients in the cefadroxil group had an incision and drainage to treat their infection. A greater percentage of these procedures occurred on or prior to day 1 in the linezolid group (91.7%, 11/12) than in the cefadroxil group (56.3%, 9/16). Seven patients (1 linezolid, 6 cefadroxil) had incision and drainage > 2 days after starting study medication and were classified as failed (1 linezolid, 3 cefadroxil) or indeterminate (3 cefadroxil).

The following table (Sponsor table 21, page 71 final study report) summarizes the occurrence and timing of the procedures that occurred during this study (7 days prior to receiving study medication through the F-U visit).

Table 10 Sponsor: Incision and drainage

Incision and Drainage (I/D)	Treatment Group	
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)
No. of Patients who had an I/D	12 (4.8)	15 (6.0)
Day Procedure performed		
-2	1	0
-1	1	1
1	9	8
4	0	2
6	1	0
8	0	2
0P	0	2
21P	0	1

Extent of Exposure

In the ITT population the mean duration of treatment was 12.0 ±3.6 days for the patients in the linezolid arm and 11.9 ±3.9 days for the patients in the cefadroxil arm. The duration of treatment and the number of doses received by patients in the ITT population are summarized in the following table (Sponsor table 22, page 72 final study report)

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Table 11 Sponsor: Extent of exposure

Extent of Exposure	Treatment Group	
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)
Number of Days Treated		
<10	19 (7.7)	25 (10)
10-21	218 (87.9)	214 (85.3)
>21	11 (4.4)	12 (4.8)
Mean \pm SD (days)	12.0 \pm 3.6	11.9 \pm 3.9
Number of Doses Taken		
Mean \pm SD (doses)	22.3 \pm 7.2	22.1 \pm 7.5

Comments

Almost five percent of patients in both treatment arms received study medications for > 21 days. It is unusual to treat uncomplicated skin infections in children for such a prolonged period of time. It is thus possible that these children had complicated rather than uncomplicated infections hence necessitating prolonged therapy or had pre-existing conditions complicating therapy.

Treatment Compliance

The treatment compliance of each patient was evaluated by examination of the unused study medication at the EOT visit and by patient diaries. In both arms three patients were deemed clinically non-evaluable due to noncompliance with the treatment regimen. The identity of the study medication for 5 patients was unblinded.

Primary Efficacy Variables

The sponsor's assessments of clinical outcomes are presented and discussed in this report. Overall, cure rates were lower using the sponsor defined clinical outcome compared to the investigator defined clinical outcomes.

Sponsor's Assessment of Clinical Outcome

In the ITT population, 88.7% (205/231) of patients in the linezolid group and 86.2% (193/224) in the cefadroxil group were considered cured at the F-U visit (95% CI, -3.5, 8.7, $p = 0.405$).

The following table (Sponsor table 28, page 79 final study report) summarizes the efficacy results at EOT and FU for the ITT population, defined as excluding missing and indeterminate outcomes.

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Table 12 Sponsor: Clinical outcomes in the ITT population excluding missing and indeterminate outcomes

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)	P-Value	95% CI
End of Treatment	No. Assessed	233 (100)	241 (100)	0.840	
	Cured	198 (85.0)	200 (83.0)		
	Improved	23 (9.9)	27 (11.2)		
	Failed	12 (5.2)	14 (5.8)		
	Indeterminate	3	0		
Follow-Up	Missing	12	10	0.405	-3.5, 8.7
	No. Assessed	231 (100)	224 (100)		
	Cured	205 (88.7)	193 (86.2)		
	Failed	26 (11.3)	31 (13.8)		
	Indeterminate	15	22		
	Missing	2	5		

A supplementary analysis of the sponsor's assessment of clinical outcome was conducted in which indeterminate and missing outcomes were classified as failures. The percentage of patients (82.7% in the linezolid group versus 76.9% in the cefadroxil group) with an outcome of cured was similar between treatment groups at the F-U visit (95% CI, -1.3, 12.8, p = 0.109)

The following table summarizes the efficacy results at EOT and FU for the ITT population, classifying missing and indeterminate as failures.

Table 13 Sponsor: Clinical outcomes in the ITT population (missing and indeterminate outcomes = failures)

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)	P-Value	95% CI
End of Treatment	Cured	198 (85.0)	200 (83.0)	0.783	
	Improved	23 (9.9)	27 (11.2)		
	Failed	27 (5.2)	24 (5.8)		
Follow-Up	Cured	205 (82.7)	193 (76.9)	0.109	-1.3, 12.8
	Failed	43 (17.3)	58 (23.1)		

In the CE population, 91% (201/221) of patients in the linezolid group and 90%

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(189/210) in the cefadroxil group were considered cured at the F-U visit. The cure rates were similar between treatment groups (95% CI, -4.6, 6.5, $p = 0.737$). The results for the CE population are summarized in the following table (Sponsor table 30, page 81 final study report)

Table 14 Sponsor: Clinical outcomes in the CE population excluding missing and indeterminate outcomes

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 224 n (%)	Cefadroxil N = 216 n (%)	P-Value	95% CI
End of Treatment	No. Assessed	211 (100)	212 (100)	0.901	
	Cured	184 (87.2)	182 (85.8)		
	Improved	21 (10.0)	24 (11.3)		
	Failed	6 (2.8)	6 (2.8)		
	Indeterminate	3	0		
	Missing	10	4		
Follow-Up	No. Assessed	221 (100)	210 (100)	0.737	-4.6, 6.5
	Cured	201 (91.0)	189 (90.0)		
	Failed	20 (9.0)	21 (10.0)		
	Indeterminate	3	6		

Supplementary analysis of the CE population in which indeterminate and missing outcomes were classified as failures showed no difference between the treatment groups at the F-U visit (89.7% in the linezolid group versus 87.5% in the cefadroxil group, (95% CI, -3.7, 8.2, $p = 0.461$, Source: Final study report, Section 14, Table 6.2.20).

Comments

As patients with missing or indeterminate outcomes were excluded in the sponsor's analysis of the ITT population, this does not represent a true ITT population. Using both approaches (excluding missing and indeterminate outcomes and by considering them as failures), no significant treatment differences between the groups were seen. The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero. Similar results were seen in the CE population.

In the MITT population the sponsor has included some pathogens like coagulase negative Staphylococci that may only represent skin flora and not true pathogens. As these numbers were small (8 in the linezolid arm and 11 in the cefadroxil arm, Source Section 14, Table 6.2.18a, final study report) and hence unlikely to affect

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the overall results no additional analyses excluding these pathogens were performed.

In the MITT population, 89.6% (147/164) of patients in the linezolid group and 87.1% (135/155) of patients in the cefadroxil group were considered cured at the F-U visit. The cure rates were similar between groups (95% CI, -4.5, 9.6, $p = 0.479$). Results for the MITT population are summarized in the following table (Sponsor table 29, page 80 final study report)

Table 15. Sponsor: Clinical outcomes in the MITT population excluding missing and indeterminate outcomes

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 171 n (%)	Cefadroxil N = 166 n (%)	P-Value	95% CI
End of Treatment	No. Assessed	160 (100)	163 (100)	0.660	
	Cured	143 (89.4)	141 (86.5)		
	Improved	12 (7.5)	14 (8.6)		
	Failed	5 (3.1)	8 (4.9)		
	Indeterminate	3	0		
	Missing	8	3		
Follow-Up	No. Assessed	164 (100)	155 (100)	0.479	-4.5, 9.6
	Cured	147 (89.6)	135 (87.1)		
	Failed	17 (10.4)	20 (12.9)		
	Indeterminate	7	11		

In the ME population, 90.4% (142/157) of patients in the linezolid group and 90.5% (133/147) of patients in the cefadroxil group were considered cured at the F-U visit. The cure rates were similar between treatment groups (95% CI, -6.6, 6.6, $p = 0.993$, Section 14, Table 6.2.3). The results for the ME population are summarized in the following table (Sponsor table 31, page 82 final study report).

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Table 16. Sponsor: Clinical outcomes in the ME population excluding missing and indeterminate outcomes

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 159 n (%)	Cefadroxil N = 150 n (%)	P-Value	95% CI
End of Treatment	Number Assessed	148 (100)	148 (100)	0.978	
	Cured	133 (89.9)	132 (89.2)		
	Improved	12 (8.1)	13 (8.8)		
	Failed	3 (2.0)	3 (2.0)		
	Indeterminate	3	0		
	Missing	8	2		
Follow-Up	Number Assessed	157 (100)	147 (100)	0.993	-6.6, 6.6
	Cured	142 (90.4)	133 (90.5)		
	Failed	15 (9.6)	14 (9.5)		
	Indeterminate	2	3		

Supplementary analysis of the ME population in which indeterminate and missing outcomes were classified as failures showed no difference between the treatment groups at the F-U visit (89.3% in the linezolid group versus 88.7% in the cefadroxil groups, (95% CI, -6.3, 7.6, p = 0.857, Section 14, Table 6.2.21).

Comments

As patients with missing or indeterminate outcomes were excluded in the sponsor's analysis of the MITT population, this does not represent a true MITT population. Using both approaches (excluding missing and indeterminate outcomes and by considering them as failures), no significant treatment differences were seen between the two treatment arms. The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero. Similar results were seen in the ME population.

FDA Analyses

The FDA statistical reviewer, Dr. Nancy Silliman Ph.D. performed an additional analysis using an algorithm in which patients were analyzed by the treatment group to which they were randomized and not taking into account the length of treatment. Patients were considered cures if they were assessed as cures at F-U by the investigator.

They were assessed as failures if either of the following applied:

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- They were assessed as failures by the investigator at either the EOT or F-U visit
 - They had died by the F-U visit and were not assessed as a cure by the investigator at the F-U visit (note: no patients died in this study)
 - They were prescribed an additional antibiotic for lack of efficacy at any time during the study up to and including the F-U visit;
- All other patients were assessed as missing.

Results were similar to those found for the sponsor's assessment of clinical outcome at F-U, except that the treatment differences were somewhat smaller, mostly because the cure rates for cefadroxil are slightly higher in this analysis. The difference in cure rates between the two groups in the ITT population using this approach was 1.1% (90% in the linezolid arm versus 88.9% in the cefadroxil arm, 95% CI -5.1, 7.2). For a detailed analysis please see the statistical review by Dr. Silliman.

Subgroup analyses

No significant differences between the groups in the percentages of patients considered cured at the F-U visit were seen in the ITT, CE, and ME populations by age, gender, or race.

Analysis by pathogen

The sponsor's assessment of clinical outcome at the F-U visit was similar in the two arms without regard to pathogen. *Staphylococcus aureus* and *Streptococcus pyogenes* were the two most common pathogens identified. Seven patients in the linezolid arm and 11 in the cefadroxil arm had species of CONS identified (Source: Section 14, Table 6.2.18a, final study report).

The Sponsor's assessment of clinical outcome of patients with selected baseline pathogens in the MITT population is summarized in the following table (Sponsor table 34, page 86 final study report)

Table 17 Sponsor: Clinical outcome by pathogen at FU (MITT)

Pathogen	Treatment Group		P-Value	95% CI
	Linezolid n/N (%)	Cefadroxil n/N (%)		
<i>Staphylococcus aureus</i>	123/136 (90.4)	113/133 (85.0)	0.171	-2.4, 13.3
<i>Streptococcus pyogenes</i>	33/36 (91.7)	26/27 (96.3)	0.456	-16.1, 6.9
<i>Streptococcus agalactiae</i>	1/1 (100)	2/2 (100)		
<i>Streptococcus dysgalactiae</i>	2/2 (100)	3/3 (100)		
<i>Enterococcus faecalis</i>	1/1 (100)	1/1 (100)		

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Comments

Staphylococcus aureus and *Streptococcus pyogenes* were the two most common pathogens identified and there were no differences in the cure rates between the two arms for either pathogen. The number of patients with other pathogens were too small to draw any conclusions.

Secondary efficacy variables

Patient Microbiologic Outcome

The collapsed microbiological success rate at the F-U visit is summarized in for the MITT and ME populations (Sponsor table 36, page 88 final study report).

Table 18. Sponsor: Microbiological outcome

Patient Population Assessment	Microbiological Success Rate			
	Treatment Group		Statistical Test	
	Linezolid n (%)	Cefadroxil n (%)	P-Value	95% CI
MITT Population				
Total Number of Patients	171	166		
No. of Patients Assessed*	164 (100)	155 (100)		
Microbiological Success	146 (89.0)	135 (87.1)	0.595	-5.2, 9.1
ME Population				
Total Number of Patients	159	150		
No. of Patients Assessed*	158 (100)	147 (100)		
Microbiological Success	142 (89.9)	133 (90.5)	0.860	-7.3, 6.1

* Exclude patients with missing or indeterminate outcomes

Individual Pathogen Outcome

No significant differences in the eradication rates were seen for any of the pathogens. The pathogen eradication rates for the MITT population are summarized in the following table (Sponsor table 39, page 91 final study report)

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Table 19. Sponsor: Pathogen eradication rate

Pathogen	Treatment Group	
	Linezolid n/N (%)	Cefadroxil n/N (%)
<i>Staphylococcus aureus</i>	123/137 (89.8)	113/133 (85.0)
MRSA	13/14 (92.9)	7/9 (77.8)
MSSA	110/123 (89.4)	106/124 (85.5)
<i>Streptococcus pyogenes</i>	33/37 (89.2)	26/27 (96.3)
<i>Streptococcus agalactiae</i>	1/1 (100)	2/2 (100)
<i>Streptococcus dysgalactiae</i>	2/2 (100)	3/3 (100)
<i>Enterococcus faecalis</i>	1/1 (100)	1/1 (100)

Size of Lesion

The mean size of the primary lesion of patients in both treatment arms decreased from the baseline visit to the F-U visit.

The change in lesion size is summarized in the following table (Sponsor table 46, page 82 final study report).

Table 19. Sponsor: Change in lesion size

Dimension	Treatment Group		P-value
	Linezolid N=196	Cefadroxil N=192	
Length (cm)			
Baseline mean	4.24	3.69	
Change from Baseline to F-U	-4.12 ± 6.03	-3.62 ± 4.30	0.342
Within Treatment P-value	<0.001	<0.001	
Width (cm)			
Baseline mean	3.17*	2.73	
Change from Baseline to F-U	-3.09 ± 3.94*	-2.68 ± 2.83	0.238
Within Treatment P-value	<0.001	<0.001	
Area (cm²)			
Baseline mean	34.24	19.16	
Change from Baseline to F-U	-33.87 ± 117.12	-19.05 ± 45.67	0.103
Within Treatment P-value	<0.001	<0.001	

Outcomes in patients with Methicillin resistant *Staphylococcus aureus*

The baseline features in patients diagnosed with MRSA infections in the ME population are summarized in the following table (Sponsor table 42, page 94 final study report).

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Table 20. Sponsor: Infection characteristics in patients with MRSA

Baseline Infection Characteristics	Treatment Group	
	Linezolid N = 13	Cefadroxil N = 7
Lesion area, mean ± SD (cm ²)	26.0 ± 38.0*	12.1 ± 16.2
Involvement of infection, n (%)		
Superficial	9 (69.2)	6 (85.7)
Deep	4 (30.8)	1 (14.3)
Linezolid MIC, mean (µg/mL)	3.1	2.9
Diagnosis, n (%)		
Cellulitis, infected bite, or skin abscess	8 (61.5)	4 (57.1)
Folliculitis, furuncle, impetigo, or paronychia	5 (38.5)	3 (42.9)

In the linezolid group, 4 patients with MRSA infections had an additional pathogen isolated at the baseline visit. Two patients had *S. pyogenes* and one each had *S. dysgalactiae*, and *E. faecalis* in addition to MRSA. No patients in the cefadroxil group had more than one pathogen at the baseline visit.

The Sponsor's Clinical Outcome and Patient Microbiological Outcome for the patients diagnosed with MRSA infections are summarized in Table (Sponsor table 44, page 96 final study report)

Table 21 Sponsor: Outcomes in patients with MRSA

Population	Cure/Success Rate			
	Clinical Outcome		Microbiological Outcome	
	Linezolid n (%)	Cefadroxil n (%)	Linezolid n (%)	Cefadroxil n (%)
MITT Population				
No. of Patients Assessed	14 (100)	9 (100)	14 (100)	9 (100)
Cure/Success Rate	13 (92.9)	7 (77.8)	13 (92.9)	7 (77.8)
ME Population				
No. of Patients Assessed	13 (100)	7 (100)	13 (100)	7 (100)
Cure/Success Rate	12 (92.3)	6 (85.7)	12 (92.3)	6 (85.7)

Comments

The role of MRSA in uncomplicated SSSI is unclear. In this study, five patients with infections due to MRSA had deep infections making it more likely that they had complicated skin infections. Secondly, four patients had additional pathogens identified hence making the role of MRSA suspect. Thirdly, in the cefadroxil arm, 7/9 patients with MRSA had cures thereby raising questions about the pathogenicity of MRSA in this condition. Lastly, though community acquired (CA)

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MRSA has been reported in children, the resistance pattern of CA MRSA is different from that of the multi-drug resistant nosocomial MRSA. CA-MRSA isolates are generally susceptible to clindamycin and trimethoprim-sulfamethoxazole and resistant to erythromycin.¹

Study 0082 (Suspected or Proven resistant Gram Positive Infections)

The following description of the study protocol is largely excerpted from the sponsor's final study report for study 0082. The medical reviewer's comments are provided in italics.

Study Title: Linezolid IV/PO versus vancomycin IV for the treatment of resistant Gram-positive bacterial infections in children.

Study Objectives

Primary Objectives

- To compare the safety, tolerability, and clinical efficacy of intravenously and orally administered linezolid with intravenously administered vancomycin in the treatment of antibiotic-resistant Gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus* species (MRSS), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin resistant Enterococcus (VRE) in children from birth through 11 years of age.
- To assess population pharmacokinetic parameters of linezolid in children from birth through 11 years of age.

Secondary Objective

To obtain information on additional safety and efficacy variables in children from birth through 11 years of age.

Endpoints

Primary Endpoints

- Safety endpoints including adverse events and laboratory assay results.
- Pharmacokinetic assessments using population pharmacokinetics.
- Efficacy endpoints assessed by clinical and microbiological criteria.

¹ Sattler CA et al. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infection in children. *Pediatr Infect Dis J* 2002 Oct;21(10):910-7.

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Secondary Endpoints

- Safety endpoints including evaluation of vital signs and the use of concomitant medication and non-medication therapy.
- Efficacy endpoints including patient microbiological outcome, clinical signs and symptoms, individual pathogen eradication rates, body temperature, white blood cell counts (WBC), chest radiograph findings (pneumonia patients), and size of lesion (skin/skin structure infection patients).

Comments

Study objectives are clearly stated. Vancomycin is an appropriate comparator as it is used commonly in hospitalized children with suspected Gram positive infections and is effective against most Gram positive cocci except VRE and the recently described vancomycin resistant Staphylococcus aureus (VRSA).^{2,3} For infections due to susceptible organisms like methicillin sensitive Staphylococcus aureus (MSSA), vancomycin may be less efficacious than the semisynthetic penicillins like methicillin or nafcillin.

METHODS

Overall Study Design and Plan

This was a phase 3, randomized, open-label, comparator controlled, multicenter study. The study was open-label because of the need to adjust vancomycin doses.

Time period: February 20 2001 – December 28 2001

Study Sites: 39 in USA, 2 in Argentina, 3 in Brazil, 5 in Chile, 2 in Colombia, 4 in Mexico, 1 in Peru, 3 in Venezuela

CV's of investigators: CV's of all the investigators were provided and reviewed by the medical officer.

Hospitalized pediatric patients and those in chronic care facilities were eligible for treatment if they had known or suspected infections due to resistant Gram-positive bacteria, including hospital-acquired pneumonia (HAP), complicated skin and skin structure infections (cSSSI), catheter-related bacteremia, bacteremia of unidentified source, and other infections. Patients with endocarditis, CNS infections, and skeletal infections including osteomyelitis/septic arthritis were excluded.

Patients were stratified by age as follows: birth through 90 days, 91 days through 4 years, and 5 years through 11 years.

Enrolled patients were randomized in a 2:1 ratio to receive linezolid or vancomycin, respectively. An interactive voice response system was used to assign and verify randomization codes for this study. The master randomization code was maintained at Pharmacia. Each site was provided a dispensing guide to

² *Staphylococcus aureus* resistant to vancomycin – United States, 2002. MMWR 2002;51:565–7.

³ Vancomycin-Resistant *Staphylococcus aureus* – Pennsylvania, 2002. MMWR 2002;51: 902

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dispense the clinical supplies that corresponded to the randomization medication code.

Patients with documented VRE on or before day 3 who were randomized to vancomycin were switched to linezolid. During the first 3 days of treatment, patients were required to receive either linezolid IV 10 mg/kg (up to 600 mg/dose) every 8 hours or vancomycin IV at varying doses (10-15 mg/kg) and intervals (6-24 hours) depending on age and weight. After 3 days of treatment, patients \geq 91 days of age could be switched from IV to oral medication at the discretion of the investigator. Patients randomized to linezolid and switched to oral therapy received linezolid ¹ suspension. Patients randomized to vancomycin could receive an appropriate oral step-down medication based on susceptibility of the infecting organism. Planned duration of therapy for the study was at least 10 days and up to 28 days.

Patients were allowed to receive the initial 72 hours of study medication before microbiological laboratory assay results were obtained; however, they were not allowed to continue if entry criteria were not met.

Screening activities included history and physical examination, collection of suitable specimens for Gram stain, culture and antibiotic susceptibility testing, chest radiograph for patients with a clinical diagnosis of pneumonia, and blood sampling for laboratory assays.

Post-baseline visits comprised scheduled visits on days 3, 10, 17, and 24 during treatment (depending on treatment duration), an end-of-treatment (EOT) visit within 72 hours after the last dose of study medication, and a follow-up (F-U) visit 12 to 28 days after treatment completion. Clinical response was evaluated at EOT and F-U visits and the F-U visit evaluation was considered the test of cure. Assessments performed at study visits included site culture and Gram stain as clinically indicated, blood culture if positive at baseline, chest radiograph (as clinically indicated and at F-U for pneumonia patients), vital signs, clinical observations, sampling for laboratory assays and linezolid pharmacokinetic (PK) analysis, concomitant therapy, and adverse events.

Comments

There are no well-defined criteria by which patients with suspected resistant Gram positive infections can be identified. Patients who are more likely to have infections due to resistant bacteria are those with prolonged hospitalization, indwelling intravascular lines, prior antibiotic use or ICU stay.⁴ Community acquired infections due to resistant organisms are less common though there have been increasing reports of community acquired MRSA infections in children with

⁴ Kollef MH. Antibiotic resistance in the Intensive Care Unit. Ann Intern Med 2001;134:298-314

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no known risk factors.^{5,6} *It is acceptable to enroll patients with suspected resistant Gram positive infections in order to increase the likelihood of identifying patients with truly resistant infections. However, allowing patients with either susceptible organisms or with no baseline pathogens to remain in the study if they met other study entry criteria will overestimate the efficacy of study medications against resistant organisms.*

Although the protocol allowed for oral switch after 3 days of intravenous therapy, in reality in young children with such severe infections oral treatment is often not feasible. These children are either too sick to take oral medications or the multitude of medications they are receiving precludes effective oral therapy. So, the role of oral linezolid therapy in children with resistant infections could be very limited. In this study a _____ l linezolid suspension _____, was used to _____ This formulation will not be used commercially. If the formulation to be marketed has _____ could be a post marketing issue.

Timing of the test of cure visit seems appropriate. As both linezolid and vancomycin do not have long half- lives it is unlikely that significant serum levels will be present at the test of cure visit. It is however possible that some hospitalized patients especially those with multiple invasive devices could develop another nosocomial infection prior to the follow up visit thereby increasing the number of failures.

Statistical Methods

Determination of Sample Size

No formal sample size calculations were done. The study protocol does not appear to specify the confidence limits to determine equivalence. The sponsor used the nQuery Advisor® software package and determined that a sample size of 100 for the comparator and 200 for linezolid (representing the targeted intent-to-treat population) would yield a 77% power that the lower limit of a 95% confidence interval for the difference in success rates (linezolid - comparator) will exceed -10%, assuming that the true success rate in each treatment group is 90%.

The final study report states the following in the section on Statistical and Analysis plans:

All data listings, summaries, and statistical analyses were generated using SAS® Version 6.12. All statistical tests were 2-sided. P-values less than or equal

⁵ Fergie JE, Purcell K. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in south Texas children. *Pediatr Infect Dis J*. 2001; 20(9):860-3.

⁶ Sattler CA et al. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infection in children. *Pediatric Infect Dis J* 2002; 21(10):910-917.

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to 0.05 were considered statistically significant. All 95% confidence intervals were based on the normal approximation to the binomial distribution and were considered consistent with equivalence if the lower limit of the confidence interval exceeded -10%. Patients who received the wrong study medication (i.e., the treatment other than the one they were randomized to receive) were included in their actual treatment group (i.e., the one representing the medication they actually received) for both safety and efficacy analyses.

Selection of Study Population

Inclusion Criteria

To be eligible for enrollment, patients were to meet all of the general criteria and the appropriate diagnosis specific criteria.

General Criteria

- Hospitalized male and female patients, birth through 11 years of age
- Expectation of survival with effective antibiotic therapy and appropriate supportive care throughout the study
- Willingness to complete all study-related activities. Patient's parent/legal guardian was to provide informed consent, return the patient for the required visits, and respond to questions regarding adverse events and study medication compliance.
- Known or suspected infection due to a resistant gram-positive bacterial pathogen as determined by laboratory findings (e.g., Gram's stain or culture results) or clinical signs and symptoms of an active infection as outlined below for each clinical syndrome.
- Patients with mixed infections due to gram-positive pathogens and gram-negative bacteria were allowed to enroll in the study.
- Requirement for a minimum of 3 days of IV medication.

Pneumonia

In addition to the general criteria, patients with a diagnosis of pneumonia must have met the following criteria. For patients with a diagnosis of empyema, the empyema was to be drained.

1. Clinical profile compatible with a diagnosis of hospital-acquired pneumonia (HAP) or pneumonia due to PRSP with at least 2 of the following signs and symptoms:
 - Cough
 - Production of purulent sputum or a change (worsening) in character of tracheal aspirate fluid
 - Auscultatory findings on pulmonary examination of rales and/or pulmonary
 - Consolidation (dullness on percussion, bronchial breath sounds, decreased breath sounds, or egophony)

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- Signs of respiratory distress (including dyspnea, tachypnea, cyanosis, intercostal retractions, labored breathing, grunting, or nasal flaring)
2. At least 2 of the following additional symptoms:
 - Fever
 - Hypothermia
 - Leukocytosis or leukopenia or a left shift of >10% band neutrophils for children, infants, and neonates >1 week old or a left shift of >20% band neutrophils for neonates <1 week
 - Increased pulse (\geq 98th percentile of normal for age)
 - Increased respiration rate (>2 standard deviations of normal for age)
 - Requirement for mechanical ventilation or increase in ventilator settings
 - Altered mental status, lethargy, or irritability (infants <1 year of age)
 3. Chest radiograph (posteroanterior and lateral) at baseline or within 48 hours of initiation of treatment (after rehydration) consistent with a diagnosis of pneumonia.

Skin and Skin Structure Infection

Patients with skin and skin structure infections were eligible for enrollment if they met the general criteria and had a complicated infection. It was considered complicated if in addition to the presence of erythema, induration, tenderness, warmth, fluctuance, or discharge of the wound/lesion, the patient had 2 or more of the following symptoms:

- Fever
- Hypothermia
- Leukocytosis or leukopenia or a left shift of >10% band neutrophils for children, infants, and neonates >1 week old or a left shift of >20% band neutrophils for neonates <1 week old
- Significant skin and skin structure infection, requiring hospital care (e.g., a major abscess, ulcer, burn, or cellulitis)

Catheter-Related Bacteremia

If a patient had an indwelling venous or arterial catheter, the catheter could be designated as the source of bacteremia if no other potential source could be found and at least one positive culture was obtained from blood drawn through the catheter.

Catheters infected with *S epidermidis* or coagulase-negative Staphylococci could be retained only with the approval of the medical monitor. If the catheter was retained the patient was to receive study medication through the infected catheter and oral antimicrobials were not allowed. If the catheter-related bacteremia was

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due to any other pathogen the catheter was to be removed for the patient to remain in the study.

In addition to the general criteria, patients with a diagnosis of catheter-related bacteremia were required to have 2 or more of the following signs and symptoms:

- Fever
- Hypothermia
- Petechiae or purpura
- Chills or rigors
- Leukocytosis or leukopenia or a left shift of >10% band neutrophils for children, infants, and neonates >1 week old or a left shift of >20% band neutrophils for neonates <1 week old
- Increased pulse (\geq 98th percentile of normal for age)
- Increased respiration rate (>2 standard deviations of normal for age)
- Other signs of septic shock (decreased peripheral perfusion or hypotension)

Bacteremia, Unidentified Source

If a patient had a diagnosis of bacteremia, and if the source of the bacteremia could not be identified, the infection was classified as "bacteremia, unidentified source." In addition to the general criteria, patients with a diagnosis of bacteremia from an unidentified source, including bacteremia due to PRSP, were required to have 2 or more of the signs and symptoms listed above for catheter-related bacteremia.

Other Infections (Including Pyelonephritis and Peritoneal Infections)

In addition to the general criteria, patients whose diagnosis had not been confirmed or who had another infection were required to have a specimen available for bacterial culture and 3 or more of the following signs and symptoms:

- Fever
- Hypothermia
- WBC casts in urine sediment
- Chills or rigors
- Nausea and/or vomiting
- Diarrhea or constipation
- Flank/abdominal tenderness
- Leukocytosis or leukopenia or a left shift of >10% band neutrophils for children, infants, and neonates >1 week old or a left shift of >20% band neutrophils for neonates <1 week

Comments

Overall, the entry criteria are fairly specific and indicative of the underlying diagnoses. No microbiologic criteria were defined for study inclusion except for CRBSI where at least one positive blood culture was to be obtained through the

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vascular catheter. As a positive blood culture was not a requirement for bacteremia of unidentified source, patients with this diagnosis and a negative blood culture could have had a viral syndrome or some other non-infectious etiology as a cause of their symptoms. Inclusion of such patients could over estimate efficacy of the study medication for resistant pathogens.

Gram-negative rods are the most common cause of HAP in children.⁷

Endotracheal cultures are often not the best indicators of the actual etiologic agents as patients are often colonized with one or more organisms. The exact significance of each bacterium in such situations is often difficult to ascertain.

Patients with HAP are more likely to be enrolled with mixed Gram positive and Gram negative infections compared to patients with other clinical diagnoses.

Additionally, such patients are more likely to receive concomitant broad-spectrum antibiotics further confounding the efficacy of study drugs.

Exclusion Criteria

Patients were to be excluded from the study if they met any of the following criteria:

- Previous antibiotic treatment for > 24 hours with a potentially effective antibiotic within 48 hours of study entry, unless the treatment failed defined as no clinical improvement after 3 days of treatment or the pathogen showed drug resistance to the assigned study medication.
- Infections with a high surgical incision cure rate- isolated furunculosis, single abscess
- Medical conditions in which inflammation could have been prominent for an extended period even after successful bacterial eradication, e.g., superinfected eczema or atopic dermatitis
- Known or suspected preexisting pulmonary condition (i.e., tuberculosis or sequestration) likely to preclude the evaluation of therapeutic response
- Infections requiring potentially effective concomitant systemic antibiotic therapy
- Decubitus, and ischemic ulcers (unless associated with cellulitis), necrotizing fasciitis, gas gangrene, or burns on greater than 20% of total body surface
- No record of *H influenzae* type b vaccine or incomplete vaccination in patients <5 years of age with a diagnosis highly suspicious of *H influenzae* type b
- Infection due to gram-positive pathogens known to be resistant to the study medication, except for VRE
- An infected device due to *S aureus* or *Enterococcus* species that could not be removed

⁷ Richards MJ et al. Nosocomial infections in pediatric intensive care units in the United States. *Pediatrics*. 1999;103(4). <http://www.pediatrics.org/cgi/content/full/103/4/e39>

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- Pneumonia or bacteremia due to penicillin-susceptible *S pneumoniae* (MIC <2 µg/mL)
- Endocarditis, skeletal infections including osteomyelitis/septic arthritis and central nervous system infections
- Known pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension
- Hypersensitivity to linezolid or vancomycin or one of the excipients in either drug formulation
- Previous enrollment in this or another linezolid study
- Concurrent use of another unapproved investigational medication
- Female patients who have reached menarche
- Patients with phenylketonuria who were likely to receive linezolid suspension

Comments

*The reviewer is in agreement with the exclusion criteria. It is possible that some patients with osteomyelitis, especially those complicating wounds or surgical procedures will be enrolled, as it is often difficult to clinically suspect osteomyelitis in some of these children. It is unclear why patients with penicillin-susceptible *S pneumoniae* were excluded as patients with other susceptible bacteria were allowed to remain in the study. It is acceptable to treat vascular catheter associated bacterial infections in children without removing the device.⁸ Enrolling patients with prior antibiotic exposure could decrease the yield on bacterial cultures. It is acceptable to enroll patients with prior antibiotic exposure in whom a resistant pathogen is isolated. However, enrolling patients based on lack of clinical improvement after 3 days of therapy with no identified pathogen may not be indicative of treatment failure, as morbidity in some of these sick children is often multifactorial.*

No hematologic parameters (WBC, platelets or hematocrit) were specified as exclusion criteria. Hence the myelosuppressive effects of linezolid will be difficult to assess in patients with low values at baseline.

Treatments

Linezolid: A dose of 10 mg/kg (maximum dose 600 mg) was to be administered intravenously approximately every 8 hours, infused over a 30-120 minute period.

Vancomycin: Vancomycin solution (maximum 5 mg/mL) was to be infused intravenously at a rate of no more than 10 mg/min over at least 60 minutes. Dosing was to follow the schedule shown below or another documented schedule. The optimal dosage was to be based on the determination of vancomycin serum concentration, especially in low-birth-weight (<1500 g) infants.

⁸ Mermel LA et al. Guidelines for the management of intravascular catheter-related infections. *Clinical Infectious Diseases* 2001;32:1249-72

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Neonates <7 days old:

- <1.2 kg: 15 mg/kg every 24 hours
- 1.2-2 kg: 10 - 15 mg/kg every 12 - 18 hours
- >2 kg: 10 - 15 mg/kg every 8 - 12 hours

Neonates ≥7 days - 1 month old:

- <1.2 kg: 15 mg/kg every 24 hours
- 1.2 - 2 kg: 10 - 15 mg/kg every 8 - 12 hours
- >2 kg: 10 - 15 mg/kg every 6 - 8 hours

Children >1 month: 15 mg/kg every 8 hours

Length of treatment

The maximum duration of treatment was 28 days. Typical lengths of treatment were suggested based on the clinical diagnosis as follows:

- Complicated skin and skin structure infection: 10 - 21 days
- Pneumonia: 10 - 21 days
- Bacteremia (unidentified source): 10 - 28 days
- Other infections (including pyelonephritis and peritoneal infections): 10 - 28 days

Comments

*Suggested length of therapy should be adequate for most infections included in this study. Proposed vancomycin dosing is consistent with commonly used dosing guidelines.*⁹

Prior and Concomitant Treatment

Patients could receive up to 24 hours of a potentially effective antibiotic for the current Gram positive infection prior to enrollment. During the study, additional antibiotic coverage for gram-negative and anaerobic bacterial pathogens could be given as long as the additional coverage had no activity against the primary gram-positive pathogen (per recommended, labeled dosing guidelines). Aztreonam or gentamicin could be administered concomitantly if needed for adequate gram-negative coverage. All medications received 7 days prior to the start of study medication and during the study were to be recorded on the case report form (CRF).

For skin and skin structure infections, use of non-antibiotic antimicrobial topical solutions and daily debridement or dressing changes were acceptable adjunctive therapies that could be employed throughout the treatment period as long as they

⁹ Saez-Llorens X, McCracken GH. Clinical pharmacology of antibacterial agents. In: Remington JS and Kline JO (Ed). Infectious Diseases of the Fetus and Newborn Infant 5th edition. WB Saunders Philadelphia 2001, 1454.

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did not exceed the investigator's hospital and outpatient normal standards of therapy. Topical steroids could be used provided they were not in direct contact with the site of infection.

Comments

Several antibiotics like carbapenems and extended spectrum penicillin/beta lactamase inhibitor combinations used for Gram-negative coverage also have significant activity against many Gram positive organisms. Though the protocol states that additional antibiotic therapy is permitted if the antibiotic had no activity against the primary Gram positive pathogen per recommended label, it is possible that organisms like MSSA/vancomycin sensitive Enterococcus will be susceptible to meropenem which is currently labeled for use in complicated appendicitis and peritonitis and bacterial meningitis. Gram positive organisms for which meropenem is approved include viridans group streptococci, Streptococcus pneumoniae and Peptostreptococcus species. Additionally, in patients with no baseline pathogen the role of such concomitant antimicrobial therapy cannot be assessed.

Treatment Compliance

Each site maintained an investigational medication record form itemizing all study medications administered to or taken by each patient during the study. To assist with outpatient compliance, each linezolid patient/parent or legal guardian was given a medication worksheet and appointment schedule to use as a memory aid and the patient's parent or legal guardian brought unused medication and empty bottles to each study visit and returned any remaining medication at their EOT visit.

Removal of Patients from Treatment or Assessment

A patient could be discontinued from the study if in the opinion of the investigator it was medically necessary, or if it was the wish of the patient or patient's legal guardian. In addition, study medication was to be discontinued for the following reasons:

- Completion of the protocol-defined dosing period
- Disease progression (e.g., septic shock, acute renal failure).
- Patient non-compliance or a major protocol violation
- Request of the sponsor or regulatory agency
- Isolation of a Gram-positive pathogen not susceptible to study medication by the criteria of the National Committee for Clinical Laboratory Standards (NCCLS). Vancomycin resistant enterococci (VRE) isolates only need to be susceptible to linezolid.
- Isolation of only Gram-negative and/or anaerobic pathogens
- Catheter-associated bacteremia due to Enterococcus species or *S. aureus* if the catheter was not removed

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Patients withdrawing from the study were to undergo a clinical assessment, including appropriate EOT activities on the day that the study medication was stopped. A F-U visit was also to be completed, if appropriate. If a patient did not return for a scheduled visit, every effort was to be made to contact the patient's parent/legal guardian.

Efficacy Evaluations

Clinical

The following clinical efficacy evaluations were conducted:

- **Clinical observations:** Clinical observations were evaluated daily, while hospitalized, and recorded on the CRF at baseline, on days 3, 10, 17, and 24 while on treatment, and at the EOT and F-U visits.
- **Vital signs:** Body temperature was considered an efficacy variable. Vital signs were monitored daily, while hospitalized, and recorded on the CRF at baseline, on Days 3, 10, 17 and 24 while on treatment and at the EOT and F-U visits.
- **Radiography:** A chest radiograph was obtained for patients with a clinical diagnosis of pneumonia at baseline and repeated at the F-U visit.
- **Lesion evaluation:** A lesion evaluation including lesion size and degree of involvement was obtained at baseline and F-U for patients with a clinical diagnosis of skin/skin structure infection.

Safety Evaluations

The following safety evaluations were conducted

- **Vital signs:** Blood pressure, pulse, and respiration rate were considered safety measures. Vital signs were monitored daily, while hospitalized, and recorded on the CRF at baseline, on Days 3, 10, 17 and 24 while on treatment; and at the EOT and F-U visits. When multiple vital sign measurements were obtained in a single day, the vital signs were recorded at the time of the most abnormal temperature reported.
- **Laboratory assays:** Safety laboratory assays were obtained at Baseline, Days 3, 10, 17, 24 (while on therapy), and at the EOT and F-U visits.
- **Adverse events:** Information on adverse events was collected throughout treatment and follow-up.
- **Concomitant medications:** Information on concomitant medications and non-medication therapy was collected from 7 days prior to baseline through the final visit.

Efficacy variables

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The primary efficacy variables were patient clinical outcome at the EOT and F-U visits. The test of cure assessment was performed at the F-U visit.

Investigator-Defined Patient Clinical Outcome

At the EOT and F-U visits, the investigator assessed each patient and assigned a clinical outcome according to the following criteria:

Cured: Resolution of clinical signs and symptoms of infection, when compared with baseline. Pneumonia patients were also to show improvement or lack of progression of infection-related radiographic abnormalities at F-U; this criterion also applied at EOT if a chest radiograph was clinically indicated.

Improved (applicable for EOT only): Incomplete resolution of clinical symptoms. For pneumonia patients, if a chest radiograph was clinically indicated, it was to show improvement or lack of progression of infection related radiographic abnormalities.

Failed:

- Persistence, incomplete resolution (at F-U), or worsening of baseline clinical signs and symptoms of infection
- Progression of baseline infection related radiographic abnormalities in patients with pneumonia
- Development of new clinical signs and symptoms consistent with active infection that required additional Gram-positive antimicrobial therapy.
- Adverse event requiring discontinuation of study medication.
- Patients who withdrew from the study due to lack of clinical improvement after at least 48 hours of treatment.

Indeterminate:

- Circumstances precluding classification to one of the above outcomes.
- Patients whose infection required an incision and drainage more than 48 hours after the first dose of study medication.

Sponsor-Defined Patient Clinical Outcome

The sponsor-defined patient clinical outcome at EOT and F-U were based primarily on the evaluations made by the investigator, and also on the number of days and doses of study medication received and whether a concomitant antibiotic had been administered. The patient must have received at least 5 days and 15 doses of study medication for a cure or improvement and at least 2 days and 6 doses of study medication for treatment failure. The sponsor-defined patient clinical outcome supersedes the investigator's assessments. The algorithm used by the sponsor to classify outcomes is summarized below:

Failed

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- If a patient was given a non-investigational antibiotic for lack of efficacy at any time between day 2 and the day after the investigator's clinical assessment
- If no assessment was made in the FU window and the patient received antibiotics for lack of efficacy between day 2 and upper limit of FU window.
- If a patient had no assessment in the EOT and F-U window or the assessments were indeterminate at both time points
- If a patient had no data or if the outcome was indeterminate at the F-U visit, an outcome of Failed at EOT was carried forward to the F-U visit.

Indeterminate: If the sponsor assessed a patient as improved or cured at the EOT visit and assessment at F-U visit was indeterminate or missing.

Missing: Patients who received fewer than 2 days of treatment or less than 6 doses.

Comments

Clinical outcome definitions used in the FDA analyses were slightly different from that used by the sponsor. The statistical reviewer's alternate approach attempts to assign "cure" to patients with known good outcomes, "failure" to patients with known bad outcomes, and "missing" to patients with truly unknown outcomes, regardless of the duration of therapy.

The following is excerpted from the statistical review by Dr. Erica Brittain Ph.D. For further details please refer to Dr. Brittain's review.

FDA clinical outcomes

Failures

Patients were assessed as failures if they were

- assessed as a failure by the investigator at either the End of Treatment or Follow-up visit
- had died by time of the Follow-up visit, or
- were prescribed an additional antibiotic for lack of efficacy, as stated by the investigator, during the study up to and including the Follow-up visit.

Cures

Patients who did not meet any of the criteria for failure, and who were assessed as cures by the investigator at the Follow-up visit, were considered cures in the reviewer's analyses.

Missing

Patients, who were neither failures nor cures by the above criteria were considered missing by the reviewer.

Secondary Efficacy Variables

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Sponsor-Defined Patient Microbiologic Outcome

The sponsor classified each baseline organism as a pathogen or a non-pathogen. All Gram-positive bacteria considered by the investigator to be a pathogen for a given indication were studied. Coagulase-negative staphylococcus was considered a pathogen only in catheter-related bacteremia and in neonates. Each baseline pathogen was assigned a sponsor-defined microbiologic outcome at the F-U visit. Multiple pathogens identified in culture samples from the same patient were assigned separate outcomes. Patients must have received at least 2 days and 6 doses of study medication to be evaluated as documented or presumed microbiologic persistence.

The categories for sponsor-defined microbiologic outcome are described below:

Eradication:

- Documented Microbiologic Eradication - The absence of the original pathogen or pathogens from a culture at the F-U visit.
- Presumed Microbiologic Eradication - The patient's outcome was classified as clinically Cured at the F-U visit, and no microbiological data were available.

Persistence:

- Documented Microbiologic Persistence - The presence of at least one of the original pathogens from a culture obtained at the F-U visit
- Presumed Microbiologic Persistence - The presence of either of the following:
 - The patient's outcome was classified as clinical Failure at the F-U visit, and no microbiological data were available.
 - A concomitant antibiotic therapy was used due to a lack of efficacy before the F-U culture, or in the absence of a culture, after the first dose of study medication and before the end of the F-U window.

Superinfection - The patient's outcome was classified as clinically Failed, Indeterminate, or Missing, and a pathogen was isolated from a culture at the F-U visit that was different from the original pathogen(s).

Colonization - The patient's outcome was classified as clinically Cured at the F-U visit, and a pathogen other than the one isolated at the baseline visit was present in a culture at the F-U visit.

Indeterminate - The patient's outcome was classified as clinically Indeterminate at the F-U visit, and no microbiological data were available.

Missing - Any patient whose Sponsor-Defined Clinical Outcome at the F-U visit was missing, and no microbiological data were available at the F-U visit or the

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response was Documented or Presumed Microbiological Persistence, but the patient received less than 2 days or 6 doses of study medication.

The above microbiologic outcome categories were collapsed into the following categories:

- Microbiologic Success - Any patient who had a documented or presumed eradication or colonization
- Microbiologic Failure - Any patient who had a documented or presumed persistence or superinfection
- Indeterminate - Any patient who was classified as Indeterminate
- Missing - Any patient who was classified as Missing

Sponsor-Defined Pathogen Microbiologic Outcome

Each baseline pathogen was assigned a sponsor-defined microbiologic outcome at the F-U visit and collapsed as follows:

- Eradication: Documented or presumed eradication of the given pathogen
- Non-eradication: Documented or presumed persistence of the given pathogen
- Indeterminate: Any pathogen for which the outcome is indeterminate
- Missing: Any pathogen for which the outcome is missing

Other Secondary Efficacy Variables

- Presence or absence of specified signs and symptoms corresponding to the primary infection was assessed at all scheduled visits.
- Body temperature was assessed at each scheduled visit.
- WBC count was assessed at each scheduled visit.
- For SSSI patients, lesion size was measured at Baseline and F-U visits. The degree of involvement was rated as none (if resolved, at F-U only), superficial, or deep.

Adverse Events

Definition and Reporting

The adverse event reporting period for this study was to begin after the first dose of investigational medication and end at the follow-up visit. Any reaction, injury, or other untoward medical occurrence that occurred during the reporting period, whether or not the event was considered drug related was to be reported as an adverse event. In addition, any known untoward event occurring after the reporting period that the investigator assessed as possibly related to the investigational medication was to be reported as an adverse event.

Assessment of Gravity and Severity

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Each adverse event was to be classified by the investigator as serious or non serious. A serious adverse event is one that is fatal or life-threatening; requires or prolongs hospitalization; produces persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above, based on appropriate medical judgment.

Assessment of Causality

The investigator was asked to assess the possible relationship between adverse events and the investigational medication, as well as any concomitant medications.

Exposure in Utero

If a pregnancy was discovered during the treatment period, study medication was to be discontinued and the patient considered withdrawn from the study at the time that pregnancy was confirmed; participation in post-treatment activities was not required. If any patient became or was found to be pregnant while receiving or within 30 days of discontinuing investigational medication, the investigator was to report the pregnancy, follow the patient until completion of the pregnancy, and report the outcome of pregnancy.

Follow-up of Unresolved Events

All adverse events were to be followed until resolution or assessment by the investigator as chronic or stable, or until the end of patient participation in the study. All adverse events assessed by the investigator as possibly related to the investigational medication, were to be followed even after the patient's participation in the study was over until they resolved or the investigator assessed them as chronic or stable.

Clinical Laboratory Evaluations

The following laboratory evaluations were performed during the course of the study:

- Hematology: Complete blood count with differential and platelet count was obtained at baseline, days 3, 10, 17, 24 (while on therapy), and at the EOT and F-U visits. Reticulocyte count was obtained at baseline and at the EOT and F-U visits.
- Chemistry
 - All patients: Total bilirubin, ALT, creatinine, and electrolytes (sodium, potassium, chloride, and bicarbonate) were obtained at Baseline, Days 3, 10, 17, 24 (while on therapy), and at the EOT and F-U visits.
 - Children ≥ 91 days old: Amylase (with fractionation to pancreatic amylase if amylase was elevated >5 x upper limit of reference range), transferrin, and serum iron were obtained at Baseline and at the EOT and F-U visits.

Patient subsets

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The following subsets of patients were defined:

- **Intent To Treat (ITT)** – All patients who received one or more doses of study medication. This population was used for the analyses of safety and primary efficacy variables.
- **Modified Intent To Treat (MITT)**- All ITT patients who had a pathogen isolated from a culture taken in the ITT baseline window. This population was used for the analyses of primary and secondary efficacy variables.
- **Clinically Evaluable (CE)** - All ITT patients unless they met 1 or more of the following criteria:
 - Eligibility criteria not met.
 - Prior antibiotic usage - if the antibiotic was started before the start of study medication and continued beyond day 1 and was potentially effective against the condition under study. Patients whose prior antibiotics were stopped on day 1 were not excluded.
 - Insufficient therapy - a patient who discontinued study medication for any reason other than lack of efficacy before the minimum requirement of 7 days.
 - Noncompliance with study medication regimen - a patient who did not take at least 80% of the prescribed study medication based on their study medication record or who had noncompliance documented elsewhere in the CRF.
 - Concomitant antibiotics given for intercurrent illness - a patient who was prescribed an antibiotic for an adverse event or intercurrent illness after day 1 and before the F-U visit if the antibiotic was potentially effective against the condition under study. Use of concomitant antibiotics for lack of efficacy was not a reason for exclusion from the CE population.
 - No post baseline assessment - a patient without an assessment in the F-U visit analysis window was not evaluable unless
 - the investigator's clinical outcome was a failure at EOT
 - the patient was given an antibiotic for lack of efficacy between day 2 and the last day of the F-U analysis window.
- **Microbiologically Evaluable (ME)** - All CE patients unless they met either of the following criteria:
 - No baseline pathogen was isolated from a culture taken in the evaluable window
 - All baseline pathogens in the evaluable window were resistant to linezolid or vancomycin. VRE isolates only needed to be susceptible to linezolid.

Comments

Definition of the ITT population is very broad permitting patients with and without a positive culture or patients with either resistant or sensitive organisms to be enrolled. Enrolling patients with only documented resistant Gram positive

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infections would have been more helpful to assess the efficacy against resistant pathogens, however it would be difficult to accrue sufficient patients in a reasonable time frame.

Patients who received prior antibiotics that were stopped on day 1 should have been excluded from the CE population as they could have received effective therapy for > 24 hours prior to enrollment.

FDA defined populations

The following definitions of differences from the sponsor-defined populations are excerpted from the statistical review by Dr. Erica Brittain Ph.D.

ITT: Eight patients who were identified by any source as having VRE i.e., VREflag = 'Yes' at baseline were excluded from the ITT population and analyzed as a separate group. One non-VRE patient who was randomized to vancomycin and received linezolid instead, was included in the vancomycin arm for analyses.

CE: In addition to patients who were excluded from the sponsor's CE population the following were excluded from the FDA's CE population:

- Prior use of antibiotics with activity against Gram-positive organisms for >24 hours in the 48-hour period not excluding those stopped on day 1.
- Patients without a baseline pathogen, who received at least one of these antibiotics in the 48 hour period prior to enrolling in the study or during the study.
- Five patients with baseline pathogens were excluded as they received concomitant drugs during the study that were appropriate therapy for their baseline pathogen: 8211115, 821154, 8222179, 8233161, and 8222232.

All four patients who were randomized to vancomycin but treated with linezolid were excluded from the CE analysis for other reasons, so no decision was necessary about these patients.

MITT: Patients with coagulase-negative staphylococci who were not diagnosed with catheter related bacteremia or were not neonates (≤ 28 days old) and who did not have any other Gram-positive pathogen isolated were excluded from the MITT population.

Visit Windows

Study days were numbered relative to the first day of dosing. Start of the study (day 1) was defined as the date on which a patient took the first dose of study medication as recorded on the CRF. Relative to the study start, days were numbered (-2, -1, 1, 2) with day -1 being the day prior to the start of study medication. Relative to the EOT, post-study medication days were numbered 0P (last day of dosing), 1P, 2P, etc.

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The following table lists the analysis windows used for the ITT and evaluable population:

Visit	Day Relative to Treatment Start	Visit Window for evaluable analysis	Visit Window for ITT Analysis
Baseline	1	-2 to 1 (72 hours)*	≤1
End of Treatment	10 to 28	0P to 6P	0P to 6P
Follow-Up	12P to 28P	7P to 35P	7P to 35P

* -3 to 1 for microbiologic data, -4 to 3 for radiographic data

Comments

All pathogens included in the FDA MITT analysis were in the baseline evaluable window of -3 to 1 days for microbiologic data. A FU visit as early as 7 days after completing therapy is acceptable as both linezolid and vancomycin have relatively short half-lives. However, it possible that extending the window to 35 days could overestimate failures as some sick hospitalized children can develop repeated nosocomial infections.

Protocol Amendments

General Amendments

Both amendments were approved prior to start of patient enrollment.

Amendment 1, approved October 6, 2000:

- Performance of hematology and chemistry assays at local laboratories rather than a central laboratory was instituted; as a consequence, estimated blood collection volumes were adjusted and randomization strata were revised.
- Criteria for recording vital sign data when multiple daily measurements were taken were clarified.
- Inclusion criteria for pneumonia and bacteremia of unidentified source were expanded and/or clarified.
- The definition of clinical failure in the evaluation of efficacy was clarified.
- The panel of chemistry assays required and their frequency were revised to focus on overall rather than continuous monitoring and to minimize required blood draws for patients ≤90 days old.
- Study populations for which chest radiograph results were to be analyzed were specified.
- Various clarifications were made and errors corrected in the schedule of activities and the sample informed consent form.

Amendment 2, approved February 16, 2001:

- Background information on nonclinical toxicology was updated.

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- Criteria for fever and hypothermia stated in the inclusion criteria were revised to correlate with oral temperature conversion factors specified in the Statistics section, and references to axillary readings were deleted.
- For patients with catheter-related bacteremia in whom the catheter was allowed to remain, it was specified that study medication was to be administered through the catheter, and that oral antimicrobial medication was prohibited.
- Criteria for clinical efficacy evaluation for pneumonia patients at the EOT visit were revised to account for results of clinically indicated chest radiography.
- Timing and procedures for laboratory assays and population PK sampling were clarified.
- The included text for the Declaration of Helsinki was updated to the October 2000 version.

Country-specific amendments

Only amendment C was approved after patient enrollment had begun.

Amendment A, approved November 22, 2000

Applied to Canada only. References to the trademark ZYVOX™ were deleted, since it is not used in Canada.

Amendment B, approved December 4, 2000

Applied to Venezuela only. Since Venezuelan local regulations require that children must be 6 years or older to be included in clinical studies, age-specific procedures and criteria in the protocol were revised to delete or qualify references to patients younger than 6 years. Following approval of the amendment, Venezuelan regulatory authorities determined that the age restriction was not required; thus, the amendment was not implemented.

Amendment C, approved January 4, 2000

Applied to Canada only. Since Canadian regulatory authorities required further specification that children 0-90 days of age were to be excluded from the protocol prior to analysis of any clinical information from the neonate PK study M/1260/0064, age-specific procedures and criteria in the protocol were revised to delete or qualify references to patients younger than 91 days. However no patients in Canada were enrolled.

Amendment D, approved October 8, 2001

Applied to the US only. The protocol was revised to provide for keeping open the VRE arm for children with known VRE infections and closing the comparative arm with vancomycin as the comparator. The study design was changed to an open-label, multi-center study with linezolid as the only study medication, with a new protocol number and title (M/1260/0082-VRE: Linezolid IV/PO for the Treatment of Vancomycin-Resistant Enterococcus Infections in Children). Data

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for patients enrolled in this arm of the study will be analyzed and reported separately.

RESULTS

The sponsor's results are excerpted from the final study report. For details of the FDA analyses the reader is referred to Dr. Erica Brittain's review.

Disposition of patients

A total of 59 investigators enrolled 321 patients, 219 randomized to the linezolid arm and 101 to the vancomycin arm. Five patients (4 in the linezolid arm and 1 in the vancomycin arm) did not receive study medication, so a total of 316 patients were included in the ITT population. Of these, 168 (76.7%) in the linezolid arm and 76 (74.5%) in the vancomycin arm completed the study.

The primary reasons for study discontinuation in the ITT population are provided in the following table (Sponsor table 11, page 62 final study report)

Table 1 Sponsor: Disposition of patients

Reasons for Discontinuation	Treatment Group	
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)
Discontinued Patients	47 (21.9)	25 (24.8)
Adverse event	16 (7.4)	7 (6.9)
Protocol violation	2 (0.9)	3 (3.0)
Withdrawn consent	4 (1.9)	0 (0.0)
Lost to follow-up	7 (3.3)	10 (9.9)
Protocol-specific withdrawal criteria	13 (6.0)	4 (4.0)
Lack of efficacy	2 (0.9)	1 (1.0)
Progression of disease	3 (1.4)	0 (0.0)

The percentages of patients discontinuing the study were similar in the two treatment arms. More patients were lost to follow up in the vancomycin arm compared to the linezolid arm (9.9% vs.3.3%).

Protocol deviations

Reasons for protocol deviations were similar between the two groups. Recording of axillary temperature was the most common deviation. The following table (Sponsor table 12, page 63 final study report) lists the common protocol deviations in the ITT population:

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Table 2 Sponsor: Protocol deviations

Description of Deviation	Treatment Group	
	Linezolid N = 215	Vancomycin N = 101
Laboratory	10 (4.7)	3 (3.0)
PRSP not confirmed before enrollment	7 (3.3)	2 (2.0)
Study Medication	27 (12.6)	16 (15.8)
Neonate treated with oral medication	10 (4.7)	2 (2.0)
Received/took incorrect dose/route	9 (4.2)	1 (1.0)
Other protocol deviations	117 (54.4)	55 (54.5)
Axillary baseline temperature taken	72 (33.5)	39 (38.6)
Catheter line not pulled	17 (7.9)	3 (3.0)
Inclusion/Exclusion criteria not met deviation requested	17 (7.9)	8 (7.9)
Inclusion/Exclusion criteria not met deviation not requested	5 (2.3)	2 (2.0)

Data sets analyzed

The percentages of randomized patients in each analysis population were similar in both treatment groups. No baseline pathogens were identified in 36.3% (78/215) of patients in the linezolid arm and 38.6% (39/101) in the vancomycin arm. Four patients randomized to the vancomycin arm received linezolid and were included in the linezolid group for analysis. One patient received linezolid before a patient number was assigned and in 3 patients VRE was isolated and per protocol received only linezolid.

The following table (Sponsor table13, page 64 final study report) provides the numbers of patients in the ITT, MITT, CE and ME populations and the reasons for exclusion from the respective groups as determined by the sponsor.

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Table 3. Sponsor: Analyses populations

Analysis Population Reasons for Exclusion*	Treatment Group	
	Linezolid N = 219 n (%)	Vancomycin N = 102 n (%)
Intent-to-Treat (ITT)	215 (98.2)	101 (99.0)
Never received study medication	4 (1.8)	1 (1.0)
Modified Intent-to-Treat (MITT)	137 (62.6)	62 (60.8)
No baseline pathogen (ITT window)	78 (36.3)	39 (38.6)
Clinically Evaluable (CE)	151 (68.9)	73 (71.6)
Eligibility criteria not met	3 (1.4)	1 (1.0)
Prior antibiotic usage	3 (1.4)	1 (1.0)
Insufficient therapy	33 (15.3)	16 (15.8)
Noncompliant with therapy regimen	13 (6.0)	6 (5.9)
Concomitant antibiotics for intercurrent illness	10 (4.7)	2 (2.0)
No postbaseline clinical outcome	20 (9.3)	14 (13.9)
Microbiologically Evaluable (ME)	93 (42.5)	46 (45.1)
Not clinically evaluable	64 (29.8)	28 (27.7)
No baseline pathogen (evaluable window)	86 (40.0)	42 (41.6)

* Patients could have more than one reason for exclusion

Comments

According to the sponsor only four patients were excluded from the CE population due to prior antibiotic use, though a large number (> 85%) of patients had received antimicrobials prior to or on the first day of study. Some of these antimicrobials had no significant Gram positive activity. All the remaining patients probably received antibiotics within the parameters of the protocol and hence were eligible for enrollment.

Patient demographics

No statistically significant differences between the two groups were noted for age, race, sex or geographic region. A slightly higher number of preterm infants (gestational age < 34 weeks) were in the linezolid group.

The following table (Sponsor table 14, page 67 final study report) summarizes demographic characteristics of the ITT population.

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Table 4 Sponsor: Demographics

Demographic Characteristic	Category or Statistic	Treatment Group		p-value
		Linezolid N = 215	Vancomycin N = 101	
Age category	Total patients reported	215	101	
	0-7 days, pre-term*	1 (0.5)	2 (2.0)	0.3264
	0-7 days, full term*	1 (0.5)	0	
	8-90 days, pre-term*	25 (11.6)	6 (5.9)	
	8-90 days, full term*	16 (7.4)	10 (9.9)	
	8-90 days, ? term	0	2 (2.0)	
	91-182 days	10 (4.7)	5 (5.0)	
	183 days - <1 year	24 (11.2)	11 (10.9)	
	1 year-4 years	88 (40.9)	42 (41.6)	
	5 years-11 years	50 (23.3)	23 (22.8)	
	Age, years	Total patients reported	215	101
Mean ± SD		2.91 ± 3.16	2.94 ± 3.13	0.9387
Median		1.50	1.80	
Race	Total patients reported	214	101	
	White	93 (43.5)	38 (37.6)	
	Black	26 (12.1)	23 (22.8)	
	Asian or Pacific Islander	4 (1.9)	2 (2.0)	
	Mixed/multiracial	91 (42.5)	38 (37.6)	
Sex	Total patients reported	215	101	
	Male	117 (54.4)	59 (58.4)	0.505
	Female	98 (45.6)	42 (41.6)	
Geographic region	Total patients reported	215	101	
	North America	95 (44.2)	46 (45.5)	0.821
	Latin America	120 (55.8)	55 (54.5)	

The following table (Sponsor table 16, page 71 final study report) summarizes postnatal and gestational age in patients < 91 days of age:

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Table 5 Sponsor: Characteristics of patients < 91 days of age

Characteristic	Category or Statistic	Treatment Group		p-value
		Linezolid N = 43	Vancomycin N = 20	
Age, days	Total patients reported	43	20	
	Mean ± SD	25.7 ± 19.2	40.3 ± 28.3	0.0196
	Median	18	36	
Gestational age at delivery weeks	Total patients reported	43	18	
	Mean ± SD	32.4 ± 5.1	33.4 ± 5.3	0.5142
	Median	32	35	

* Estimated by physical maturity if present, else best obstetric estimate

Comments

Overall, patients enrolled in the study were very young with children aged 1-4 years being the largest group. Only two neonates in each arm were < 7 days of age, which is not surprising as nosocomial infections like HAP and CRBSI occur more commonly after the first week of life.¹⁰ Sepsis in the first week of life is more likely due to Gram negative organisms or Group B streptococci.⁷ Prematurity is usually defined as gestational age < 37 weeks. The mean and median age of infants < 91 days in the vancomycin group was higher compared to the linezolid group. A median age of 36 days in the vancomycin group and 18 days in the linezolid group suggests that there were more neonates (≤ 28 days) in the linezolid group.

Medical history

Any past or present significant medical conditions in the patients besides the condition under study were analyzed. For nearly all conditions studied, no statistically significant differences were noted between the two treatment groups. Significant differences between groups were noted only in histories of hypogammaglobulinemia (present history: linezolid 0.0% [0/215], vancomycin 2.0% [2/101]; p=0.038) and HIV (present history: linezolid 0.0% [0/215], vancomycin 2.0% [2/101]; p=0.038).

Baseline vital signs and physical examination findings unrelated to condition under study were similar between the two groups in the ITT population. Statistically significant differences between treatment groups in the ITT population were observed for mean baseline WBC (linezolid 12.46 ± 7.47, vancomycin 14.47 ± 8.89; p=0.040) and neutrophil count (linezolid 7.21 ± 5.59,

¹⁰ Edwards MS, Baker CJ. Nosocomial infections in the neonate. In: Long SS, Pickering LK, Prober CG (eds): Principles and Practice of Pediatric Infectious Diseases 2nd ed. New York, NY: Churchill Livingstone;2003:547-553.

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vancomycin 8.67 ± 6.49 ; $p=0.050$). Baseline laboratory values analyzed by age showed a significant difference between treatment groups for WBC in patients 5-11 years of age (linezolid 8.90 ± 7.38 , vancomycin 13.24 ± 8.82 ; $p=0.033$).

Comments: *Given the myelosuppressive effects of linezolid, this difference at the time of enrollment could have a bearing on the assessment of hematologic toxicity.*

Baseline Diagnosis

No statistically significant difference between treatment groups in the ITT population was observed for the distribution of types of primary infections. Hospital-acquired pneumonia was more common in the vancomycin group and vascular catheter associated bacteremia was more common in the linezolid group. The following table (Sponsor table 18, page 74 final study report) shows the various baseline diagnoses in the ITT population

Table 6. Sponsor: Baseline diagnosis

Baseline Diagnosis	Treatment Group	
	Linezolid N = 215 n (%) [*]	Vancomycin N = 101 n (%) [*]
Hospital-Acquired Pneumonia	23 (10.7)	16 (15.8)
Skin / Skin Structure Infection	80 (37.2)	40 (39.6)
Bacteremia, Catheter-Associated	48 (22.3)	13 (12.9)
Bacteremia of Unknown Source	33 (15.3)	19 (18.8)
Other Infection	31 (14.4)	13 (12.9)

Clinical signs and symptoms

No significant differences were observed between the two treatment groups for most signs and symptoms present at baseline within different diagnosis categories. Statistically significant differences between groups were observed for percentages of skin/skin structure infection patients with induration (linezolid 77.2% [61/79], vancomycin 95.0% [38/40]; $p=0.014$) and "other infection" patients with flank pain (linezolid 40.0% [6/15], vancomycin 0% [0/8]; $p=0.037$). For hospital-acquired-pneumonia patients, the linezolid group had slightly higher frequencies of some signs and symptoms than did the vancomycin group: cyanosis (linezolid 36.4%, vancomycin 18.8%), intercostal retractions (linezolid 81.8%, vancomycin 62.5%), oxygen requirement (linezolid 86.4%, vancomycin 68.8%), and mechanical ventilation requirement (linezolid 54.5%, vancomycin 31.3%). No significant differences were seen between groups for the mean duration of infection in any diagnosis category. Mean and median duration of infection prior to enrollment for hospital-acquired-pneumonia patients in the

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vancomycin group was twice that in the linezolid group (4.4 ± 4.4 and 4.0 , 2.2 ± 2.5 and 2.0 respectively, $p = 0.054$)

Comments

The two groups were comparable with regard to baseline signs and symptoms. The difference in frequency of induration in patients with SSSI and flank pain in patients with "other infections" has no significant bearing on clinical outcome. For patients with HAP, it appears that patients in the linezolid arm were sicker though the difference was not statistically significant. On the other hand, patients in the vancomycin arm had a longer duration of infection prior to enrollment suggesting that they either had more severe or more refractory infections.

Concomitant non study antimicrobials

Frequencies of noninvestigational antibiotic use were generally comparable between treatment groups. Fusidic acid, Synercid, linezolid [reported as noninvestigational], or teicoplanin were administered to $\leq 2\%$ of patients in either group starting prior to or on the first day of study medication and $\leq 1\%$ of patients in either group starting after the first day of study medication.

The following table (Sponsor table 22, page 79 final study report) shows the percentages of patients receiving non-investigational antimicrobials that were administered to $\geq 5\%$ of patients in the linezolid group.

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Table 7. Sponsor: Non study antimicrobials administered prior to or during study

Timing of drug administration	Treatment Group	
	Linezolid N = 215 n (%)	Vancomycin n N = 101 n (%)
Prior to or on first day of study medication	181 (84.6)	91 (90.1)
Vancomycin	64 (29.9)	26 (25.7)
Amikacin	41 (19.2)	10 (9.9)
Gentamicin systemic	38 (17.8)	21 (20.8)
Cefotaxime	31 (14.5)	12 (11.9)
Ampicillin	25 (11.7)	9 (8.9)
Ceftazidime	20 (9.3)	8 (7.9)
Clindamycin	19 (8.9)	14 (13.9)
Nystatin tablets	19 (8.9)	6 (5.9)
Metronidazole	18 (8.4)	7 (6.9)
Bactrim	15 (7.0)	6 (5.9)
Amphotericin B systemic	15 (7.0)	2 (2.0)
Tobramycin	13 (6.1)	2 (2.0)
Amoxicillin	12 (5.6)	4 (4.0)
Aztreonam	11 (5.1)	5 (5.0)
Started after first day of study medication	113 (52.8)	56 (55.4)
Vancomycin	25 (11.7)	10 (9.9)
Gentamicin systemic	24 (11.2)	9 (8.9)
Amphotericin B systemic	15 (7.0)	6 (5.9)
Meropenem	14 (6.5)	6 (5.9)
Ceftazidime	13 (6.1)	6 (5.9)
Ciprofloxacin	13 (6.1)	3 (3.0)
Fluconazole	12 (5.6)	2 (2.0)
Amikacin	11 (5.1)	11 (10.9)

Antibiotics with Gram positive activity are in bold type.

Comments

Prior to study entry a large percentage of patients in both groups received antibiotics like vancomycin and clindamycin that have significant Gram positive activity. In all patients who had negative baseline cultures, antibiotic use in the 48 hours preceding study entry was assessed; 68/117 (58.1%) patients (both arms combined) had received one or more antibiotics with Gram positive activity. In patients who received additional antibiotics with Gram positive activity during therapy (not for lack of efficacy) and considered clinically evaluable by sponsor,

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the susceptibilities of the baseline pathogen to the antibiotic administered was assessed. A total of 5 patients had received antibiotics that could be potentially effective against the baseline pathogen. These 5 patients had the following pathogen-antibiotic combination and were excluded from FDA's CE population.

Vancomycin-susceptible Enterococcus-Meropenem

Vancomycin-susceptible Enterococcus-Meropenem

Methicillin sensitive Staphylococcus aureus-Meropenem

Methicillin sensitive Staphylococcus species-Meropenem

Methicillin resistant Staphylococcus species-Vancomycin

Extent of exposure

Majority of ITT patients in the linezolid group (53%, 114/215) received oral treatment, while 31% (31/100) of the vancomycin group received oral step-down medication. Duration of treatment was generally longer for the vancomycin group than the linezolid group for both IV and oral dosing. The mean number of doses received was higher for the vancomycin group than the linezolid group for both IV and oral dosing (Sponsor table 23, page 81 final study report)

Table 8. Sponsor: Extent of exposure

	Linezolid N = 215			Vancomycin N = 101		
	IV	Oral	Overall	IV	Oral	Overall
Days of treatment						
Total Reported	215	114	214	100	31	100
Mean ± SD	7.7 ± 4.8	7.8 ± 3.0	11.3 ± 5.0	9.8 ± 6.2	8.8 ± 4.1	12.2 ± 6.4
Median	6.0	7.5	11.0	10.0	8.0	11.0
Number of doses						
Total Reported	215	114	215	100	31	100
Mean ± SD	19.6 ± 14.0	20.0 ± 9.5	30.3 ± 14.7	25.0 ± 16.8	21.0 ± 10.5	31.5 ± 17.2
Median	15.0	19.0	30.0	24.5	19.0	30.0

Relative to the linezolid group, the vancomycin group on average was treated for about 1 more day (mean duration 11.3 ± 5.0 days vs. 12.2 ± 6.4 days) and received about 1 more dose (mean number of doses 30.3 ± 14.7 vs. 31.5 ± 17.2). Only 13 (6.1%) of patients received more than 21 days of therapy in the linezolid arm and 6 (6%) in the vancomycin arm.

Treatment Compliance

Treatment compliance was assessed based on information collected on the study medication report for numbers of doses prescribed and administered. In the linezolid arm 15.3% (33/215) and in the vancomycin arm 15.8% (16/101) of

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patients were excluded from the CE population due to insufficient therapy (<7 days of treatment unless patient discontinued due to lack of efficacy). In the linezolid arm 6.0% (13/215) and in the vancomycin arm 5.9 % (6/101) of patients were excluded from the CE population due to noncompliance with therapy regimen (<80% of prescribed medication administered).

Nine patients in the linezolid group erroneously received study medication twice daily and were excluded from the CE population. All except one of these patients were assessed as cures at FU by the investigator.

EFFICAY RESULTS

The sponsor-defined patient clinical outcome superseded the investigator's assessments and were usually more conservative than investigator defined outcomes. Sponsor-defined patient clinical outcomes for the ITT, MITT, CE and ME populations is provided. Patients with missing or indeterminate outcomes were not included in the sponsor's ITT analysis. A supplementary analysis of the sponsor's assessment of clinical outcome for the ITT and CE population in which indeterminate and missing outcomes were classified as failures is also provided. Investigator assessment of clinical outcome will not be presented in this review.

ITT

The difference in cure rates at follow up between the two arms was 5% (95% CI - 6.0, 15.9, p value 0.359). The following table (Sponsor table 29, page 89 final study report) shows the sponsor's assessment of clinical outcome at EOT and FU visits in the ITT population excluding missing/indeterminate.

Table 9. Sponsor: Clinical outcome in ITT (missing/indeterminate excluded)

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	p-value	95% CI
End of Treatment	Cured	149 (74.1)	59 (71.1)	0.547	
	Improved	21 (10.4)	7 (8.4)		
	Failed	31 (15.4)	17 (20.5)		
	No. Assessed	201 (100.0)	83 (100.0)		
	Indeterminate	2	1		
	Missing	12	17		
Follow-Up	Cured	155 (79.1)	63 (74.1)	0.359	-6.0, 15.9
	Failed	41 (20.9)	22 (25.9)		
	No. Assessed	196 (100.0)	85 (100.0)		
	Indeterminate	7	6		
	Missing	12	10		

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A supplementary analysis of the sponsor's assessment of clinical outcome for the ITT population in which indeterminate and missing outcomes were classified as failures showed no significant difference in outcomes between treatment groups at the follow up visit.

**Table 10. Sponsor: Clinical outcome in ITT
(missing/indeterminate = Failures)**

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	p-value	95% CI
End of treatment	Cured	149 (69.3)	59 (58.4)	0.031	
	Improved	21 (9.7)	7 (6.9)		
	Failed	45 (20.9)	35 (34.6)		
Follow up	Cured	155 (72.1)	63 (62.4)	0.082	-1.5, 20.9
	Failed	60 (27.9)	38 (37.6)		

CE

The following table (Sponsor table 31, page 91 final study report) shows the sponsor's assessment of clinical outcome for the CE population, excluding missing and indeterminate outcomes.

Table 11. Sponsor: Clinical outcome in CE (missing/indeterminate excluded)

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 151 n (%)	Vancomycin N = 73 n (%)	P-Value	95% CI
End of Treatment	Cured	128 (84.8)	53 (82.8)	0.500	
	Improved	15 (9.9)	5 (7.8)		
	Failed	8 (5.3)	6 (9.4)		
	No.Assessed	151 (100.0)	64 (100.0)		
	Indeterminate	0	1		
Follow-Up	Missing	0	8	0.306	-4.9, 14.6
	Cured	134 (89.3)	60 (84.5)		
	Failed	16 (10.7)	11 (15.5)		
	No.Assessed	150 (100.0)	71 (100.0)		
	Indeterminate	1	1		
	Missing	0	1		

Results for sponsor-assessed clinical outcome for the CE population showed higher cure rates than those observed for the ITT population. Percentages of

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assessed patients in the CE population considered cured at the F-U visit were equivalent for both treatment groups.

A supplementary analysis of the sponsor's assessment of clinical outcome for the CE population was conducted in which indeterminate and missing outcomes were classified as failures. The difference in cure rates was not statistically significant. (linezolid 88.7%, vancomycin 82.2%, $p=0.177$; 95% CI -3.6 to 16.7). No major differences were noted in the cure rates with this approach as very few patients had missing or indeterminate outcomes.

Comments

As patients with missing or indeterminate outcomes were excluded in the sponsor's analysis it is not a true ITT population. Additionally patients randomized to the vancomycin arm who had VRE were included in the linezolid arm for analysis, thus not truly maintaining randomization. In the ITT population, using both approaches (excluding missing and indeterminate outcomes and by considering them as failures) cure rates in both arms were similar at the test of cure visit. The cure rates at FU were lower in both groups when missing and indeterminate outcomes were classified as failures. The difference was higher in the vancomycin arm as a larger percentage of patients were lost to follow up or had indeterminate outcomes in the vancomycin arm. In the CE population, using both approaches (excluding missing and indeterminate outcomes and by considering them as failures) cure rates in both arms were similar at the test of cure visit. Since no non-inferiority margin was pre-specified it is not possible to conclude that the two drugs were equally effective.

MITT

The following table (Sponsor table 30, page 62 final study report) shows the sponsor's assessment of clinical outcome at EOT and FU visits for the MITT population, excluding patients with missing or indeterminate outcomes.

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**Table 12. Sponsor: Clinical outcome in MITT
(missing/indeterminate excluded)**

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 137 n (%)	Vancomycin N = 62 n (%)	P-Value	95% CI
End of Treatment	Cured	94 (72.3)	44 (86.3)	0.088	
	Improved	19 (14.6)	2 (3.9)		
	Failed	17 (13.1)	5 (9.8)		
	No. assessed	130 (100.0)	51 (100.0)		
	Indeterminate	1	1		
	Missing	6	10		
Follow-Up	Cured	101 (80.8)	43 (81.1)	0.959	-12.9, 12.3
	Failed	24 (19.2)	10 (18.9)		
	No. assessed	125 (100.0)	53 (100.0)		
	Indeterminate	6	4		
	Missing	6	5		

Percentages of assessed patients in the MITT population considered cured at the F-U visit were similar for both treatment groups.

ME

In the ME population there were no missing or indeterminate outcomes and hence no supplementary analysis was required. The following table (Sponsor table 32, page 92 final study report) summarizes the sponsor assessed clinical outcome for the ME population.

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Table 13. Sponsor: Clinical outcome in ME

Visit	Assessment	Treatment Group		Statistical Test	
		Linezolid N = 93 n (%)	Vancomycin N = 46 n (%)	P-Value	95% CI
End of Treatment	Cured	77 (82.8)	37 (80.4)	0.007	
	Improved	12 (12.9)	1 (2.2)		
	Failed	4 (4.3)	8 (17.4)		
	No. Assessed	93 (100.0)	46 (100.0)		
	Indeterminate	0	0		
	Missing	0	0		
Follow-Up	Cured	82 (88.2)	40 (87.0)	0.837	-10.5, 13.0
	Failed	11 (11.8)	6 (13.0)		
	No. Assessed	93 (100.0)	46 (100.0)		
	Indeterminate	0	0		
	Missing	0	0		

Comments

The same concerns (See page 101, MO comments) as in the definitions for ITT population hold true here as patients had to be in the ITT population and in addition have a pathogen identified at baseline to be in the MITT population. In the MITT and ME populations cure rates in both arms were similar at the test of cure visit. In a study like this specifically addressing the role of linezolid in gram positive infections the MITT and ME populations are the more important populations as they represent patients with truly identified bacteriologic disease.

FDA assessment of clinical outcome

The following table provides analysis of FDA clinical endpoints using FDA defined primary analysis populations. For all other FDA analyses the reader is referred to Dr. Brittain's review.

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Table 14. FDA analysis: missing data excluded

Population	Linezolid		Vancomycin		Difference (L-V)	95% Confidence Interval	
	Cure Rate	N	Cure Rate	N		Lower	Upper
FDA ITT	0.806	186	0.831	83	-.025	-.132	0.082
FDA MITT	0.796	108	0.898	49	-.102	-.230	0.027
FDA CE	0.906	117	0.891	55	0.015	-.096	0.126
FDA ME	0.888	80	0.905	42	-.017	-.148	0.113

Comments

Using a different approach in the FDA analysis, wherein patients with known good outcomes were assigned "cure", those with known bad outcomes "failure", and those with truly unknown outcomes "missing" regardless of the duration of therapy, no significant treatment differences were seen between the groups. However it is noteworthy that the largest treatment difference was seen in the MITT group, with a slight advantage of vancomycin over linezolid. The significance of this finding is difficult to ascertain at this point since it is not statistically significant.

Analysis by age groups

The following table (Sponsor table 33, page 93 final study report) summarizes sponsor's assessment of clinical outcome by age in the ITT population, excluding patients with missing or indeterminate outcomes. No statistically significant differences between treatment groups in cure rates were observed for any age category at any visit.

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Table 15. Sponsor: clinical outcome by age

Age Category	Visit	Assessment	Treatment Group		Statistical Test	
			Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	P-value	95% CI
0-90 days	EOT	Cured	28 (65.1)	12 (63.2)	0.213	
		Improved	8 (18.6)	1 (5.3)		
		Failed	7 (16.3)	6 (31.6)		
		No. Assessed	43 (100.0)	19 (100.0)		
	F-U	Cured	31 (77.5)	11 (61.1)	0.196	-9.6, 42.4
		Failed	9 (22.5)	7 (38.9)		
No. Assessed		40 (100.0)	18 (100.0)			
91 days - <1 year	EOT	Cured	24 (77.4)	10 (83.3)	0.795	
		Improved	5 (16.1)	1 (8.3)		
		Failed	2 (6.5)	1 (8.3)		
		No. Assessed	31 (100.0)	12 (100.0)		
	F-U	Cured	25 (83.3)	11 (84.6)	0.917	-25.0, 22.4
		Failed	5 (16.7)	2 (15.4)		
No. Assessed		30 (100.0)	13 (100.0)			
1-4 years	EOT	Cured	67 (80.7)	27 (73.0)	0.609	
		Improved	4 (4.8)	3 (8.1)		
		Failed	12 (14.5)	7 (18.9)		
		No. Assessed	83 (100.0)	37 (100.0)		
	F-U	Cured	66 (80.5)	27 (75.0)	0.502	-11.1, 22.0
		Failed	16 (19.5)	9 (25.0)		
No. Assessed		82 (100.0)	36 (100.0)			
5-11 years	EOT	Cured	30 (68.2)	10 (66.7)	0.887	
		Improved	4 (9.1)	2 (13.3)		
		Failed	10 (22.7)	3 (20.0)		
		No. Assessed	44 (100.0)	15 (100.0)		
	F-U	Cured	33 (75.0)	14 (77.8)	0.817	-25.9, 20.3
		Failed	11 (25.0)	4 (22.2)		
No. Assessed		44 (100.0)	18 (100.0)			

Comments

No significant differences were seen between the two arms in the different age categories. However the numbers were small in most groups. This study population was very heterogeneous as children with a variety of clinical diagnoses were enrolled. Hence the nature and severity of illness could vary

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significantly between the different age categories making it difficult to draw conclusions about the efficacy of the study drugs in children of different ages.

Analysis by primary diagnosis:

The following table (Sponsor table 35, page 96 final study report) summarizes sponsor-assessed clinical outcome at F-U by diagnosis of primary infection for the ITT population defined as excluding missing and indeterminate outcomes.

Table 16. Sponsor: Clinical outcome by diagnosis

Baseline Diagnosis	Assessment	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	P-Value	95% CI
Hospital acquired pneumonia	Cured	13 (68.4)	11 (84.6)	0.299	-44.9, 12.5
	Failed	6 (31.6)	2 (15.4)		
	No. Assessed	19 (100.0)	13 (100.0)		
Skin/skin structure infection	Cured	64 (86.5)	28 (82.4)	0.574	-10.9, 19.1
	Failed	10 (13.5)	6 (17.6)		
	No. Assessed	74 (100.0)	34 (100.0)		
Bacteremia (catheter-related)	Cured	31 (73.8)	8 (72.7)	0.942	-28.4, 30.6
	Failed	11 (26.2)	3 (27.3)		
	No. Assessed	42 (100.0)	11 (100.0)		
Bacteremia (unknown source)	Cured	23 (69.7)	10 (58.8)	0.442	-17.3, 39.0
	Failed	10 (30.3)	7 (41.2)		
	No. Assessed	33 (100.0)	17 (100.0)		
Other infection	Cured	24 (85.7)	6 (60.0)	0.087	-7.3, 58.7
	Failed	4 (14.3)	4 (40.0)		
	No. Assessed	28 (100.0)	10 (100.0)		

No statistically significant differences between treatment groups in cure rates were observed for any diagnosis category. Cure rates for HAP were lower in the linezolid group than for the vancomycin group (68.4% and 84.6%, respectively). The cure rates for other diagnoses were somewhat higher for the linezolid group than in the vancomycin group. Overall, in the linezolid group lower cure rates were seen in patients with HAP or bacteremia of unknown source and in the vancomycin group in patients with bacteremia of unknown source and other infections.

The FDA clinical endpoint by baseline diagnosis in the ITT population is provided in the following table:

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Table 17. FDA: Clinical Endpoint by Baseline Diagnosis in ITT Population

	Site	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
Missing Values Excluded	BUO	0.759	29	0.688	16	0.071	-.253	0.395
	CRB	0.732	41	0.667	12	0.065	-.288	0.418
	HAP	0.722	18	0.917	12	-.194	-.523	0.134
	OTH	0.923	26	0.889	9	0.034	-.270	0.338
	SSSI	0.847	72	0.912	34	-.065	-.213	0.084
Missing Values Counted as Failures	BUO	0.688	32	0.579	19	0.109	-.207	0.424
	CRB	0.667	45	0.615	13	0.051	-.296	0.399
	HAP	0.565	23	0.688	16	-.122	-.480	0.235
	OTH	0.828	29	0.615	13	0.212	-.142	0.566
	SSSI	0.792	77	0.756	41	0.036	-.142	0.214

BUO = Bacteremia of unknown origin, CRB = Catheter related bacteremia, HAP = Hospital acquired pneumonia, OTH= Other infections, SSSI = Skin and skin structure infections

Comments: It is difficult to assess the significance of the difference in cure rates in various disease categories as some groups had very few patients. In both the sponsor's analysis and FDA analysis the largest difference in cure rates between the two arms was seen in patients with HAP with cure rates being higher in the vancomycin arm. This difference in cure rates between the arms may be secondary to the difference in severity of illness at baseline.

Use of concomitant antibiotics for Gram negative coverage

The following table (Sponsor table 51, page 120 final study report) summarizes sponsor-assessed clinical outcome by use of concomitant antibiotics for Gram-negative coverage in the ITT population defined as excluding patients with missing or indeterminate outcomes.

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Table 18. Sponsor: Use of concomitant antibiotics

Concomitant Antibiotic Usage	Assessment	Linezolid n (%)	Vancomycin n (%)	P-Value	95% CI
Aminoglycoside used	Cured	43 (56.6)	20 (58.8)	0.826	-22.2, 17.7
	Failed	33 (43.4)	14 (41.2)		
	No. Assessed	76 (100.0)	34 (100.0)		
No aminoglycoside used	Cured	112 (93.3)	43 (84.3)	0.064	-1.9, 20.0
	Failed	8 (6.7)	8 (15.7)		
	No. Assessed	120 (100.0)	51 (100.0)		
Aztreonam used	Cured	8 (61.5)	3 (75.0)	0.622	-63.5, 36.5
	Failed	5 (38.5)	1 (25.0)		
	No. Assessed	13 (100.0)	4 (100.0)		
No aztreonam used	Cured	147 (80.3)	60 (74.1)	0.255	-4.9, 17.4
	Failed	36 (19.7)	21 (25.9)		
	No. Assessed	183 (100.0)	81 (100.0)		
Any gram-negative coverage used	Cured	98 (71.0)	48 (73.8)	0.675	-15.9, 10.3
	Failed	40 (29.0)	17 (26.2)		
	No. Assessed	138 (100.0)	65 (100.0)		
No gram-negative coverage used	Cured	57 (98.3)	15 (75.0)	<0.001	4.0, 42.5
	Failed	1 (1.7)	5 (25.0)		
	No. Assessed	58 (100.0)	20 (100.0)		

In both arms of the study cure rates at the FU visit were higher in patients not receiving concomitant antibiotics for Gram negative coverage compared to patients receiving such antibiotics. The difference was most marked in patients receiving aminoglycosides. For patients receiving no antibiotics for Gram-negative coverage, cure rates in the linezolid arm were significantly higher than in the vancomycin arm.

Comments

Lower cure rates in patients who received additional antibiotics for Gram negative coverage may indicate that these children were either sicker or had

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mixed infections or had no baseline pathogen identified compared to those who did not receive additional antibiotics.

Analysis by pathogen

No statistically significant differences between treatment groups in cure rates were observed for any selected pathogen category in the MITT or ME populations.

The following table summarizes sponsor-assessed clinical outcome by selected pathogen for patients in the MITT population defined as excluding patients with missing or indeterminate outcomes. (Sponsor table 39, page 102 final study report)

Table 19. Sponsor: Clinical outcome by pathogen

Pathogen	Linezolid N/no. assessed (%)	Vancomycin N/no. assessed (%)	P-Value	95% CI
<i>Staphylococcus aureus</i>	41/50 (82.0)	26/30 (86.7)	0.584	-20.8, 11.5
<i>Staphylococcus epidermidis</i>	26/33 (78.8)	11/13 (84.6)	0.654	-29.9, 18.2
<i>Enterococcus faecalis</i>	10/15 (66.7)	3/4 (75.0)	0.750	-57.0, 40.3
<i>Enterococcus faecium</i>	6/7 (85.7)	0/0 (0.0)	--	--
<i>Streptococcus pneumoniae</i>	4/5 (80.0)	1/1 (100.0)	0.624	-55.1, 15.1
<i>Streptococcus pyogenes</i>	3/3 (100.0)	1/3 (33.3)	0.083	13.3, 100

Multiple pathogens identified in culture samples from the same patient were assigned separate outcomes

Comments

The number of organisms in certain categories of pathogens is very small. Pathogens listed here include all Gram positive cocci including susceptible and resistant pathogens thus providing relatively little information about resistant organisms. Though the study was designed to gain real life experience in the use of linezolid, few patients with resistant infections were enrolled.

Patients with VRE

According to the sponsor, eight patients in the ITT population had VRE infections. This includes patients whose VRE could have been identified by a local laboratory. Central laboratory culture results are available for only five patients, one of who had vancomycin sensitive *Enterococcus faecalis*. Hence only details of the four patients with documented culture for vancomycin resistant *Enterococcus faecium* are included in this discussion. In one of these four patients

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the positive culture was on day -4, which was outside the microbiologically evaluable window.

The following table summarizes clinical/microbiology data on these 4 patients:

Table 20: Patients with VRE infections

Patient ID	Clinical diagnosis	Age (years)	Day culture positive	Outcome	Site
8211135	SSSI	0.2	-3,-4, 1	Cured	Skin
8222118	CRBSI	0.5	-4, 10	Failed	Blood
8222132	Others	1.3	-1, 2, -3, 2	Failed	Blood, Peritoneal fluid
8233127	Bacteremia	5.5	-4, 1, 2, 4	Cured	Blood

Source: Appendix 14: Efficacy Listings for Patients with Vancomycin- Resistant Enterococcus Infections

Patient number 8222132 who was s/p liver transplant died due to vancomycin resistant *Enterococcus faecium* sepsis, acute renal failure and peritonitis after having received 10 doses of linezolid.

Patients with *Staphylococcus aureus* infections:

FDA clinical endpoints in patients with *S.aureus* infections are presented in the following table:

Table 21. FDA: Clinical endpoints for *S. aureus*

	Baseline Pathogen	Linezolid		Vancomycin		Diff (L-V)	95% Confidence Interval	
		Cure Rate	N	Cure Rate	N		Lower	Upper
FDA MITT ¹	<i>S Aureus</i>	0.851	47	0.966	29	-.114	-.264	0.035
	MRSA	0.889	18	1.000	9	-.111	-.340	0.117
FDA MITT ²	<i>S Aureus</i>	0.727	55	0.824	34	-.096	-.294	0.102
	MRSA	0.842	19	0.692	13	0.150	-.215	0.514
FDA ME	<i>S Aureus</i>	0.947	38	0.958	24	-.011	-.152	0.130
	MRSA	0.941	17	1.000	9	-.059	-.256	0.138

1= Missing Values Excluded

2= Missing Values counted as Failures

Comments

No significant differences in cure rates were seen between the two arms for all *S.aureus* isolates combined and for MRSA isolates.

Patient microbiologic outcome

No statistically significant differences between treatment groups in success rates were observed for either the MITT or ME population.

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The following table shows collapsed patient microbiologic outcome at F-U for the MITT, defined as excluding patients with missing/indeterminate outcomes (Sponsor table 40, page 103 final study report) and the ME populations:

Table 22. Sponsor: Patient microbiologic outcome

Population	Assessment	Treatment Group		Statistical Test	
		Linezolid n (%)	Vancomycin n (%)	P- Value	95% CI
MITT	Microbiologic success	94 (79.7)	42 (82.4)	0.685	-15.4, 10.0
	Microbiologic failure	24 (20.3)	9 (17.6)		
	Number Assessed	118 (100.0)	51 (100.0)		
	Indeterminate	5	3		
	Missing	14	8		
ME	Microbiologic success	81 (88.0)	40 (87.0)	0.855	-10.7, 12.9
	Microbiologic failure	11 (12.0)	6 (13.0)		
	Number Assessed	92 (100.0)	46 (100.0)		
	Indeterminate	1	0		

Pathogen microbiologic outcome

No significant differences were seen between the two treatment groups by baseline susceptibility. The following table (Sponsor table 42, page 105 final study report) summarizes collapsed pathogen microbiologic outcome at FU by susceptibility pattern in the MITT population for some of the more commonly isolated pathogens:

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Table 23. Sponsor: Pathogen microbiologic outcome

Baseline Pathogen	Sus. Profile	Assessment	Linezolid N = 137 n (%)	Vancomycin N = 62 n (%)	P-Value	95% CI
<i>Enterococcus faecalis</i>	V:S	Eradication	10 (66.7)	3 (75.0)	0.75	-57.0, 40.3
		No. Assessed	15 (100.0)	4 (100.0)		
<i>Enterococcus faecium</i>	V:R	Eradication	2 (66.7)	0		
		No. Assessed	3 (100.0)	0		
	V:S	Eradication	4 (100.0)	0		
		No. Assessed	4 (100.0)	0		
<i>Staphylococcus aureus</i>	M:R	Eradication	15 (83.3)	9 (75.0)	0.576	-21.6, 38.3
		No. Assessed	18 (100.0)	12 (100.0)		
	M:S	Eradication	25 (78.1)	17 (94.4)	0.131	-34.1, 1.5
		No. Assessed	32 (100.0)	18 (100.0)		
<i>Staphylococcus epidermidis</i>	M:R	Eradication	25 (80.6)	10 (90.9)	0.433	-32.2, 11.7
		No. Assessed	31 (100.0)	11 (100.0)		
	M:S	Eradication	2 (100.0)	1 (50.0)	0.248	-19.3, 100
		No. Assessed	2 (100.0)	2 (100.0)		
<i>Streptococcus pneumoniae</i>	P2:R	Eradication	3 (75.0)	0		
		No. Assessed	4 (100.0)	0		
	P:I	Eradication	1 (100.0)	1 (100.0)		
		No. Assessed	1 (100.0)	1 (100.0)		
<i>Streptococcus pyogenes</i>	All	Eradication	3 (100.0)	1 (33.3)	0.083	13.3, 100
		No. Assessed	3 (100.0)	3 (100.0)		

Antibiotic codes: M=Oxacillin, P=Penicillin, V=Vancomycin
 Susceptibility codes: R=Resistant, I=Intermediate, S=Susceptible
 P2:R= Resistance to penicillin and at least 1 other antibiotic

D. Efficacy Conclusions

Study 0065

This study comparing the use of linezolid with cefadroxil in the treatment of uncomplicated skin and skin structure infections due to *Staphylococcus aureus* and *Streptococcus pyogenes* showed that both drugs were equally effective in the treatment of this condition. Overall, linezolid and cefadroxil had comparable efficacy with regard to clinical and microbiologic cure rates in the ITT, MITT, CE and ME populations. The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10 %,

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the confidence intervals cross zero and the p values are > 0.05 . Analyses done by the sponsor and FDA were comparable. No differences were seen among subgroups of age, gender, race, diagnosis or baseline pathogen. No significant safety concerns were noted during the study.

Study 0082

This study in hospitalized sick children with suspected or proven Gram positive infections showed that no significant differences between the efficacy of linezolid compared to that of vancomycin. However in the FDA analysis using a slightly different definition of patient populations and different outcome definitions there is a trend towards superiority of vancomycin over linezolid. This was noted most markedly in the FDA defined modified intent to treat population. Though the exact significance of this finding is difficult to interpret it is an important finding, as it may be a suggestion that when Gram positive bacterial pathogens are identified vancomycin may have better cure rates than linezolid. In a study specifically for resistant Gram positive infections, the MITT population is a better population in which to assess cure rates rather than the ITT population as patients in the latter group do not necessarily have a Gram positive pathogen as a cause of their illness. In all pediatric indications, other than complicated skin infections, Gram negative pathogens may also be the causative pathogen.

Though the study was designed to enroll children with resistant gram positive infections only about 60% of patients had a pathogen identified and only a small fraction of that had resistant pathogens.

The study enrolled children with a variety of clinical diagnoses like bacteremia, hospital acquired pneumonia, complicated skin and skin structure infections. The severity of illness, prognosis and nature of underlying illnesses will vary significantly in these groups of children. Hence combining them all into one group for overall efficacy analysis makes it difficult to assess efficacy in each individual indication. Additionally, the numbers of patients in each group were quite small and therefore it may be difficult to detect differences between the groups.

No significant safety concerns were noted during the study. However, as the study size was small it is possible that some adverse events may not have been detected during the study. Some effects like myelosuppression may not have been detected since some patients in this study had low values at baseline. Higher death rates in the linezolid arm may be a random finding but merits close supervision once the drug is used more widely in children. These children had major underlying illnesses and hence direct causality with drug could not be ascertained.

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VII. Integrated Review of Safety

A. Brief Statement of Conclusions

In the two phase 3 comparator controlled clinical studies submitted by the sponsor in this supplemental NDA in pediatric patients, no significant adverse events were more common in patients treated with linezolid compared to the comparator drugs. Supportive evidence from the uncontrolled studies also showed no specific areas of concern. In the phase 3 studies, diarrhea, fever, vomiting, headache and skin rash were the most common adverse events reported in patients treated with linezolid. Reduction in hemoglobin, platelet counts, white blood cell counts, and elevation of alanine aminotransferase (ALT) levels were the most common laboratory abnormalities noted in patients treated with linezolid in the phase 3 studies.

However, it is important to note that the dosing regimens and hence the systemic exposure to linezolid varied between studies. Pediatric patients less than 12 years of age were treated with an eight-hourly (q 8h) dosing regimen in only one study (0082). Patients in all other studies received 12-hourly dosing. The recommended frequency of administration in children less than 12 years of age is q 8h except for children ages 5-11 years with uncomplicated skin and skin structure infections. Hence, the frequency of adverse events observed in all clinical studies combined may not truly represent the likelihood of adverse events in pediatric patients at the recommended dosing regimens.

B. Description of Patient Exposure

Phase 1 studies

The majority of patients (71%, 126/177) enrolled in the phase 1 studies received single dose of linezolid 10 mg/kg (up to a maximum of 600 mg). A total of 43 patients received single dose of linezolid 1.5 mg/kg infused over 30 minutes and 8 patients, received five doses of linezolid 10 mg/kg (up to a maximum of 600 mg).

Phase 2 studies

Studies 0045 (Community Acquired Pneumonia) and 0049 (Acute Otitis Media)

In study 0045, IV or oral (suspension) linezolid (10 mg/kg, up to 600 mg) was administered every 12 hours. Patients who received at least 2 doses of IV linezolid could have been switched to oral linezolid if clinically indicated. The mean duration of IV treatment was 4.4 ± 4.1 days and of oral treatment was 8.3 ± 3.0 days; the mean total duration of treatment (IV and oral) was 11.2 ± 6.4 days.

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In study 0049, all patients received oral linezolid 10 mg/kg BID for 7 to 10 days. The mean duration of treatment was 7.5 ± 2.0 days.

Study 0025 (Compassionate use)

Patients ≤ 13 years of age or weighing ≤ 40 kg were administered linezolid 10 mg/kg (maximum of 600 mg) every 12 hours. Patients >13 years of age received 600 mg every 12 hours. Patients were administered IV linezolid, oral tablets or suspension, or IV followed by oral administration. The recommended duration of therapy was 10 to 21 days. However, patients could continue to receive linezolid for up to 3 months. Of the 22 enrolled patients 12 (55%) received linezolid for >21 days. The mean duration of treatment was 35.0 ± 30.7 days.

Study 0065 (Uncomplicated Skin and Skin Structure Infections)

Patients were randomized in a 1:1 ratio to receive one of the following treatments for 10-21 days:

Linezolid: Suspension 10 mg/kg up to 600 mg/dose BID (children aged 5-11 years) or tablets 600 mg BID (children aged 12-17 years).

Cefadroxil: Suspension 15 mg/kg up to 500 mg/dose BID (children aged 5-11 years) or capsules 500 mg BID (children aged 12-17 years).

The mean number of doses taken was 22.3 in the linezolid group and 22.1 in the cefadroxil group. Treatment duration is summarized in the following table (Sponsor table 9, page 28 ISS).

Table 1.Sponsor: Treatment duration

	Linezolid	Cefadroxil
	Days of treatment	
Total Reported	248	251
Mean \pm SD	12.0 ± 3.6	11.9 ± 3.9
Median	11.0	11.0
Number of doses		
Total Reported	248	251
Mean \pm SD	22.3 ± 7.2	22.1 ± 7.5
Median	20.0	20.0

Study 0082 (Suspected or Proven Resistant Gram positive Infections)

Hospitalized pediatric patients and those in chronic care facilities were eligible for treatment if they had known or suspected infections due to resistant Gram-positive bacteria, including hospital-acquired pneumonia (HAP), complicated skin and skin structure infections (cSSSI), catheter-related bacteremia, bacteremia of

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unidentified source, and other infections. Patients with endocarditis, CNS infections, and skeletal infections including osteomyelitis/septic arthritis were excluded. Patients were randomized in a 2:1 ratio (linezolid:vancomycin) to receive one of the following treatments for 10 to 28 days.

Linezolid: 10 mg/kg every 8 hours IV, optional switch to oral suspension (10 mg/kg TID); maximum IV/oral dose was 600 mg per dose.

Vancomycin: 10-15 mg/kg every 6-24 hours, per accepted dosing guidelines followed by optional switch to oral antibiotics based on pathogen susceptibility.

All patients were to receive at least 3 days (minimum of 6 doses) of IV therapy, following which patients ≥ 91 days of age could be switched to oral medication at the discretion of the investigator.

A larger number of ITT patients in the linezolid group (53%, 114/215) received oral treatment compared to the vancomycin group (31.0%, 31/100). Duration of treatment was generally longer for the vancomycin group than the linezolid group for both IV and oral dosing. The vancomycin group on average was treated for approximately 1 more day (mean duration 11.3 ± 5.0 days versus 12.2 ± 6.4 days) and received approximately 1 more dose (mean number of doses 30.3 ± 14.7 versus 31.5 ± 17.2) compared to the linezolid group.

The following table (Sponsor table 10, page 30 ISS). summarizes the treatment duration and number of doses received in both treatment groups:

Table 2. Sponsor: Duration of treatment and number of doses

	Linezolid N = 215			Vancomycin N = 101		
	IV	Oral	Overall	IV	Oral	Overall
	Days of treatment					
Total Reported	215	114	214	100	31	100
Mean \pm SD	7.7 ± 4.8	7.8 ± 3.0	11.3 ± 5.0	9.8 ± 6.2	8.8 ± 4.1	12.2 ± 6.4
Median	6.0	7.5	11.0	10.0	8.0	11.0
	Number of doses					
Total Reported	215	114	215	100	31	100
Mean \pm SD	19.6 ± 14.0	20.0 ± 9.5	30.3 ± 14.7	25.0 ± 16.8	21.0 ± 10.5	31.5 ± 17.2
Median	15.0	19.0	30.0	24.5	19.0	30.0

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C. Methods and Specific Findings of Safety Review

Data is excerpted from the sponsor's final study reports and the integrated summary of safety (ISS). Adverse events (AEs) for studies in all three phases are discussed separately. Data for the two phase 2 studies (0045 and 0049) will be combined and additionally combined safety results for all three studies using a BID dosing regimen (studies 0045, 0049 and 0065) will be presented. For each study, premature discontinuations, study emergent AE, drug related AE, serious adverse events (SAE) and deaths are discussed. This is followed by a discussion of laboratory abnormalities for two phase 2 studies (0045 and 0049) and the two phase 3 studies. For study 0025 only adverse events reported as serious and deaths will be discussed. Laboratory values for study 0025 will not be discussed.

Additional FDA analyses for laboratory parameters will be presented in the section on laboratory values. Overview of the sponsor's methods used to assess safety in phase 2 and phase 3 studies is discussed below.

ADVERSE EVENTS

All AEs that occurred between the first dose of study medication and the follow-up visit were to be recorded in the case report form (CRF) and reported to P&U. Any reaction, injury, or other untoward medical occurrence that occurred during the reporting period, whether or not the event was considered drug-related, was to be reported as an AE. In addition, any known untoward event occurring after the reporting period that the investigator assessed as possibly related to the study medication was to be reported as an AE. Abnormalities in physiological testing or physical examination findings were to be recorded as AEs if they required clinical intervention or further investigation (beyond a confirmatory test). These criteria also applied to abnormal laboratory test results not associated with a clinical event already reported.

The investigator was to report all directly observed AEs and all AEs spontaneously reported by the patient/parent using concise medical terminology. In addition, the parents/legal guardians of each patient were to be questioned about AEs at each clinic visit following the initiation of treatment. Investigators were required to record the date of onset and cessation of the event, the maximum intensity (mild, moderate, or severe) of the event, the action taken with the study medication because of the event (none, drug temporarily or permanently withdrawn), and the outcome of the event (recovered, recovered with sequelae, death, unknown, not recovered). In addition, the investigator was to classify the event as serious or nonserious and to judge whether or not the adverse event was related to study medication.

A SAE was one that was fatal or life-threatening (i.e., resulted in an immediate risk of death); required or prolonged hospitalization; produced persistent or

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significant disability/incapacity; was a congenital anomaly/birth defect; or could have jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed above, based on appropriate medical judgment. This category also included any other event the investigator or sponsor judged to be serious, or any event defined as serious by the regulatory agency in the country in which the AE occurred. If an AE was serious, expedited and supplemental reporting was required.

All AEs were to be followed until they resolved, the investigator assessed them as chronic or stable, or the patient's participation in the study ended (i.e., until a final report was completed for that patient). In addition, all SAEs and those non serious events assessed by the investigator as possibly related to the study medication were to be followed, even after the patient's participation in the study was over, until they resolved or the investigator assessed them as "chronic" or "stable."

Data Safety Monitoring Committees (DSMC) were established to review the safety information collected in Studies 0065 and 0082. The DSMC met once during each study and no safety issues were identified.

LABORATORY PARAMETERS

Laboratory assays (hematology and chemistry) for all sites were to be performed by a local or central laboratory. All blood samples, collected at times specified in the study protocols in accordance with accepted laboratory procedures, were obtained for the following tests:

Hematology

Complete blood count (CBC) with differential and platelet counts in all four studies; reticulocyte count in studies 0045, 0049, and 0082

Chemistry

Studies 0045 and 0049: aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase, amylase, bilirubin, blood urea nitrogen (BUN), calcium, creatinine, creatine phosphokinase, sodium, potassium, bicarbonate, chloride, glucose, gamma glutamyl transferase (GGT), lactic dehydrogenase (LDH), lipase, total protein, and uric acid

Study 0065: AST, ALT, GGT, BUN, creatinine, and lipase

Study 0082: total bilirubin, ALT, creatinine, electrolytes (sodium, potassium, chloride, and bicarbonate) in all patients and amylase, transferrin, and serum iron in children ≥ 91 days old

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Any laboratory evaluation that was flagged by the laboratory at the follow-up visit and was classified as "panic (high or low) abnormal" was to be repeated by the investigator until the assay results returned to "within normal limits."

Frequency tables for substantially abnormal values for selected hematology and chemistry assays are presented for the 2 Phase 3 studies and the 2 Phase 2 studies. In addition, a summary of laboratory shifts by toxicity grade is presented for selected laboratory assays for each of the 2 Phase 3 studies. See Appendix 3 for definition of substantially abnormal values and Appendix 4 for the pediatric AIDS Clinical Trial Group (ACTG) criteria for shifts in laboratory values.

Phase 1 Studies

Adverse Events

Frequencies of adverse events were similar in the two single-dose groups and higher in the multiple-dose group.

Overall, 13% (23/177) of the patients experienced an adverse event. Adverse events that occurred in > 1% were injection/vascular catheter site pain/reaction (4%, 7/177), rash (2.3%, 4/177), nausea (1.1%, 2/177), vomiting (1.1%, 2/177), and hypokalemia (1.1%, 2/177).

In the single-dose (1.5 mg/kg) group, 9.3% (4/43) of patients experienced one or more AEs including rash (4.7%, 2/43), disorder tongue (2.3%, 1/43), and injection/vascular catheter site inflammation (2.3%, 1/43).

In the single-dose (10 mg/kg) group, 11.9% (15/126) experienced one or more AEs including injection/vascular catheter site pain/reaction (4.7%, 6/126), nausea (1.6%, 2/126), and hypokalemia (1.6%, 2/126).

In the multiple-dose (10 mg/kg) group, 4/8 patients experienced one or more AEs. These included fatigue, edema (generalized and local), ventricular bigeminy, ventricular extrasystoles, vasodilatation, vomiting, hemiplegia, pleural effusion, pneumothorax, and hydronephrosis; none were reported for more than one patient. Five of the 11 events, including fatigue, ventricular bigeminy, ventricular extrasystoles, vasodilatation, and hemiplegia, were reported in 1 patient in study 0059 who had a history of congenital heart defect, bigeminy, and hydrocephalus at baseline.

The following table (Sponsor table 3, page 16 ISS) provides the overall summary of adverse events by linezolid dose group.

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Table 3. Sponsor: Study emergent adverse events

	All doses N=177 n (%)	Single Dose 1.5 mg/kg N=43 n (%)	Single Dose 10 mg/kg N=126 n (%)	Multiple Dose 10 mg/kg N=8 n (%)
Patients with ≥ 1 AE	23 (13.0)	4 (9.3)	15 (11.9)	4 (50.0)
Patients with ≥ 1 drug-related AE	14 (7.9)	3 (7.0)	10 (7.9)	1 (12.5)
Patients with ≥ 1 serious AE	2 (1.1)	0	1 (0.8)	1 (12.5)
Patients ≥ 1 AE leading to D/C	1 (0.6)	0	1 (0.8)	0

Drug related adverse events

A total of 7.9% (14/177) of patients experienced one or more AEs that were considered drug-related. The frequency of drug-related AEs was 7.0% (3/43) in the single-dose (1.5 mg/kg) group, 7.9% (10/126) in the single-dose (10 mg/kg) group, and 12.5% (1/8) in the multiple-dose (10 mg/kg) group.

Serious Adverse Events

Two SAEs were reported and neither was considered related to study medication. One (bone pain localized) occurred in the single-dose (10 mg/kg) group, and the other (pneumothorax) occurred in the multiple-dose (10 mg/kg) group. The first SAE occurred in a 3.4 year-old with septic arthritis who developed bone pain in the opposite hip 7 hours after completion of linezolid infusion. The second SAE was a pneumothorax that developed during insertion of the distal portion of a CNS shunt in the pleural space.

Deaths

No deaths were reported in any of the phase I studies.

AE leading to discontinuation

One patient discontinued treatment due to an injection/vascular catheter site reaction. The investigator recorded the intensity of this adverse event as mild. This patient was less than 1 year of age.

Comments

Majority of the injection site reactions/pain occurred in patients receiving a single 10 mg/kg dose and did not occur in any patient receiving multiple dose regimen. Very few patients received the multiple dose regimen and hence this adverse event may not have been noted during the study. Cardiac adverse events were seen in the multiple dose regimen, but as they occurred in one patient with known cardiac morbidity, causality is difficult to ascertain.

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Phase 2 studies

0045 and 0049 combined

Premature discontinuations

A total of 143 patients received at least one dose of linezolid. A slightly greater percentage of patients completed the scheduled treatment in study 0049 (86.2%, 56/65) than in study 0045 (84.6%, 66/78). Discontinuations from treatment were primarily due to AEs in study 0045 and due to lack of efficacy in study 0049.

The following table (Sponsor table 19, page 28 ISS) presents the primary reasons patients discontinued treatment in these two studies.

Table 4. Sponsor: Reasons for discontinuation

Reasons for Discontinuation	Linezolid N = 143 n (%)
Total discontinued	21 (14.7)
Adverse events	5 (3.5)
Ineligible, but started study medication	5 (3.5)
Lack of efficacy	4 (2.8)
Patient's personal request	4 (2.8)
Other (not specified)	3 (2.1)

Comments

Discontinuation due to AE was only seen in study 0045 (community acquired pneumonia) where patients are more likely to be sicker than in study 0049 (otitis media).

Adverse events

Overall, 56% (80/143) of patients experienced one or more AEs. The most common AEs (incidence $\geq 5\%$) were diarrhea (16.8%), vomiting (11.9%), rash (9.8%), and loose stools not elsewhere classified (NEC) (5.6%).

AEs that occurred in $\geq 2\%$ of patients are presented in the following table (Sponsor table 27, page 47 ISS).

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Table 5. Sponsor: Study emergent adverse events that occurred in $\geq 2\%$ of patients

COSTART Body System Classification Adverse Event (MET*)	Linezolid N=143 n (%) [†]
Total Patients Reported	143
Patients with ≥ 1 AE	80 (55.9)
Body	15 (10.5)
Fever	6 (4.2)
Trauma	5 (3.5)
Upper respiratory infection	4 (2.8)
Digestive	52 (36.4)
Diarrhea	24 (16.8)
Vomiting	17 (11.9)
Loose stools (NEC)	8 (5.6)
Constipation	3 (2.1)
Hemic and Lymphatic	3 (2.1)
Neutropenia	3 (2.1)
Respiratory	19 (13.3)
Rhinitis	7 (4.9)
Cough	5 (3.5)
Pharyngitis	4 (2.8)
Pneumonia	3 (2.1)
Skin	17 (11.9)
Rash	14 (9.8)
Pruritus non-application site	3 (2.1)

MET= Medical Equivalent Term

[†]All percentages are based on the number of patients reported

Comments: *Diarrhea and vomiting were the most common adverse events noted. It is noteworthy that three patients developed neutropenia, one patient had thrombocytopenia and none had anemia. (Source: Section 14, table 7.3 final study report 0045)*

Drug related adverse events

Overall, 20.3% (29/143) of the patients experienced one or more AEs that were considered related to linezolid. The most common AE was diarrhea/loose stools, which was experienced by 12.6% (18/143) of patients.

In all three patients with neutropenia the AE was considered drug related. Two patients developed neutropenia on day 4 of the study and the third patient developed neutropenia after 9 days of linezolid therapy. Neutropenia resolved in all three patients.

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The frequencies of drug-related AEs that occurred in >1% of patients are presented in the following table (Sponsor table 35, page 62 ISS).

Table 6. Sponsor: Drug-related AEs that occurred in >1% of patients

COSTART Body System Classification Adverse Event (MET)	Linezolid N = 143 n (%)
Total Patients	143
Patients with ≥ 1 drug-related AE	29 (20.3)
Digestive	
Diarrhea	13 (9.1)
Loose Stools (NEC)	5 (3.5)
Vomiting	6 (4.2)
Hemic and Lymphatic	
Neutropenia	3 (2.1)
Skin	
Rash	4 (2.8)

[†]All percentages are based on the number of patients reported

Adverse events leading to treatment discontinuation

No patients in study 0049 discontinued study medication as the result of an AE. In study 0045 seven separate adverse events reported by five patients led to discontinuation of study medication. These were abdominal pain, sepsis, diarrhea, vomiting, neutropenia, rash and otitis media. AEs for four of these patients were considered related to the study medication. All of the events were rated as mild or moderate, except for neutropenia, which was rated as severe.

Serious Adverse Events

One patient in study 0049 developed an SAE of bronchiolitis. Four patients in study 0045 experienced an SAE: one patient each with vomiting, neutropenia, seizures and pneumothorax. The SAE of neutropenia was considered to be drug-related. A one-year old child with CAP developed severe neutropenia (absolute neutrophil count, $1.06 \times 10^3/\mu\text{L}$) after 3 days of treatment. Linezolid was discontinued the following day and the event resolved 11 days later (absolute neutrophil count, $2.73 \times 10^3/\mu\text{L}$). Concomitant medications consisted of ceftriaxone, albuterol, acetaminophen and ibuprofen. The SAE of seizures occurred in a 1-year old child one day after completing a 9-day course of linezolid. The seizure was thought to be either a febrile seizure or a dystonic reaction due to hydroxyzine.

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DEATHS

There were no deaths in either of these studies.

Study 0025 (Compassionate use)

Premature discontinuations

Of the 22 patients, 11 (50%) completed their planned course of linezolid therapy and 11 (50%) discontinued prior to completing their planned course of therapy. The following table (Sponsor table 20, page 39 ISS) presents the primary reasons patients discontinued treatment in the compassionate use study.

Table 7. Sponsor: Premature discontinuations

Reasons for Discontinuation	Linezolid N = 22 n (%)
Total discontinued	11 (50.0)
Death	6 (27.3)
Adverse event(s)	4 (18.2)
Other	1 (4.5)

Comments

The higher percentage of patients in study 0025 who discontinued treatment is most likely a reflection of the sicker population enrolled in this study.

Adverse events

In this study only data on SAEs were collected and therefore discussion on AEs pertain only to SAEs.

Serious adverse events

Of the 22 patients, 15 (68.2%) experienced one or more SAEs. Sepsis, reported by 3 patients, was the most common SAE, followed by anemia, intestinal perforation, and multiple organ failure, each reported by 2 patients. The other SAEs, each reported by 1 patient, included cholelithiasis, disorder auditory, fever, injection/vascular catheter site infection, lactic acidosis, marrow depression, pain kidney, pancreatitis, pneumothorax, septic shock, thrombocytopenia, trauma, and urolithiasis.

Drug related adverse events

Four (18.2%) patients experienced SAEs that were thought to be related to linezolid. In the 10 mg/kg BID group, 1 patient developed thrombocytopenia on study day 3 and was discontinued from the study and 1 patient developed anemia on study day 54 and no action was taken with linezolid. Both patients recovered from the AEs, with no residual effects. In the 600 mg BID group, 1 patient developed anemia on study day 43 that was continuing at the last contact and 1 patient developed bone marrow depression on study day 41 from which the

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patient recovered, with no residual effects. Both patients were discontinued from the study due to the drug-related AEs.

Adverse Events leading to treatment discontinuation

0025

Five (22.7%) of the 22 patients discontinued linezolid due to a SAE. In 3 patients, the SAE was considered to be drug-related (thrombocytopenia, anemia, and bone marrow depression in 1 patient each) and in 2 patients, the SAE was considered not related to linezolid but rather to the patient's underlying condition (worsening VRE sepsis and lactic acidosis in 1 patient each). Three of the 5 patients recovered from the SAE, 1 patient died (sepsis), and in 1 patient the SAE (anemia) was continuing at time of last contact.

Deaths

Six of the 22 patients (27.3%) enrolled died during the treatment period. Three patients died of sepsis or septic shock and 1 patient each died of cardiac arrest, acute lymphoblastic leukemia, and multiple organ failure. All deaths were considered to be unrelated to study drug. The only cardiac cause of death was cardiac arrest in a 17-year-old (2500250) with toxic epidermal necrolysis, VRE bacteremia, and multi-organ failure who died due to overwhelming sepsis. The following table (Sponsor table 45, page 79 ISS) summarizes the deaths in this study.

Table 8. Sponsor: Cause of death

Age (yrs)/ Sex	Days on Treatment	Cause of Death
5/M	7	Septic shock
12/F	3	Sepsis
5/F	1	Septic shock
17/M	4	Cardiac arrest (NEC)
14/M	12	Acute lymphoblastic leukemia
17/M	16	Multiple organ failure

Comments

This study provides only limited information, as it was uncontrolled, all patients enrolled were very sick and only data on SAE were obtained. Overall, hematologic adverse events were the most common (4 patients). All 4 hematologic adverse events were thought to be drug related and three of them occurred in patients receiving linezolid for > 28 days. The incidence of hematologic toxicity was higher in this group of patients. It is possible that this reflects the severity of underlying illnesses in these patients, or may be related to the prolonged linezolid therapy or it may be possible that sicker patients are more predisposed to the hematologic toxicity of linezolid.

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Phase 3 studies

Study 0065

Premature discontinuations

Of the 508 patients randomized nine were withdrawn from the study before receiving study medication. Thus, a total of 499 patients (248 linezolid, 251 cefadroxil) received study medication and were included in the ITT population. Of these, 232 (93.5%) in the linezolid group and 229 (91.2%) in the cefadroxil group completed the study. The reasons for study discontinuation were similar between the treatment groups.

The following table lists the primary reasons for patient discontinuation from the study. (Sponsor table 17, page 37 ISS).

Table 9. Sponsor: Reasons for Discontinuation

Reasons for Discontinuation	Treatment Group	
	Linezolid N = 248 N (%)	Cefadroxil N = 251 N (%)
Discontinued Patients	16 (6.5)	22 (8.8)
Lost to follow-up	5 (2.0)	8 (3.2)
Adverse event	3 (1.2)	4 (1.6)
Protocol specific withdrawal criteria	3 (1.2)	3 (1.2)
Protocol violation	3 (1.2)	2 (0.8)
Progression of disease	1 (0.4)	2 (0.8)
Withdrawn consent	1 (0.4)	2 (0.8)
Lack of efficacy	0	1 (0.4)

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Overall Adverse Events

No statistically significant differences were observed between treatment groups in the percentages of patients with any AEs, drug-related AEs, SAEs, or discontinuations due to AEs. The number reported is the number of patients in whom the case report forms document that they either had or did not have adverse events. So, adverse event data for three patients in the linezolid arm and two in the cefadroxil arm are missing.

The following table (Sponsor table 21, page 40 ISS) summarizes results for overall categories of AEs.

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Table 10. Sponsor: Summary of adverse events

Adverse Event Category	Treatment Group		P value†
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)*	
Total Patients Reported	245	249	
Patients with ≥1 AE	111 (45.3)	117 (47.0)	0.7077
Patients with ≥1 drug-related AE	47 (19.2)	35 (14.1)	0.1257
Patients with ≥1 AE leading to D/C	5 (2.0)	9 (3.6)	0.2920
Patients with ≥1 drug-related AE leading to D/C	4 (1.6)	6 (2.4)	0.5398
Patients with ≥1 serious AE	2 (0.8)	4 (1.6)	0.4228

*All percentages are based on number of patients reported

†P values is based on a chi-square test

Study emergent adverse events

The most frequently reported (incidence $\geq 5\%$) AEs in the linezolid group were diarrhea (7.8%) and headache (6.5%) and in the cefadroxil group were diarrhea (8.0%), vomiting (6.4%), and upper respiratory infection (5.2%). Overall, study-emergent AEs were similar in the two groups. Skin disorders not elsewhere classified (NEC) were reported more commonly in the linezolid group and rhinitis in the cefadroxil group. Disorder skin NEC included blister right thumb, induration of skin on neck, lesion right buttock, papule (L) buttock, and recurrence of vesicular lesion.

The following table (Sponsor table 24, page 42 ISS) displays the frequencies of AEs reported in $\geq 2\%$ of patients in either treatment group.

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Table 11. Sponsor: Study emergent adverse events reported by $\geq 2\%$ of patients in either treatment arm

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P value†
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)	
Total Patients Reported	245	249	
Patients with ≥ 1 AE	111 (45.3)	117 (47.0)	0.7077
Body			
Headache	16 (6.5)	10 (4.0)	0.2108
Upper respiratory infection	9 (3.7)	13 (5.2)	0.4045
Trauma	8 (3.3)	12 (4.8)	0.3809
Fever	7 (2.9)	9 (3.6)	0.6345
Abdominal pain generalized	6 (2.4)	7 (2.8)	0.8014
Abdominal pain localized	6 (2.4)	7 (2.8)	0.8014
Localized pain	5 (2.0)	4 (1.6)	0.7181
Digestive			
Diarrhea	19 (7.8)	20 (8.0)	0.9091
Nausea	9 (3.7)	8 (3.2)	0.7789
Vomiting	7 (2.9)	16 (6.4)	0.0598
Respiratory			
Pharyngitis	7 (2.9)	4 (1.6)	0.3462
Cough	6 (2.4)	10 (4.0)	0.3253
Rhinitis	2 (0.8)	10 (4.0)	0.0209
Skin			
Disorder skin (NEC)	5 (2.0)	0	0.0235

*All percentages are based on number of patients reported

†P values is based on a chi-square test

Comments

No significant differences in the frequencies of adverse events were noted between the two groups. One patient in the linezolid arm reported neutropenia and one patient in cefadroxil arm reported leukopenia (Source: ISS Section 14, table 7.2). These were not included in the table as the frequency was less than 2%. There were no reports of thrombocytopenia in either treatment arm.

Adverse events by age

Among patients treated with linezolid, 41.7% (60/144) of patients aged 5 to 11 years and 50.5% (51/101) of patients aged 12 to 17 years reported one or more study-emergent AEs. No statistically significant differences were observed between treatment groups in either age subgroup in the overall incidence of AEs.

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Rhinitis and vomiting were more common in the linezolid group among patients aged 5 to 11 years.

Drug related adverse events

The most frequently reported drug-related AE was diarrhea. There were no statistically significant differences between the groups in the incidence of any drug-related AE.

The following table (Sponsor table 32, page 59 ISS) displays the frequencies of drug-related AEs reported by >1% of patients in either treatment group.

Table 12. Sponsor: Drug-related adverse events reported by >1% of patients in either treatment group.

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P value†
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)	
Total patients reported	245	249	
Patients with ≥1 drug-related AE	47 (19.2)	35 (14.1)	0.1257
Body			
Headache	6 (2.4)	2 (0.8)	0.1474
Abdominal pain generalized	4 (1.6)	3 (1.2)	0.6875
Abdominal pain localized	4 (1.6)	3 (1.2)	0.6875
Digestive			
Diarrhea	14 (5.7)	13 (5.2)	0.8094
Nausea	8 (3.3)	5 (2.0)	0.3828
Vomiting	3 (1.2)	6 (2.4)	0.3247
Loose stools (NEC)	3 (1.2)	2 (0.8)	0.6400
Nervous			
Vertigo	3 (1.2)	1 (0.4)	0.3076
Skin			
Rash	1 (0.4)	3 (1.2)	0.3232

*All percentages are based on number of patients reported

†P values is based on a chi-square test

Comments: *No significant differences in the frequencies of drug related adverse events were noted between the two groups, though the incidence was slightly higher in the linezolid arm. Leukopenia and neutropenia seen in one patient in each arm were thought to be drug related.*

Adverse events leading to discontinuation of treatment

In the linezolid arm, 2.0% (5/245) of patients discontinued study medication due to an adverse event compared to 3.6% (9/249) in the cefadroxil arm. Adverse

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events that led to the discontinuation were generally considered moderate or severe. There were no statistically significant differences between the groups in frequencies of events leading to discontinuation.

The following table (Sponsor table 37, page 64 ISS). (Table 37) shows the frequencies of AEs that resulted in discontinuation of study medication.

Table 13. Sponsor: Adverse events that resulted in discontinuation of study medication.

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P value†
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)	
Total Patients Reported	245	249	
Patients with ≥1 AE leading to D/C	5 (2.0)	9 (3.6)	0.2920
Body			
Abdominal pain localized	1 (0.4)	0	0.3129
Headache	1 (0.4)	0	0.3129
Abscess	0	1 (0.4)	0.3207
Cellulitis	0	1 (0.4)	0.3207
Infection (NEC)	0	1 (0.4)	0.3207
Digestive			
Diarrhea	1 (0.4)	3 (1.2)	0.3232
Nausea	0	1 (0.4)	0.3207
Vomiting	0	1 (0.4)	0.3207
Hemic and Lymphatic			
Adenopathy	1 (0.4)	0	0
Metabolic and Nutritional			
Lipase high	1 (0.4)	0	0.3129
Skin			
Rash	1 (0.4)	2 (0.8)	0.5720
Pruritus non-application site	1 (0.4)	0	0.3129
Rash maculopapular	0	1 (0.4)	0.3207

*All percentages are based on number of patients reported

†P values is based on a chi-square test

Comments: Most adverse events that lead to discontinuation were not severe. No significant hematologic toxicity lead to study drug discontinuation.

Serious adverse events

SAEs were reported in 0.8% (2/245) of patients in the linezolid group and in

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1.6% (4/249) of patients in the cefadroxil group. There were no statistically significant differences between the groups in the frequencies of SAEs. All patients recovered from their SAEs. The following is a brief description of the two patients in the linezolid arm who developed SAEs.

- A 9.6-year-old female (6500436) with impetigo of the upper lip had an elevated lipase value (7390 IU/L) on day 8 of the study. The only other concomitant medications were multivitamins. A follow-up lipase level repeated within 3 days was within normal limits (26 IU/L). The AE was considered drug related by the investigator and the drug was permanently withdrawn.
- A 12.7-year-old female (6500601) with superficial impetigo developed diabetic ketoacidosis almost a month after stopping study medication. She was a known diabetic when the event occurred.

The following table (Sponsor table 41, page 70 ISS) shows the frequencies of all SAEs.

Table 14. Sponsor: Frequencies of all serious adverse events

COSTART Body System Classification Adverse Event (MET)	Treatment Group	
	Linezolid N = 248 n (%)	Cefadroxil N = 251 n (%)*
Total Patients Reported	245	249
Patients with ≥1 SAE	2 (0.8)	4 (1.6)
Body		
Abscess	0	1 (0.4)
Cellulitis	0	1 (0.4)
Infection (NEC)	0	1 (0.4)
Metabolic and Nutritional		
Diabetic acidosis	1 (0.4)	0
Lipase high	1 (0.4)	0
Nervous		
Hostility	0	1 (0.4)

*All percentages are based on number of patients reported

Deaths

No patients died during this study.

Study 0082

Premature Discontinuations

Of the 321 patients randomized, five were withdrawn from the study before receiving study medication. Thus, a total of 316 patients (215 linezolid, 101 vancomycin) received study medication and were included in the ITT population.

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Of these, 168 (78.1%) in the linezolid group and 76 (75.2%) in the vancomycin group completed the study. Reasons for discontinuing were similar in both treatment groups, except that a higher percentage of patients were lost to follow-up in the vancomycin group compared to the linezolid group (9.9% versus 3.3%).

The following table lists the primary reasons assigned by investigators for patient discontinuation from the study (Sponsor table 18, page 38 ISS). (table 18)

Table 15. Sponsor: Reasons for Discontinuation

Reasons for Discontinuation	Treatment Group	
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)
Discontinued Patients	47 (21.9)	25 (24.8)
Adverse event	16 (7.4)	7 (6.9)
Protocol violation	2 (0.9)	3 (3.0)
Withdrawn consent	4 (1.9)	0
Lost to follow-up	7 (3.3)	10 (9.9)
Protocol-specific withdrawal criteria	13 (6.0)	4 (4.0)
Lack of efficacy	2 (0.9)	1 (1.0)
Progression of disease	3 (1.4)	0

ADVERSE EVENTS

Overview

No significant differences were observed between treatment groups in the percentages of patients with any AEs. Drug-related AEs were reported more frequently in the vancomycin group than in the linezolid group. The number reported is the number of patients in whom the case report forms document that they either had or did not have adverse events. So, adverse event data for two patients in each arm are missing

The following table (Sponsor table 22, page 40 ISS) summarizes results for overall categories of AEs.

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Table 16. Sponsor: Summary of adverse events

Adverse Event Category	Treatment Group		P value†
	Linezolid N = 215 n (%)*	Vancomycin N = 101 n (%)*	
Total Patients Reported	213	99	
Patients with ≥1 AE	155 (72.8)	78 (78.8)	0.2552
Patients with ≥1 drug-related AE	40 (18.8)	34 (34.3)	0.0026
Patients with ≥1 AE leading to D/C	15 (7.0)	7 (7.1)	0.9927
Patients with ≥1 drug-related AE leading to d/c	2 (0.9)	6 (6.1)	0.0077
Patients with ≥1 serious AE	42 (19.7)	16 (16.2)	0.4523

*All percentages are based on number of patients reported

†P values is based on a chi-square test

Study emergent adverse events

The most frequently reported AEs in the linezolid group (incidence ≥5%) were fever (14.1%), diarrhea (10.8%), vomiting (9.4%), sepsis (8%), anemia (5.6%), and rash (7%). In the vancomycin group they were rash (15.2%), fever (14.1%), diarrhea (12.1%), anaphylaxis (10.1%), vomiting (9.1%), sepsis (7.1%), oral moniliasis (7.1%), and anemia (7.1%).

Overall, study-emergent AEs were similar in the two groups. Rash and anaphylaxis were significantly more common in the vancomycin group. All reported events coded to the COSTART term "anaphylaxis" were described by investigators as "red man syndrome." Other adverse events for which statistically significant differences between groups in frequency were observed included several events reported for 2% to 3% of the vancomycin group but not reported for the linezolid group. Thrombocytopenia was reported more frequently in the linezolid group but the difference was not statistically significant.

The following two tables (Sponsor table 25, pages 43, 44 ISS) displays frequencies of AEs reported by ≥2% of patients in either treatment group.

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Table 17 A. Sponsor: Study emergent AEs reported by $\geq 2\%$ of patients in either treatment group

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P value†
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	
Total Patients Reported	213	99	
Patients with ≥ 1 AE	155 (72.8)	78 (78.8)	0.2552
Body			
Fever	30 (14.1)	14 (14.1)	0.9893
Sepsis	17 (8.0)	7 (7.1)	0.7788
Upper respiratory infection	9 (4.2)	1 (1.0)	0.1334
Injection/vascular catheter site reaction	7 (3.3)	5 (5.1)	0.4508
Trauma	6 (2.8)	2 (2.0)	0.6786
Generalized edema	5 (2.3)	1 (1.0)	0.4234
Laboratory test abnormality other	2 (0.9)	4 (4.0)	0.0634
Infection parasitic (NOS)	2 (0.9)	3 (3.0)	0.1709
Reaction unevaluable#	2 (0.9)	3 (3.0)	0.1709
Abdominal pain generalized	2 (0.9)	2 (2.0)	0.4295
Infection viral (NOS)	2 (0.9)	2 (2.0)	0.4295
Anaphylaxis	0	10 (10.1)	<0.0001
Generalized pain	0	2 (2.0)	0.0374
Radiological imaging test abnormal (NOS)	0	2 (2.0)	0.0374
Cardiovascular			
Hypertension	4 (1.9)	2 (2.0)	0.9321
Tachycardia	0	3 (3.0)	0.0107
Patent ductus arteriosus	0	2 (2.0)	0.0374
Digestive			
Diarrhea	23 (10.8)	12 (12.1)	0.7303
Vomiting	20 (9.4)	9 (9.1)	0.9326
Gastrointestinal bleeding	5 (2.3)	1 (1.0)	0.4234
Loose stools (NEC)	5 (2.3)	3 (3.0)	0.7225
Monilia oral	3 (1.4)	7 (7.1)	0.0082
Disorder gastrointestinal (NOS)	1 (0.5)	3 (3.0)	0.0613

*All percentages are based on number of patients reported

† p value is based on a chi-square test

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Table 17 B. Sponsor: Study emergent AEs reported by $\geq 2\%$ of patients in either treatment group

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P value†
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	
Hemic and Lymphatic			
Anemia	12 (5.6)	7 (7.1)	0.6213
Thrombocytopenia	10 (4.7)	2 (2.0)	0.2529
Thrombocythemia	6 (2.8)	2 (2.0)	0.6786
Anemia iron deficiency	0	2 (2.0)	0.0374
Leukocytosis	0	2 (2.0)	0.0374
Metabolic and Nutritional			
Hypokalemia	6 (2.8)	3 (3.0)	0.9165
Hyperglycemia	3 (1.4)	2 (2.0)	0.6888
SGPT increased	1 (0.5)	2 (2.0)	0.1914
Nervous			
Convulsion	6 (2.8)	2 (2.0)	0.6786
Respiratory			
Dyspnea	7 (3.3)	1 (1.0)	0.2364
Pneumonia	6 (2.8)	2 (2.0)	0.6786
Apnea	5 (2.3)	2 (2.0)	0.8559
Respiratory failure	4 (1.9)	2 (2.0)	0.9321
Rhinitis	4 (1.9)	2 (2.0)	0.9321
Hyperventilation	0	3 (3.0)	0.0107
Skin			
Rash	15 (7.0)	15 (15.2)	0.0237
Moniliasis skin	3 (1.4)	2 (2.0)	0.6888
Pruritus non-application site	3 (1.4)	2 (2.0)	0.6888
Dermatitis	1 (0.5)	3 (3.0)	0.0613
Skin infection	1 (0.5)	3 (3.0)	0.0613
Skin erosion (NEC)	0	2 (2.0)	0.0374
Urogenital			
Infection urinary tract	3 (1.4)	2 (2.0)	0.6888

*All percentages are based on number of patients reported

† p value is based on a chi square test

Comments

The high incidence of adverse events in this study is not unexpected as most patients enrolled in this study had significant underlying illnesses and hence were often severely ill. Overall, the frequency of adverse events was similar between the two groups. Red man syndrome is a known adverse event of vancomycin and

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hence the higher incidence of anaphylaxis and/ or skin rash in this group is not surprising. Of the hematologic parameters, thrombocytopenia was more common in the linezolid arm although the difference was not statistically significant. There are two reports each of neutropenia, leukopenia and pancytopenia in the linezolid arm and none in the vancomycin arm. These were not listed in the table as the frequency was less than 2% (Source: Section 11, table 7.2)

Adverse events by age

Among patients treated with linezolid, 76.7% (33/43) of patients aged 0 to 90 days, 88.2% (30/34) of patients aged 91 days to <1 year, 70.9% (61/86) of patients aged 1 to 4 years, and 62% (31/50) of patients aged 5 to 11 years reported one or more study-emergent AEs. In the vancomycin group, 73.7% (14/19) of patients aged 0 to 90 days, 87.5% (14/16) of patients aged 91 days to <1 year, 76.2% (32/42) of patients aged 1 to 4 years, and 81.8 % (18/22) of patients aged 5 to 11 years reported one or more study-emergent AEs. No specific adverse events were more common in any one particular age group.

Among patients 0 to 90 days old, statistically significant differences were observed between treatment groups in the incidence of oral monilia, laboratory test abnormality other, tachycardia, patent ductus arteriosus, rash, and skin erosion NEC, each of which was reported in vancomycin patients and no linezolid patients (p 0.04).

Among patients aged 91 days to <1 year, rash was reported by 8.8% (3/34) of the linezolid group and 37.5% (6/16) of the vancomycin group (p=0.0138). Statistically significant treatment differences were also observed for injection/vascular catheter site reaction, disorder gastrointestinal (NOS), and dermatitis, which were reported by no patients in the linezolid group (p=0.0354).

Among patients 1 to 4 years of age, vomiting was reported by 12.8% (11/86) of patients in the linezolid group and no patients in the vancomycin group (p=0.0153). Statistically significant treatment differences were also observed for anaphylaxis and reaction unevaluable, which were reported by no patients in the linezolid group (p 0.02).

Among patients 5 to 11 years of age, a statistically significant difference between treatment groups was observed for anaphylaxis (red-man syndrome), which was reported by 13.6% (3/22) of patients in the vancomycin group and no patients in the linezolid group (p=0.0076).

Comments

No specific adverse events were more common in any one particular age group.

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Drug related adverse events

The most common drug-related AE was diarrhea in the linezolid group and anaphylaxis in the vancomycin group. Statistically significant differences between treatment groups in frequency of drug-related AEs were seen for anaphylaxis (linezolid 0.0%, vancomycin 10.1%; $p < 0.0001$), non-application-site pruritus (linezolid 0.0%, vancomycin 2.0%; $p = 0.0374$), and rash (linezolid 1.4%, vancomycin 7.1%; $p = 0.0082$). Drug-related thrombocytopenia was reported more frequently in linezolid-treated patients (1.9%) than in vancomycin-treated patients (0.0%), but the difference was not statistically significant ($p = 0.1700$).

The following table (Sponsor table 33, page 60 ISS) displays the frequencies of drug-related AEs reported by $>1\%$ of patients (and >1 patient) in either treatment group.

Table 18. Sponsor: Drug-related AEs reported by $>1\%$ of patients (and >1 patient) in either treatment group

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P Value
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	
Total Patients Reported	213	99	
Patients with ≥ 1 drug-related AE	40 (18.8)	34 (34.3)	0.0026
Body			
Fever	1 (0.5)	3 (3.0)	0.0613
Anaphylaxis	0	10 (10.1)	<0.0001
Digestive			
Diarrhea	8 (3.8)	6 (6.1)	0.3601
Vomiting	4 (1.9)	1 (1.0)	0.5699
Loose stools (NEC)	4 (1.9)	0	0.1700
Nausea	3 (1.4)	0	0.2354
Monilia oral	2 (0.9)	4 (4.0)	0.0634
Hemic and Lymphatic			
Thrombocytopenia	4 (1.9)	0	0.1700
Anemia	3 (1.4)	1 (1.0)	0.7710
Eosinophilia	3 (1.4)	0	0.2354
Skin			
Rash	3 (1.4)	7 (7.1)	0.0082
Pruritus non-application site	0	2 (2.0)	0.0374

*All percentages are based on number of patients reported

† p value is based on a chi square test

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Comments

Drug related adverse events in the vancomycin group were mainly related to the red man syndrome. Drug related thrombocytopenia was more common in the linezolid arm, though not statistically significant. Reversible neutropenia and rarely thrombocytopenia have been reported with vancomycin, so it is possible that some hematologic toxicity of linezolid is not apparent as the incidence is similar in both groups.

Adverse events leading to discontinuation of treatment

Most AEs leading to discontinuation were reported for only 1 patient in either treatment group. The only statistically significant difference between groups in frequencies of any adverse event leading to discontinuation was for rash (linezolid 0.0%, vancomycin 2.0%; $p=0.0374$).

The following table (Sponsor table 38, page 65 ISS) shows frequencies of all AEs leading to study medication discontinuation.

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Table 19. Sponsor: Study emergent adverse events leading to study medication discontinuation.

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P value
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	
Total Patients Reported	213	99	
Patients with ≥1 AE leading to D/C	15 (7.0)	7 (7.1)	0.9927
Body			
Sepsis	3 (1.4)	0	0.2354
Fever	1 (0.5)	0	0.4947
Infection bacterial (NOS)	1 (0.5)	0	0.4947
Injection/vascular catheter site infection	1 (0.5)	0	0.4947
Trauma	1 (0.5)	0	0.4947
Anaphylaxis	0	1 (1.0)	0.1418
Generalized pain	0	1 (1.0)	0.1418
Cardiovascular			
Endocarditis	2 (0.9)	0	0.3334
Cardiac arrest (NEC)	1 (0.5)	0	0.4947
Congestive heart failure	1 (0.5)	0	0.4947
Digestive			
Diarrhea	1 (0.5)	2 (2.0)	0.1914
Liver failure	1 (0.5)	0	0.4947
Liver function tests abnormal (NOS)	1 (0.5)	0	0.4947
Multiple organ failure	1 (0.5)	0	0.4947
Vomiting	1 (0.5)	0	0.4947
Hemic and Lymphatic			
Pancytopenia	1 (0.5)	0	0.4947
Thrombocytopenia	1 (0.5)	0	0.4947
Metabolic and Nutritional			
Dehydration	1 (0.5)	0	0.4947
Musculoskeletal			
Osteomyelitis	2 (0.9)	0	0.3334
Nervous			
Convulsion	2 (0.9)	0	0.3334
Respiratory			
Pneumonia	1 (0.5)	0	0.4947
Respiratory failure	1 (0.5)	0	0.4947
Thrombosis pulmonary	1 (0.5)	0	0.4947
Skin			
Rash	0	2 (2.0)	0.0374
Urogenital			
Function kidney abnormal	0	1 (1.0)	0.1418

*All percentages are based on number of patients reported

† p value is based on a chi square test

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Comments

The overall incidence of AEs leading to discontinuation was similar in the two groups. The nature of some AEs appears more severe in the linezolid arm for example, sepsis, cardiac arrest, congestive heart failure, liver failure convulsions and pancytopenia. The numbers of these AEs are however very small. It is interesting that nine AEs in the linezolid group were infection related compared to none in the vancomycin group. It is unclear if some of these were treatment failures and also listed as AE by investigators.

Serious adverse events

SAEs were reported in 19.7% (42/213) of patients in the linezolid group and 16.2% (16/99) of patients in the vancomycin group. No statistically significant differences between treatment groups were observed in frequencies of SAEs. However, some SAEs including cardiac arrest, congestive heart failure and convulsions were more common in the linezolid arm Drug-related SAEs were reported for two patients in the linezolid group (total of 4 events) and two patients in the vancomycin group. One patient in the linezolid group had diarrhea and fever and the second patient had anemia and thrombocytopenia. In the vancomycin group one patient had rash, and the second patient had abnormal kidney function.

The following table shows the frequencies of study-emergent serious adverse events reported by $\geq 1\%$ of patients (and > 1 patient) in either treatment group. (Sponsor table 42, page 73 ISS). (table 42)

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Table 20. Sponsor: Serious adverse events reported by > 1% of patients (and > 1 patient) in either treatment group

COSTART Body System Classification Adverse Event (MET)	Treatment Group		P Value
	Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)	
Total Patients Reported	213	99	
Patients with ≥1 SAE	42 (19.7)	16 (16.2)	0.4523
Body			
Sepsis	6 (2.8)	2 (2.0)	0.6786
Fever	3 (1.4)	0	0.2354
Reaction unevaluable	1 (0.5)	2 (2.0)	0.1914
Cardiovascular			
Cardiac arrest (NEC)	3 (1.4)	1 (1.0)	0.7710
Congestive heart failure	3 (1.4)	0	0.2354
Nervous			
Convulsion	4 (1.9)	1 (1.0)	0.5699
Respiratory			
Pneumonia	3 (1.4)	1 (1.0)	0.7710
Respiratory failure	2 (0.9)	2 (2.0)	0.4295

*All percentages are based on number of patients reported

† p value is based on a chi square test

Brief clinical summaries of the seven children (six in the linezolid arm and one in the vancomycin arm) with cardiac arrest/congestive heart failure are provided in the section entitled "Deaths". Serious adverse events of sepsis, seizures and hematologic SAEs are discussed below:

Seizures: Three of the 4 linezolid-treated patients (8222109, 8233118, 8233122) with reported convulsions had significant underlying neurologic conditions prior to enrollment including history of partial lobectomy for brain metastases, viral encephalitis, and cerebral atrophy and degeneration. The fourth child (8211160) had suspected DiGeorge anomaly with coronary heart disease and hypocalcemia and was hypocalcemic (ionized calcium 0.89 mmol/L) at the time of the seizures.

Sepsis: Six children in the linezolid arm developed sepsis as an SAE. Three children developed Gram- negative infections. Among the other three, one child had recurrence of coagulase negative staphylococcal bacteremia 23 days after completing therapy for catheter related blood stream infection (CRBSI), the second had recurrence of clinical sepsis 13 days after completing therapy for CRBSI due to *S.epidermidis* and vancomycin sensitive *Enterococcus faecalis*. The third child had received 16 days of linezolid for MRSA bacteremia and catheter site infection. Three days after stopping therapy he developed MRSA

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pneumonia and pleural effusion. Linezolid MIC for *S.aureus* in this child was 2 µg/mL.

Hematologic SAEs: Four SAEs occurred in 3 patients in the linezolid arm, two of whom had hematologic malignancies and one had bone marrow transplant for Wilm's tumor. The AEs were anemia and neutropenia (1 patient each), and thrombocytopenia (2 patients). In one patient anemia and thrombocytopenia were considered to be drug related. No patients in the vancomycin arm had hematologic SAE. (Source: ISS Section 11, table 7.8)

Comments

SAEs were slightly more common in the linezolid group. The frequency of cardiac events in the linezolid arm is concerning. However it is difficult to determine causality as these children had other co-morbidities, and cardiac arrest is often coded as a cause of death. As seizures occurred only in children with underlying neurologic abnormalities they were probably unrelated to linezolid. Two children with MRSA bacteremia developed closed space infections while on linezolid therapy. One patient (8233121) developed VP shunt infection on day 12 of therapy for HAP and bacteremia. The second patient (8222115) developed pneumonia and pleural effusion 3 days after completing a 16-day course of linezolid for MRSA bacteremia and catheter site infection. In both cases, the MIC for linezolid was 2 µg/mL. It is difficult to draw any conclusions from these two cases. It may however be possible that the role of linezolid in such closed space infections could be limited given the bacteriostatic nature of linezolid and the difficulty in attaining adequate levels in some pediatric patients due to high clearance.

Deaths

A total of 13 deaths (6%) were reported in the linezolid arm and 3 (2.9%) in the vancomycin arm. In the linezolid group there were four deaths each in the 0-90 days and 5-11 year age group and 5 deaths in the 1-4 year age groups. Based on the number enrolled in each age group, greater percentage of deaths (4/43) were reported in the 0-90 days age group and 5-11 year age group (4/50) compared to 5/88 in the 1-4 year category. Causes of death in the linezolid group included cardiac arrest, cardiac failure, and gastrointestinal bleeding.

Following are brief clinical summaries of the 13 children who died in the linezolid arm grouped by cause of death.

Cardiac arrest: Three deaths were reported due to cardiac arrest.

Patient number 8222114: The patient was a 17-month old ex-premature neonate with catheter related bacteremia due to coagulase negative staphylococcus. The child had received 63 doses of linezolid and was considered cured at the follow up

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visit. Patient died of sudden cardiac arrest about 4 weeks after stopping study medication. The case report form (CRF) does not provide any further details about the cause of death or events leading to death. The infant had underlying multi-system involvement related to prematurity. The underlying cardiac abnormality was moderate pulmonary hypertension and history of patent ductus arteriosus correction.

Comment: *The event was probably not drug related as it occurred about 4 weeks after stopping study medication and additionally the child had underlying multi-system morbidity.*

Patient number 8211109: The patient was a 16-day old neonate, 27-week gestation with underlying transposition of the great arteries. The neonate received 7 doses of linezolid for HAP and died of cardiac arrest 1 day after stopping medication. Linezolid was stopped due to lack of clinical improvement. The investigator attributed death to hyperkalemia or sepsis, though no record of a positive blood culture or elevated potassium was provided.

Comment: *The underlying severe cardiac defect was most likely responsible for death.*

Patient number 8211105: The patient was a 21-day old otherwise relatively stable neonate, 23-25-week gestation with coagulase negative staphylococcus bacteremia and HAP who died of cardiac arrest after 10 doses of linezolid. The cause of death was postulated to be pneumothorax by the investigator, however the case report form provides no radiological documentation of barotrauma. On the day prior to death this neonate had pulmonary hemorrhage and DIC that resolved in one day. No platelet abnormalities were noted.

Comment: *Cause of death is unclear and concerning as this was an otherwise relatively stable neonate who had no underlying cardiac defect.*

Cardiac failure: Three deaths were reported due to cardiac failure.

Patient number 8211132 was a 13-day old neonate, 27-week gestation with underlying patent ductus arteriosus and cardiomegaly who died due to complications of necrotizing enterocolitis (NEC). In patient numbers 8222132 and 8222187 cardiac failure was multifactorial and probably was an end stage phenomenon rather than a specific drug effect.

Gastrointestinal bleeding: Three patients, 8233151, 8233169 and 8233131 had gastrointestinal bleeding as the cause of death. One patient was a 7-year old with aplastic anemia and a baseline platelet value of $2 \times 10^3 \mu/L$. The second patient was a 10-year old with disseminated intravascular coagulation following abdominal surgery for intestinal perforations and mesenteric thrombosis who had a baseline

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platelet count of $73 \times 10^3 \mu\text{L}$. The third child was a 7-year old with systemic lupus erythematosus who developed gastrointestinal bleeding 17 days after completing a 10-day course of linezolid and had platelet values of $112 \times 10^3 \mu\text{L}$ at baseline and $323 \times 10^3 \mu\text{L}$ at end of therapy.

Comment: *As two of these three children with gastrointestinal hemorrhage had low platelet values at baseline and died within 4 days of starting linezolid therapy the contribution of linezolid administration is difficult to assess.*

Other causes: 4 children died of other causes.

Patient number 8222253: A 3-year old with acute lymphatic leukemia was enrolled with cellulitis of the thigh. The child developed rapidly progressive oral infection and died due to septic shock after receiving seven doses of linezolid.

Patient number 8233114: A 6-year old with acute myeloid leukemia died of pulmonary aspergillosis and intracranial hemorrhage.

Patient number 8211111: A 32-day old infant, 27-week gestation with multifactorial jaundice died of hepatic failure.

Patient number 8222197: An 18-month old with HAP died of Pseudomonas sepsis and pneumonia.

Following are brief clinical summaries of the three children who died in the vancomycin arm:

8222192: A 3-year old child with ventricular septal defect died in the post-operative period due to cardiac arrest. Events leading to death were not clarified in the case report form.

82333171: A 5.6-year old with acute myeloid leukemia, s/p bone marrow transplant died of hemorrhagic stroke 30 days after stopping vancomycin.

8233164: A 9.3-year old with renal sarcoma died due to worsening renal sarcoma.

Comments: *Cardiac arrest and cardiac failure together constituted the single most common cause of death. All children who died of cardiac arrest or cardiac failure were less than 5 years of age, three each in the 0-90 days age group and in the 1-4 year age group. It is difficult to assess causality by linezolid given the nature of this study population and the fact that cardiac arrest is usually a terminal event. No definite temporal association was observed as days on treatment before cardiac event occurred varied from 3-22. However, as there were no obvious antecedent causes leading to cardiac arrest in two children and no autopsy results are available this adverse event will need to be closely monitored post marketing.*

All BID doses combined

Adverse events among all patients who received BID dosing of linezolid (studies 0045, 0049, and 0065) is discussed in this section. A comparator was used only in study 0065.

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Study emergent AE

Similar proportions of patients treated with linezolid or cefadroxil reported one or more study-emergent AEs. The most common AEs (incidence $\geq 5\%$) in both the linezolid and cefadroxil groups were diarrhea (11.1% and 8.0%, respectively) and vomiting (6.2% and 6.4% respectively).

AEs that occurred in $\geq 2\%$ of patients in either treatment group in the three studies combined are presented in the following table (Sponsor table 28, page 48 ISS).

Table 21. Sponsor: Study emergent adverse events that occurred in $\geq 2\%$ of patients in either treatment group

COSTART Body System Classification Adverse Event (MET)	Linezolid N = 391 n (%)	Cefadroxil N = 251 n (%)
Total Patients Reported	388	249
Patients with ≥ 1 AE	191(49.2)	117 (47.0)
Body		
Headache	16 (4.1)	10 (4.0)
Trauma	13 (3.4)	12 (4.8)
Upper respiratory infection	13 (3.4)	13 (5.2)
Fever	13 (3.4)	9 (3.6)
Abdominal pain generalized	8 (2.1)	7 (2.8)
Abdominal pain localized	7 (1.8)	7 (2.8)
Digestive		
Diarrhea	43 (11.1)	20 (8.0)
Vomiting	24 (6.2)	16 (6.4)
Loose stools (NEC)	12 (3.1)	2 (0.8)
Nausea	9 (2.3)	8 (3.2)
Respiratory		
Cough	11 (2.8)	10 (4.0)
Pharyngitis	11 (2.8)	4 (1.6)
Rhinitis	9 (2.3)	10 (4.0)
Skin		
Rash	18 (4.6)	3 (1.2)

*All percentages are based on number of patients reported

Drug related AE

Overall, 19.6% (76/388) of the linezolid patients and 14.1% (35/249) of the cefadroxil patients experienced one or more AEs that were considered to be related to the study medication. The majority of AEs occurred in the digestive system, and the most common AE was diarrhea, reported by 7.0% (27/388) of linezolid-treated patients and 5.2% (13/249) of cefadroxil-treated patients.

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Drug-related AEs that occurred in >1% of patients in either treatment group are presented in the following table (Sponsor table 36, page 63 ISS).

Table 22. Sponsor: Drug-related adverse events that occurred in >1% of patients in either treatment group

COSTART Body System Classification Adverse Event (MET)	Linezolid N = 391 n (%)	Cefadroxil N = 251 (%)
Total Patients Reported	388	249
Patients with ≥1 drug-related AE	76 (19.6)	35 (14.1)
Body		
Headache	6 (1.5)	2 (0.8)
Abdominal pain generalized	5 (1.3)	3 (1.2)
Abdominal pain localized	4 (1.0)	3 (1.2)
Digestive		
Diarrhea	27 (7.0)	13 (5.2)
Vomiting	9 (2.3)	6 (2.4)
Loose stools (NEC)	8 (2.1)	2 (0.8)
Nausea	8 (2.1)	5 (2.0)
Skin		
Rash	5 (1.3)	3 (1.2)

*All percentages are based on number of patients reported

AE leading to discontinuation

The frequencies of AEs that resulted in treatment discontinuation were similar in the two groups. Diarrhea and rash were the most common AEs that resulted in discontinuation of study medication.

AEs that resulted in discontinuation of study medication are summarized in the following table (Sponsor table 40, page 69 ISS).

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Table 23. Sponsor: Adverse events that resulted in discontinuation of study medication

COSTART Body System Classification Adverse Event (MET)	Linezolid N = 391 n (%)	Cefadroxil N = 251 n (%)
Total Patients Reported	388	249
Patients with ≥ 1 AE leading to D/C	10 (2.6)	9 (3.6)
Body		
Abdominal pain generalized	1	0
Abdominal pain localized	1	0
Headache	1	0
Sepsis	1	0
Digestive		
Diarrhea	2	3
Vomiting	1	1
Hemic and Lymphatic		
Adenopathy	1	0
Neutropenia	1	0
Metabolic and Nutritional		
Lipase high	1	0
Skin		
Rash	2	2
Pruritus non-application site	1	0
Special Senses		
Otitis media	1	0

*All percentages are based on number of patients reported

Serious adverse events

One or more SAE was reported for 1.8% (7/388) of patients in the linezolid group and 1.6% (4/249) of patients in the cefadroxil group. No SAE was reported by more than 1 patient. SAEs for patients in the three studies combined are summarized in the following table (Sponsor table 43, page 75 ISS).

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Table 24. Sponsor: Serious adverse events

COSTART Body System Classification Adverse Event (MET)	Linezolid N = 391 n (%)	Cefadroxil N = 251 n (%)
Total Patients Reported	388	249
Patients with ≥1 SAE	7 (1.8)	4 (1.6)
Body		
Abscess	0	1
Cellulitis	0	1
Infection (NEC)	0	1
Digestive		
Vomiting	1	0
Hemic and Lymphatic		
Neutropenia	1	0
Metabolic and Nutritional		
Diabetic acidosis	1	0
Lipase high	1	0
Nervous		
Convulsion	1	0
Hostility	0	1
Respiratory		
Pneumothorax	1	0
Bronchiolitis	1	0

*All percentages are based on number of patients reported

Deaths

There were no deaths in any of the three studies combined.

Conclusions: *No predominance in the occurrence of any adverse events was seen after combining adverse events from all three studies. The SAEs that were reported in these studies were different, so no SAE was reported more than once after combining all three studies. Hematologic adverse events reported in the linezolid arm included neutropenia (4 patients) and thrombocytopenia (1 patient). One patient in the cefadroxil arm had leukopenia (Source: ISS Appendix 1, table 4.1)*

LABORATORY ASSAYS

Phase 2 studies (0045 and 0049 combined)

Hematology

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Substantially abnormal values

The following table (Sponsor table 48, page 82 ISS) shows frequencies of substantially abnormal values for selected hematology assays.

Table 25. Sponsor: Substantially abnormal values

Assay	n/N (%)
Hemoglobin (<75% of LLN)	5/138 (3.6)
Hematocrit (<75% of LLN)	5/138 (3.6)
WBC Count (<75% of LLN)	2/138 (1.4)
Neutrophils (<0.5 x LLN)	2/137 (1.5)
Platelet Count (<75% of LLN)	5/138 (3.6)

LLN= Lower limit of normal

Comments: Both thrombocytopenia and anemia were not uncommon in these phase 2 studies. As no comparator was used in either of the studies, the overall incidence of hematologic abnormalities in this population cannot be ascertained. Frequencies of substantially abnormal values especially for hemoglobin and platelet counts were higher in these phase 2 studies compared to study 0065. These children were more likely to be sicker than children in study 0065. The role of concomitant viral illness is difficult to discern, however given that all the three cell lines were affected it is more likely a drug effect.

Chemistry

None of the patients in study 0049 had substantially abnormal values for chemistry assays. The following table (Sponsor table 55, page 88 ISS) shows frequencies of substantially abnormal values for selected chemistry assays in study 0045.

Table 26. Sponsor: Substantially abnormal chemistry values

Assay	n/N (%)
ALT (>2 x ULN)	5/138 (3.6)
Total Bilirubin (>2 x ULN)	1/138 (0.7)
Lipase (>2 x ULN)	3/138 (2.2)
Amylase (>2 x ULN)	1/138 (0.7)

ULN= Upper limit of normal

Phase 3 studies

Laboratory values for both the phase 3 studies are presented by frequencies of substantially abnormal values and shifts in values from baseline to worst value.

Substantially abnormal values

Criteria for substantially abnormal values if baseline values are normal or abnormal are provided in Appendix 3.

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Shifts in hematology/chemistry values

The possible range of hematological (hemoglobin, platelet counts, neutrophils) or chemistry (ALT, bilirubin) values was divided into four categories representing different toxicity grades based on AIDS Clinical Trials Group (ACTG) criteria plus a category representing no toxicity.

The ACTG criteria were modified to fit the age groups used in study 0082.

Patients aged 0-7 days were not included because ACTG criteria were not available for this age group. The ACTG criteria used to define shifts in laboratory values are provided in the Appendix 3.

Study 0065

Hematology

Substantially abnormal values

The percentages of patients in each group with at least one substantially abnormal value for selected hematology assays are shown in the following table (Sponsor table 46, page 81 ISS).

Table 27. Sponsor: Substantially abnormal values

Assay	Linezolid n/N (%)	Cefadroxil n/N (%)
Hemoglobin (<75% of LLN)	0/243 (0.0)	0/246 (0.0)
Hematocrit (<75% of LLN)	0/243 (0.0)	0/246 (0.0)
WBC Count (<75% of LLN)	2/243 (0.8)	2/246 (0.8)
Neutrophil Count (<0.5 of LLN)	3/242 (1.2)	2/245 (0.8)
Platelet Count (<75% of LLN)	0/243 (0.0)	1/246 (0.4)

LLN= Lower limit of normal

Shifts in hematology values

No patients had a shift to a higher grade in hemoglobin value in either treatment group and only one patient in the cefadroxil group had a platelet count that shifted one grade higher during the study. Shifts to a higher grade in neutrophil count were reported for 14 of 185 patients (7.6%) in the linezolid group and 12 of 192 patients (6.3%) in the cefadroxil group.

The following table (Sponsor table 49, page 83 ISS) summarizes the shifts to a higher grade of neutrophil count.

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Table 28. Sponsor: Shifts in neutrophil count

Shift Magnitude	Linezolid n/N (%)	Cefadroxil n/N (%)
Any shift	14/185 (7.6)	12/192 (6.3)
1 grade	12/185 (6.5)	8/192 (4.2)
2 grades	1/185 (0.5)	2/192 (1.0)
3 grades	1/185 (0.5)	2/192 (1.0)

Comments

No significant difference was noted in the frequencies of hematologic abnormalities between the two groups. Shifts in neutrophil count were mostly one grade in both groups.

SERUM CHEMISTRY

Substantially abnormal values

The frequencies of patients in each group with at least one substantially abnormal value for selected chemistry assays are shown in the following table (Sponsor table 53, page 87 ISS).

Table 29. Sponsor: Substantially abnormal values

Assay	Treatment Group	
	Linezolid n/N (%)	Cefadroxil n/N (%)
ALT (>2 x ULN)	0/243 (0.0)	0/246 (0.0)
Lipase (>2 x ULN)	1/244 (0.4)	3/244 (1.2)
Creatinine (>2 x ULN)	1/243 (0.4)	0/246 (0.0)

ULN= Upper limit of normal

Shifts in chemistry values

Shifts to a higher grade in ALT values were reported in 3.9% (9/233) of patients in the linezolid group and 2.6% (6/227) in the cefadroxil group. All shifts in ALT values during the study were one grade.

Comments

No significant abnormalities were noted in the selected serum chemistry values in both arms.

0082

Hematology

Substantially abnormal values

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The following table (Sponsor table 47, page 82 ISS) shows frequencies of substantially abnormal values for selected hematology assays.

Table 30. Sponsor: Substantially abnormal values

Assay	Treatment Group	
	Linezolid n/N (%)	Vancomycin n/N (%)
Hemoglobin (<75% of LLN)	33/210 (15.7)	12/97 (12.4)
Hematocrit (<75% of LLN)	33/210 (15.7)	14/97 (14.4)
WBC Count (<75% of LLN)	26/210 (12.4)	10/97 (10.3)
Neutrophil Count (<0.5 x LLN)	12/204 (5.9)	4/93 (4.3)
Platelet Count (<75% of LLN)	27/210 (12.9)	13/97 (13.4)

LLN= Lower limit of normal

Comments: *A higher incidence of substantially abnormal values in study 0082 compared to other studies is not unexpected as patients in this study were sicker compared to other studies. Low values for hemoglobin and white cells were slightly more common in the linezolid arm. No differences were seen in the frequency of low platelet values.*

Shifts in hematology values

Shifts in values from baseline to the most abnormal value for each hematologic parameter are presented below:

- **Hemoglobin**

In the linezolid arm, 34.7% (69/199) patients had any shifts in hemoglobin values compared to 37.6% (35/93) in the vancomycin arm. Shifts to higher grades in hemoglobin values were higher in the 8-90-day-old group in both treatment groups. Percentages were similar between treatment groups in the 3 youngest age categories but higher in the vancomycin group in patients 5-11 years old. Shifts were primarily one grade in all age groups in both treatment arms except in the 8-90 days age group. In this group shifts of 2 or more grades were higher in the linezolid arm (11/23, 47.8% vs. 2/9, 22.3 %).

The following table (Sponsor table 50, page 84 ISS) shows frequencies of categorical shifts in hemoglobin values by age and magnitude of shift.

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Table 31. Sponsor: Shifts in hemoglobin values from baseline to the most abnormal value

Age Category	Shift Magnitude	Treatment Group	
		Linezolid N = 215 n (%)*	Vancomycin N = 101 n (%)
8-90 days	Any shift	23 (57.5)	9 (56.3)
	1 grade	12 (30.0)	7 (43.8)
	2 grades	9 (22.5)	2 (12.5)
	3 grades	1 (2.5)	0
	4 grades	1 (2.5)	0
	No. Assessed	40	16
91 days - <1 year	Any shift	10 (31.3)	4 (28.6)
	1 grade	7 (21.9)	2 (14.3)
	2 grades	3 (9.4)	2 (14.3)
	3 grades	0	0
	4 grades	0	0
	No. Assessed	32	14
1-4 years	Any shift	23 (28.4)	13 (31.0)
	1 grade	17 (21.0)	10 (23.8)
	2 grades	4 (4.9)	1 (2.4)
	3 grades	2 (2.5)	1 (2.4)
	4 grades	0	1 (2.4)
	No. Assessed	81	42
5-11 years	Any shift	13 (28.3)	9 (42.9)
	1 grade	9 (19.6)	7 (33.3)
	2 grades	4 (8.7)	2 (9.5)
	3 grades	0	0
	4 grades	0	0
	No. Assessed	46	21

*All percentages are based on number of patients assessed

- **Neutrophils**

In the linezolid arm, 12.3% (24/194) patients had any shifts in neutrophil values compared to 9.4% (8/85) in the vancomycin arm. Percentages of assessed patients who had shifts to higher grades in neutrophil count were higher in the 5-11 year age category and lower in the 91 days-< 1 year age category in both treatment arms. Shifts in neutrophil count were primarily 1 grade in all age groups. Both treatment arms were comparable in all age categories except in the 1-4 year old, where more patients in the linezolid arm had shifts to higher grades in neutrophil count.

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The following table (Sponsor table 51, page 85 ISS) shows frequencies of categorical shifts in neutrophil count by age and magnitude of shift.

Table 32. Sponsor: Shifts in neutrophil values from baseline to the most abnormal value

Age Category	Shift Magnitude	Treatment Group	
		Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)*
8-90 days	Any shift	5 (12.5)	2 (13.3)
	1 grade	4 (10.0)	0
	2 grades	0	2 (13.3)
	3 grades	0	0
	4 grades	1 (2.5)	0
	No. Assessed	40	15
91 days - <1 year	Any shift	1 (3.2)	0
	1 grade	0	0
	2 grades	1 (3.2)	0
	3 grades	0	0
	4 grades	0	0
	No. Assessed	31	14
1-4 years	Any shift	10 (12.5)	3 (7.9)
	1 grade	5 (6.3)	2 (5.3)
	2 grades	2 (2.5)	1 (2.6)
	3 grades	1 (1.3)	0
	4 grades	2 (2.5)	0
	No. Assessed	80	38
5-11 years	Any shift	8 (18.6)	3 (16.7)
	1 grade	5 (11.6)	2 (11.1)
	2 grades	2 (4.7)	0
	3 grades	0	1 (5.6)
	4 grades	1 (2.3)	0
	No. Assessed	43	18

*All percentages are based on number of patients assessed

- **Platelets**

In the linezolid arm, 10.4% (21/201) patients had any shifts in platelet values compared to 9.8% (9/92) in the vancomycin arm. Percentages of assessed patients in both groups who had shifts to higher grades in platelet count were lower in the 1-4-year-old group than in the other 3 categories. Percentages were higher for the linezolid group than the vancomycin group in the 91-day-to-<1-year-old group and higher in the vancomycin group in the 5-11 year age group.

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The following table (Sponsor table 52, page 86 ISS) shows frequencies of categorical shifts in platelet count by age and magnitude of shift.

Table 33. Sponsor: Shifts in platelet values from baseline to the most abnormal value

Age Category	Shift Magnitude	Treatment Group	
		Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)
8-90 days	Any shift	5 (12.5)	2 (12.5)
	1 grade	1 (2.5)	1 (6.3)
	2 grades	0	0
	3 grades	2 (5.0)	0
	4 grades	2 (5.0)	1 (6.3)
	No. Assessed	40	16
91 days - <1 year	Any shift	5 (15.6)	0
	1 grade	2 (6.3)	0
	2 grades	1 (3.1)	0
	3 grades	0	0
	4 grades	2 (6.3)	0
	No. Assessed	32	14
1-4 years	Any shift	4 (4.8)	3 (7.3)
	1 grade	2 (2.4)	1 (2.4)
	2 grades	0	1 (2.4)
	3 grades	1 (1.2)	1 (2.4)
	4 grades	1 (1.2)	0
	No. Assessed	83	41
5-11 years	Any shift	7 (15.2)	4 (19.0)
	1 grade	5 (10.9)	1 (4.8)
	2 grades	1 (2.2)	2 (9.5)
	3 grades	0	1 (4.8)
	4 grades	1 (2.2)	0
	No. Assessed	46	21

*All percentages are based on number of patients assessed

Comments

As grade 0 represents no toxicity it is possible that some patients may have had significant decline from their baseline values but did not reach the cut off for grade 0 and in whom with more follow up the nadir would have been detected.

Overall, more patients in the vancomycin arm had shifts in hemoglobin values and more patients in the linezolid arm had shifts in neutrophil values. Shifts in platelet values were similar between the two groups. However, the number of patients in each of these categories is small. Grade 4 shifts in neutrophil and

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platelet values were more common in the linezolid arm. Four patients in the linezolid arm had grade 4 shifts in neutrophil values compared to none in vancomycin arm. Six patients in the linezolid arm had grade 4 shifts in platelet values compared to one in the vancomycin arm. One patient in each arm had a grade 4 shift in hemoglobin values. Grade 4 shifts are concerning as they represent a significant change in platelet count from $\geq 100,000$ to $< 25,000$, for neutrophils from ≥ 1200 to $< 250/\mu\text{L}$ and for hemoglobin from ≥ 10 to < 6.5 g/dL.

Case summaries of all children in the linezolid arm with Grade 3 or grade 4 shifts in any hematologic parameter were reviewed. A total of 18 such events occurred in 16 patients. Eight of these patients either had an underlying malignancy or low platelets at baseline due to other causes. The remaining eight patients had no underlying conditions predisposing to hematologic toxicity and no associated clinical adverse events was seen except for the need for blood transfusion in one neonate.

Shifts in hemoglobin values were more common in the 8-90 days age group. This could reflect the fact that neonates have a physiologic decline in hemoglobin after birth. Also, iatrogenic anemia due to repeated blood draws can be contributory in young infants. No other hematologic toxicity was higher in any one particular age group. There was a slightly higher incidence of neutrophil abnormalities in older children. It is possible that more children in this age group had underlying illnesses like malignancies.

FDA ANALYSES

Additional analyses of the laboratory data were performed by the FDA statistical reviewer Dr. Erica Brittain Ph.D. The following is excerpted from the review by Dr. Brittain, for further details please refer to Dr. Brittain's review.

Instead of using a definition for either substantially abnormal values or shifts in values, the number of patients with values at or above certain cut offs were compared in the two groups at baseline, at end of therapy and at follow up. These cut offs were not pre-specified and do not take in to consideration difference in values in different age groups. Also, patients were assigned treatment groups based on the randomization and not by the treatment received, hence the linezolid arm has 206 patients, vancomycin arm has 102 patients and 8 patients are in the VRE arm .

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Table 34. FDA: Laboratory Values Below Cut-off values (ITT Population)

Laboratory value	Randomized Treatment					
	Linezolid		Vancomycin		Vreflag	
	RATE	N	RATE	N	RATE	N
B Platelets < 100	0.166	199	0.152	99.000	0.286	7.000
B Platelets < 50	0.106	199	0.071	99.000	0.143	7.000
EOT Platelets < 100	0.109	183	0.082	85.000	0.429	7.000
EOT Platelets < 50	0.066	183	0.082	85.000	0.143	7.000
FU Platelets <100	0.055	181	0.111	81.000	0.333	6.000
FU Platelets < 50	0.022	181	0.062	81.000	0.000	6.000
B Neutrophils < 1	0.077	195.000	0.065	93.000	0.143	7.000
EOT Neutrophils < 1	0.029	175.000	0.063	80.000	0.429	7.000
FU Neutrophils < 1	0.029	172.000	0.067	75.000	0.000	6.000
B Hemoglobin < 10	0.338	198.000	0.360	100.000	0.429	7.000
B Hemoglobin < 7	0.025	198.000	0.020	100.000	0.000	7.000
EOT Hemoglobin < 10	0.317	183.000	0.310	87.000	0.286	7.000
EOT Hemoglobin < 7	0.027	183.000	0.011	87.000	0.000	7.000
FU Hemoglobin < 10	0.280	182.000	0.272	81.000	0.833	6.000
FU Hemoglobin < 7	0.000	182.000	0.000	81.000	0.000	6.000

B denotes Baseline; EOT denotes End of Treatment; FU denotes Follow-up, units for neutrophil and platelet values are $\times 10^3/\mu\text{L}$, and for hemoglobin g/dL.

The number of patients with platelet values below two cut off values ($100 \times 10^3/\mu\text{L}$ and $50 \times 10^3/\mu\text{L}$) were higher in the vancomycin arm compared to the linezolid arm at follow up. These results are limited in that the cut offs were not pre specified or based on age, however they show that frequency of low values were similar in the two groups.

The following table shows the comparison between the two groups at EOT and FU among patients who did not have low values at baseline. Hemoglobin was the only hematologic parameter where a larger number of low values were seen at both visits. This was more common in the linezolid arm compared to the vancomycin arm. Missing values were however more common in the vancomycin group.

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Table 35. FDA: Laboratory Values at EOT and FU in Patients whose Baseline Values were Not Low (Non-randomized VRE patients excluded)

Population: Patients whose baseline platelet value was at least 100				
Platelet Value	End of Treatment		Follow-up	
	Linezolid	Vancomycin	Linezolid	Vancomycin
<100	6	2	4	2
≥100	145	71	143	65
Missing	15	11	19	17

Population: Patients whose baseline Neutrophil value was at least 1.2				
Neutrophil Value	End of Treatment		Follow-up	
	Linezolid	Vancomycin	Linezolid	Vancomycin
<1.2	4	3	6	4
≥1.2	152	67	143	62
Missing	20	15	25	19

Population: Patients whose baseline Hemoglobin value was at least 10				
Hemoglobin Value	End of Treatment		Follow-up	
	Linezolid	Vancomycin	Linezolid	Vancomycin
<10	17	7	16	5
≥10	97	46	97	45
Missing	12	9	13	13

Additionally, baseline laboratory values for platelets, neutrophils, and hemoglobin were plotted against the values at end of treatment and follow-up. No significant differences were noted between the two groups. For the graphical representations of these plots the reader is referred to Dr. Brittain's review.

SERUM CHEMISTRY

Substantially abnormal values

For each chemistry assay evaluated the frequency of substantially abnormal values was similar for both treatment groups.

The following table (Sponsor table 54, page 87 ISS) shows frequencies of substantially abnormal values for selected chemistry assays.

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Table 36. Sponsor: Substantially abnormal values

Assay	Treatment Group	
	Linezolid n/N (%)	Vancomycin n/N (%)
ALT (>2 x ULN)	21/208 (10.1)	12/96 (12.5)
Total Bilirubin (>2 x ULN)	13/207 (6.3)	5/96 (5.2)
Amylase (>2 x ULN)	1/176 (0.6)	1/79 (1.3)
Creatinine (>2 x ULN)	5/210 (2.4)	1/97 (1.0)

ULN= Upper limit of normal

Shifts in chemistry values

ALT: Shifts to a higher grade in ALT values were more common in the linezolid group in the 8-90 days and 5-11 years age category and higher in the vancomycin group in the 91 days-< 1 year category. Shifts were primarily one grade in all age categories in both treatment groups.

The following table (Sponsor table 57, page 89 ISS) shows frequencies of categorical shifts in ALT values by age and magnitude of shift.

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Table 37. Sponsor: Shifts in ALT values

Age Category	Shift Magnitude	Treatment Group	
		Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)
8-90 days	Any shift	11 (29.7)	3 (18.8)
	1 grade	9 (24.3)	3 (18.8)
	2 grades	1 (2.7)	0
	3 grades	1 (2.7)	0
	4 grades	0	0
	No. Assessed	37	16
91 days - <1 year	Any shift	6 (19.4)	5 (33.3)
	1 grade	6 (19.4)	5 (33.3)
	2 grades	0	0
	3 grades	0	0
	4 grades	0	0
	No. Assessed	31	15
1-4 years	Any shift	17 (21.8)	7 (18.4)
	1 grade	15 (19.2)	6 (15.8)
	2 grades	2 (2.6)	1 (2.6)
	3 grades	0	0
	4 grades	0	0
	No. Assessed	78	38
5-11 years	Any shift	11 (25.0)	3 (14.3)
	1 grade	11 (25.0)	2 (9.5)
	2 grades	0	1 (4.8)
	3 grades	0	0
	4 grades	0	0
	No. Assessed	44	21

*All percentages are based on number of patients assessed

Bilirubin: Percentages of assessed patients who had shifts to higher grades in total bilirubin values were higher in the 8-90-day-old group compared to the other three age categories. Percentages were similar between treatment groups in all age categories except in the 91 days-< 1 year group where it was higher in the vancomycin arm. Shifts were primarily one grade in all age groups.

The following table (Sponsor table 58, page 90 ISS) shows frequencies of categorical shifts in total bilirubin values by age and magnitude of shift.

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Table 38. Sponsor: Shifts in total bilirubin values

Age Category	Shift Magnitude	Treatment Group	
		Linezolid N = 215 n (%)	Vancomycin N = 101 n (%)
8-90 days	Any shift	11 (30.6)	5 (31.3)
	1 grade	8 (22.2)	4 (25.0)
	2 grades	2 (5.6)	1 (6.3)
	3 grades	1 (2.8)	0
	4 grades	0	0
	No. Assessed	36	16
91 days - <1 year	Any shift	3 (10.0)	2 (15.4)
	1 grade	3 (10.0)	1 (7.7)
	2 grades	0	0
	3 grades	0	1 (7.7)
	4 grades	0	0
	No. Assessed	30	13
1-4 years	Any shift	2 (2.7)	1 (2.6)
	1 grade	2 (2.7)	0
	2 grades	0	0
	3 grades	0	1 (2.6)
	4 grades	0	0
	No. Assessed	74	39
5-11 years	Any shift	4 (9.3)	2 (10.0)
	1 grade	4 (9.3)	2 (10.0)
	2 grades	0	0
	3 grades	0	0
	4 grades	0	0
	No. Assessed	43	20

*All percentages are based on number of patients assessed

Comments

No significant differences in ALT abnormalities were noted for any specific age category. Most ALT and bilirubin shifts were 1 grade. No 4 grade shifts were noted. Abnormalities in bilirubin values were higher in infants < 90 days of age. These children are more likely to be sicker and hyperbilirubinemia due to other etiologies is also more common in neonates and young infants.

Iron related laboratory assay results (study 0082)

Results for reticulocyte index and serum iron showed statistically significant increases from baseline for both treatment groups. No significant differences between treatment groups in mean changes from baseline values were observed for any of the selected assays.

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Drug-Drug Interactions

Selected AEs were assessed in patients taking concomitant medications that are known to interact with monoamine oxidase inhibitors (MAOI). In general, the incidence of potential MAOI-related events was low. No substantial differences were observed between treatment groups in the occurrence of the selected AEs.

Study 0065

In study 0065, 9.7% (24/248) of patients treated with linezolid and 14.3% (36/251) patients treated with cefadroxil received medications that potentially interact with MAOI agents. There were two reports of fever in the linezolid group and 1 in the cefadroxil group. These AEs did not result in discontinuation of study medication. In patients who did not receive MAOI-interacting drugs, adverse events of hyperthermia, diaphoresis or flushing were reported by 5 (2.2%) in the linezolid group and 8 (3.7%) in the cefadroxil group.

Study 0082

In study 0082, 30.7% (66/215) of patients treated with linezolid and 33.7% (34/101) patients treated with vancomycin also received medications that potentially interact with MAOI agents. Fever was reported in 12 (18.2%) patients in the linezolid group and 5 (14.7%) in the vancomycin group. In patients who did not receive MAOI-interacting drugs, adverse events of hyperthermia, diaphoresis or flushing were reported by 20 (13.4%) in the linezolid group and 9 (13.4%) in the vancomycin group.

0049/0045

In studies 0045 and 0049, 56 of 143 patients treated with linezolid received medications that potentially interact with MAOIs. Five of these 56 patients had potentially MAOI-related AEs. Four of these AEs were fever and one was mild restlessness.

D. Adequacy of Safety Testing

Given the pharmacokinetic characteristics of linezolid and the varying dosing regimens used in the different clinical studies submitted in this supplement, the overall safety database may not accurately represent the likelihood of adverse events once linezolid is used more widely in children at the recommended doses. Specifically, in children below 12 years of age an eight hourly dosing regimen is recommended and the only safety database at that dose is from the 215 patients who were treated with linezolid in study 0082. Although children between 1-12 years were enrolled in other studies, all of them received 12-hourly dosing regimens. Hence, given the small number of pediatric patients exposed to linezolid at the recommended dose, the lack of significant adverse events in

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clinical studies though reassuring does not provide convincing evidence for lack of significant toxicity with linezolid use in pediatric patients.

In the adult studies of linezolid the number of patients enrolled was much larger (n~2000) and no hematologic toxicity was evident, though there was some suggestion of increased incidence of thrombocytopenia with linezolid use in the phase 3 studies. A sufficient number of cases were also detected during post marketing surveillance resulting in the addition of a warning in the linezolid label. In all the pediatric studies submitted in this application no statistically significant difference in the incidence of myelosuppression was seen in the linezolid treated patients. Myelosuppression has been noted in studies in both adult and juvenile dogs and rats. In juvenile dogs and rats, in addition to myelosuppression, suppression of extramedullary hematopoiesis and also lymphoid depletion in the spleen, thymus and lymph nodes were seen. Lymphoid depletion and reduction of extramedullary hematopoiesis were especially striking in juvenile animals. Also, the margin of safety for linezolid toxicity between animals and humans is not large. If the toxicity of lymphoid depletion holds true for pediatric patients, T-cell depletion will be evidenced by increased risk of infections with linezolid use. Though monitoring for some of the more uncommon infections that are usually seen in patients with T-cell deficiencies is warranted, it will often be clinically difficult to make the linkage between linezolid administration and development of these infections.

Both peripheral and optic neuropathy has been reported during the postmarketing use of linezolid. Though reported mainly in patients treated for longer than 28 days it has also been reported in patients receiving shorter courses of therapy. Patients in study 0082 were allowed to receive linezolid to a maximum of 28 days. In all other studies the length of treatment was shorter. Unilateral optic neuropathy may be difficult to detect in young children unless formal vision testing is performed. Also, sensory neuropathy will be difficult to detect in younger children.

E. Summary of Critical Safety Findings and Limitations of Data

Both the sponsors analyses and FDA analyses showed no significant difference in adverse events between linezolid and comparator drugs. The only evidence of myelosuppression was in study 0082 where thrombocytopenia was slightly more common in the linezolid group though the difference was not statistically significant. However, the safety database in pediatric patients has some limitations. First, the number of patients less than 12 years of age who received 8-hourly dosing is small, while the recommended dose is 8-hourly except in children from 5-11 years of age who have uncomplicated skin and skin structure infections. Second, the only study that used an 8-hourly regimen, study 0082, had enrolled critically ill children some of whom had low hematologic parameters at

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study entry, thus limiting assessment of hematologic toxicity. Third, children in study 0045 received 12-hourly dosing for the treatment of community acquired pneumonia and the recommended dosing is 8-hourly thereby limiting our inference from this study. Lastly, dosing recommendations in preterm neonates (gestational age less than 34 weeks) and postnatal age less than seven days is made primarily based on pharmacokinetic data from a small number of preterm neonates. Clinical safety information in this population is very limited as only one preterm neonate with a postnatal age of less than seven days was enrolled in study 0082.

VIII. Dosing, Regimen, and Administration Issues

Based on the available clinical data and pharmacokinetic studies the proposed dosing regimen seems appropriate. The clearance of linezolid varies widely in pediatric patients compared to adults and with the lack of any commercially assay for therapeutic drug monitoring it is not possible to be definitive that at the recommended doses all pediatric patients will attain therapeutic levels. Hence adequacy of clinical response will be the only tool to assess attainment of therapeutic levels at this time. One specific area of concern in children with increased clearance is in the treatment of infections where the MIC of organisms is high ($= 4\mu\text{g/mL}$) especially in the context of severe life threatening infections or sequestered infection sites. At this time no recommendations can be made regarding dosage adjustments for infections due to organisms with high MIC or for children with suspected increased drug clearance. No dosage adjustments are needed for patients with renal insufficiency or mild-moderate hepatic insufficiency. Linezolid can be administered without regard to the timing of meals.

The following dosage and administration table has been included in the package insert:

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Dosage Guidelines for ZYVOX

Infection*	Dosage and Route of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	10 to 14
Community-acquired pneumonia, including concurrent bacteremia			
Nosocomial pneumonia			
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg IV or oral† q8h	600 mg IV or oral† q12h	14 to 28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral† q8h 5-11 yrs: 10 mg/kg oral‡ q12h	Adults: 400 mg oral‡ q12h, Adolescents: 600 mg oral‡ q12h	10 to 14

* Due to the designated pathogens (see INDICATIONS AND USAGE)

† Neonates <7 days: Most pre-term neonates < 7 days of age (gestational age < 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric).

‡ Oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

No differences in cure rates were seen when specific gender, race or ethnicity analyses were performed. Children of both sexes and all races are fairly well represented in the pediatric studies submitted in this supplement.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

No difference in frequencies of adverse effects by age was seen in any of the clinical studies. Limitations of the dosing regimens used in different studies have been discussed in section on Summary of Critical Safety Findings and Limitations of Data.

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X. Conclusions and Recommendations

A. Conclusions

Phase 1 Studies

The phase 1 studies were conducted in hospitalized patients rather than healthy volunteers. Adverse events occurred more often in patients who received multiple doses of linezolid (10 mg/kg) than in patients who received a single dose (1.5 mg/kg or 10 mg/kg). Overall, linezolid was well tolerated in the Phase 1 studies in children. Ventricular arrhythmia occurred in a patient with a history of cardiac defect and arrhythmia and hence it is difficult to ascertain causality. No serious adverse events were related to linezolid administration. The most common adverse events that occurred in > than 1% of the patients were injection/vascular catheter site pain/reaction, rash, hypokalemia, nausea, and vomiting. There were no deaths reported in these studies.

Phase 2 Studies

Studies 0045 and 0049

Diarrhea and vomiting were the most common adverse events reported. Three patients had neutropenia, one of which was severe and resulted in treatment discontinuation. No other hematologic toxicity was noted. The role of a concomitant viral illness cannot be excluded in two patients as the event occurred after three days of linezolid therapy. More adverse events were noted in study 0045 compared to study 0049. This could be a reflection of the difference in the population enrolled in the two studies as children with CAP are likely to be sicker than children with acute otitis media. No comparator drug was used in either of the studies so no comparisons of the overall frequency of these adverse events can be made. Though the CAP study used a BID dosing regimen, children with CAP who are younger than 12 years will need TID dosing based on pharmacokinetic data. Hence the safety information provided by this study does not truly reflect the likelihood of adverse events in children < 12 years of age with CAP who will receive TID dosing.

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Study 0025

This study provides only limited information as it was uncontrolled, all patients enrolled were very sick and only data on SAE were obtained. The incidence of hematologic toxicity was higher in this group of patients than other phase 2 studies. All 4 hematologic adverse events (thrombocytopenia, bone marrow depression and anemia) were thought to be drug related and three of them occurred in patients receiving linezolid for > 28 days.

Phase 3 Studies

Study 0065

Overall, no major toxicities were noted in this study. One patient in the linezolid arm had neutropenia and one patient in the vancomycin arm had leukopenia. No other significant hematologic toxicities were noted. There were no deaths and of the two serious adverse events in the linezolid arm only elevated lipase was probably drug related. In this study children less than 12 years of age received linezolid in a BID dose. However, children in this age group with all other clinical indications including children less than 5 years of age with uncomplicated skin and skin structure infections will be receiving TID regimens. So, safety data in children less than 12 years of age from this study may not truly reflect the potential for adverse events in this age group using recommended dosing regimens.

Study 0082

Overall, toxicities were more common in this study compared to all other studies. Most patients enrolled in this study were much sicker and often had other significant underlying medical conditions. Adverse events were more common in the vancomycin arm and were mainly related to skin rash/anaphylaxis i.e. red man syndrome. Though there was no statistically significant difference in the incidence of thrombocytopenia between the two groups, the incidence of study emergent and drug related thrombocytopenia was higher in linezolid arm. No difference in the incidence of neutropenia or anemia was seen between the arms. However, grade 4 shifts for both neutrophils and platelets were seen more commonly in the linezolid arm, though the comparison with vancomycin was not statistically significant. No specific age group had a higher incidence of hematologic abnormalities except for shifts in hemoglobin values, which were much more common in the younger age group in both arms. This could represent a physiologic decline in hemoglobin after birth or may be iatrogenic due to repeated blood draws. No significant hepatic or renal toxicity was noted in any of the studies. In adult studies, though there was a suggestion of thrombocytopenia with use of linezolid, no other hematologic toxicities were evident despite the large number of patients exposed to linezolid (n~ 2000) but became evident with post marketing surveillance. In this study, mortality was higher in the linezolid arm and this may or may not be related to linezolid use. Cardiac adverse events were also higher in the linezolid arm and post marketing surveillance for any

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potential cardiac toxicities is also warranted. No age specific differences in the incidence of adverse events were seen.

B. Recommendations

From a clinical perspective, based on the evidence from a comparator controlled clinical trial provided by the sponsor, there is adequate efficacy and safety data to recommend approval of linezolid for use in children with uncomplicated skin and skin structure infections. There is also adequate efficacy and safety data provided in the comparator controlled study in hospitalized pediatric patients with Gram positive infections, efficacy data from adult studies and pharmacokinetic data in pediatric patients to recommend approval of linezolid in children with the following Gram positive infections:

- Nosocomial pneumonia
- Community acquired pneumonia,
- Complicated skin and skin structure infections, and
- Vancomycin resistant *Enterococcus faecium* infections.

Myelosuppression is a significant side effect of linezolid that has been observed in adult and juvenile animal studies. Reports of myelosuppression during post marketing surveillance resulted in the addition of a warning in the linezolid label. No statistically significant increased incidence of myelosuppression was seen in the pediatric studies submitted. Interpretation of these pediatric studies however is limited by the small number of patients enrolled and by the different dosing regimens used in these studies. Therefore, consideration should be given to the potential risks of linezolid including myelosuppression before its use in a situation where linezolid's medical need is established.

Major changes to the proposed package insert

Following are the important changes made to the sponsor's proposed package insert:

1. Clinical Pharmacology (Pediatrics)

The proposed package insert was modified to reflect the pharmacokinetic properties of linezolid in pediatric patients in different age groups:

The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in pediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult

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population. There is wider inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours (q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h (see DOSAGE AND ADMINISTRATION).

2. Indications and Usage

The sponsor had proposed to include pediatric indications in the _____ . Consistent with CFR 201.57(9)(iii) (iv) they were included in the PRECAUTIONS, Pediatric Use section and reads as follows:

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see INDICATIONS AND USAGE and CLINICAL STUDIES):

- nosocomial pneumonia
- complicated skin and skin structure infections
- community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years)
- vancomycin-resistant *Enterococcus faecium* infections

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years (see CLINICAL STUDIES):

- uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*

3. Warnings

The following statement was added to the warnings section of the label:

In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed.

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4. Precautions, Pediatric use

The following has been added to the Pediatric Use section to reflect the concern of increased variability in clearance of linezolid in pediatric patients.

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric and DOSAGE AND ADMINISTRATION).

5. Adverse Events

The following information regarding mortality in the clinical studies was added to the adverse event section.

In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established.

6. Postmarketing experience

The following information regarding postmarketing reports of neuropathy was added:

Neuropathy (peripheral, optic) has been reported in patients treated with ZYVOX. Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy.

7. Clinical studies

- Efficacy results for the MITT population were included.
- _____
_____ted.
- List of pathogens in clinical study results was modified to concur with the pathogens listed in the Indications and Usage section.

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8. Inclusion of MRSA as a pathogen in uncomplicated skin and skin structure infections

The sponsor had proposed including MRSA as a pathogen in uncomplicated skin and skin structure infections. As the role of MRSA in uncomplicated skin and skin structure is unclear MRSA was not included as a pathogen in uncomplicated skin and skin structure infections.

9. Dosage and Administration

The proposed package insert had no specific dosage recommendations for pre-term neonates less than 7 days of age (gestational age less than 34 weeks). The following was added to reflect dosing recommendations in neonates and is also included in the Precautions, Pediatric use section:

Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life.

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XI. Appendix

Appendix 1. Pediatric Written Request

NDA 21-130; 21-131; 21-132
IND 49,195; 55,618

Pharmacia & Upjohn Company
Attention: Robert S. Gremban
Regulatory Affairs Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Gremban:

Please refer to your correspondence dated August 24, 2001, requesting changes to the December 22, 1999, Written Request for pediatric studies for linezolid. We also refer to the amended Written Request for pediatric studies dated February 28, 2002.

We reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated December 22, 1999 and the amended Written Request dated February 28, 2002.

- Type of studies (e.g., double-blind, randomized, parallel group, safety, and/or pk):

Study #1: "Assessment of Linezolid Pharmacokinetics in Full Term and Pre-Term Neonates."

Study #2: "A randomized, blinded comparison of the safety and efficacy of oral linezolid vs. a cephalosporin for treatment of skin and skin structure infections in pediatric patients aged 3 months to 18 years."

Study #3/4: "A randomized, open-label comparison of IV linezolid/oral linezolid and IV vancomycin (with other IV/oral antibiotic switch, if appropriate) in suspected resistant gram positive infections in pediatric patients." and "A Prospective Study of Vancomycin-Resistant Enterococcal Infections in Pediatric Patients."

Study #5: "A Randomized, Comparative Trial of Linezolid vs. Vancomycin in Pediatric Patients with CSF Shunt Infections."

- Indications to be studied (i.e., objective of each study):

Study #1: Objective – To assess the pharmacokinetics of linezolid in full-term and pre-term neonates following a single 10 mg/kg intravenous dose of linezolid.

Study #2: Objectives – To assess the comparative efficacy, safety and tolerance of oral linezolid vs. oral cephalosporin for the treatment of skin and skin structure infections in pediatric patients.

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Study #3/4: Objectives – To evaluate the comparative tolerance of linezolid and vancomycin in the empiric treatment of suspected resistant gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), other methicillin-resistant *Staphylococcus* species (MRSS), and penicillin-resistant *Streptococcus pneumoniae* (PRSP), in pediatric patients. Information on the safety of linezolid and experience with the use of linezolid for VRE infections in pediatric patients will also be gathered in a separate, non-comparative portion of the study. A secondary objective is to study population pharmacokinetics in pediatric patients receiving linezolid.

Study #5: Objectives – To evaluate the comparative tolerance of linezolid and vancomycin in the treatment of CSF shunt infections due to gram-positive bacteria in the pediatric population. The study may primarily enroll patients with CSF shunt infections due to coagulase-negative staphylococci.

- Age group in which studies will be performed:

Study #1: Male and female infants less than 3 months of age, stratified by post-conceptual age (< 34 weeks and ≥ 34 weeks). Further stratification based on other factors (e.g., post-natal age) may also be performed.

Study #2: Pediatric patients (male and female) from 5 through 17 years of age.

Study #3/4: Pediatric patients (male and female) from birth through 11 years of age.

Study #5: Pediatric patients (male and female) from birth through 17 years of age.

- Study endpoints

Study #1: Pharmacokinetic parameters will be determined from assessments of linezolid plasma concentrations. Tolerance of a single dose of linezolid in neonates.

Study #2-5: Clinical efficacy, microbiological response, and safety are the endpoints of interest for these studies.

- Drug information

dosage form: Intravenous Solution, Oral Tablets, and Oral Suspension

route of administration: Intravenous and/or Oral

- Statistical information, including power of study and statistical assessments:

Study #1: A comparison between Term and Pre-term groups will be made for pharmacokinetic parameters. The study should include at least 12 subjects with post-conceptual age < 34 weeks and 12 subjects > 34 weeks gestation.

Study #2: The study should include at least 240 subjects in each treatment arm. Assuming a 90% success rate and 60% clinical evaluability rate and using a 2-sided test with $\alpha=5\%$ and power=80%, this target enrollment will provide a sufficient number of clinically evaluable patients to demonstrate equivalence between the two treatment groups to within 10%. All patients may be treated with oral linezolid or comparator.

Study #3/4: The total enrollment should include at least 160 patients. At least 40 subjects should have vancomycin-resistant enterococcal infections treated with linezolid. At least 30 patients

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should be 3 months of age or less and at least 10 of these young infants should have vancomycin-resistant enterococcal infections treated with linezolid.

Study #5: The study should have a total enrollment of at least 50 patients with CSF shunt infections. This number of patients is selected to provide preliminary information on the tolerance and efficacy of linezolid for CSF shunt infections.

- Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.
- Format of reports to be submitted: Full study reports addressing the issues outlined in this request with full analysis, assessment, and interpretation should be provided for all requested studies. **INCLUDE OTHER INFORMATION AS APPROPRIATE.**
- Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before September 30, 2004, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only to existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **“PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY”** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **“PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **“SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED”** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Ms. Beth Duvall-Miller, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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Appendix 2: Pathogen List for Protocol 65 Microbiological Evaluability

Pathogen Name
<i>Enterococcus faecalis</i> *
<i>Enterococcus faecalis</i> (Resistant or Intermediate to Penicillin)*
<i>Staphylococcus aureus</i> †
<i>Staphylococcus aureus</i> Beta Lactamase Negative†
<i>Staphylococcus aureus</i> Beta Lactamase Positive†
<i>Staphylococcus aureus</i> , Methicillin Resistant†
<i>Staphylococcus aureus</i> Methicillin Resistant, Beta Lactamase Neg†
<i>Staphylococcus aureus</i> Methicillin Resistant, Beta Lactamase Pos†
<i>Staphylococcus aureus</i> Penicillinase Pos†
<i>Staphylococcus cohnii</i>
<i>Staphylococcus hemolyticus</i>
<i>Staphylococcus hemolyticus</i> Beta Lactamase Neg
<i>Staphylococcus hemolyticus</i> Beta Lactamase (Cefinase) Pos
<i>Staphylococcus hemolyticus</i> Beta Lactamase Pos
<i>Staphylococcus hemolyticus</i> Beta Lactam Neg, Meth Resistant
<i>Staphylococcus lugdunensis</i>
<i>Staphylococcus simulans</i>
<i>Staphylococcus warneri</i>
<i>Streptococcus agalactiae</i>
<i>Streptococcus anginosus</i>
<i>Streptococcus constellatus</i>
<i>Streptococcus dysgalactiae</i>
<i>Streptococcus equi</i>
<i>Streptococcus equisimilis</i>
<i>Streptococcus iniae</i>
<i>Streptococcus intermedius</i>
<i>Streptococcus pyogenes</i>
<i>Streptococcus zooepidemicus</i>
<i>Streptococcus</i> , Beta Hemolytic

* Organism used to define vancomycin-resistant enterococci (VRE)

† Organism used to define methicillin-resistant *Staphylococcus aureus* (MRSA)

‡ Organism used to define penicillin-resistant *Streptococcus pneumoniae* (PRSP)

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Appendix 3A: Criteria for Substantially Abnormal Laboratory Assay Values (Study 0065)

Lab Assay	Criteria 1: Patients with Normal Baseline Values	Criteria 2: Patients with Abnormal Baseline Values
Hemoglobin	<75% of LLN	<75% of BL (if BL > ULN) <90% of BL (if BL < LLN)
Hematocrit	<75% of LLN	<75% of BL (if BL > ULN) <90% of BL (if BL < LLN)
Red Blood Count	<75% of LLN	<75% of BL (if BL > ULN) <90% of BL (if BL < LLN)
*Platelet Count	<75% of LLN	<75% of BL (if BL < LLN)
*White Blood Count	<75% of LLN	<75% of BL (if BL < LLN)
*Neutrophils (Absolute)	<0.5 x LLN	<0.5 X BL (if BL < LLN)
*ALT/SGPT	>2 x ULN	>2 X BL (if BL > ULN)
*AST/SGOT	>2 x ULN	>2 X BL (if BL > ULN)
*Blood Urea Nitrogen (BUN)	>2 x ULN	>2 X BL (if BL > ULN)
*Creatinine	>2 x ULN	>2 X BL (if BL > ULN)
*Gamma Glutamyl Transferase	>2 x ULN	>2 X BL (if BL > ULN)
*Lipase	>2 x ULN	>2 X BL (if BL > ULN)

Abbreviations: BL = baseline; ULN = upper limit of laboratory normal range;

LLN = lower limit of laboratory normal range

* Algorithm for Assessment of Substantially Abnormal Laboratory Values:

A subject is considered abnormal at baseline if the baseline value is outside the laboratory reference range, except for those lab tests marked with a *. For these one-directional criteria, baseline values will be classified as abnormal only when they deviate from the normal range in the same direction as the substantially abnormal criteria. For example, baseline values of ALT and AST will be considered abnormal only if they are above the upper limit of normal. For subjects normal at baseline, post-baseline values are evaluated by criteria 1 to determine substantially abnormal values. For subjects abnormal at baseline, both the conditions given by criteria 1 and 2 must be met by post-baseline values to classify them as substantially abnormal values.

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Appendix 3B: Criteria for Substantially Abnormal Laboratory Assay Values (Study 0082)

Laboratory Assay	Criteria 1: Patients with Normal Baseline Values	Criteria 2: Patients with Abnormal Baseline Values*
Hemoglobin	< 75% of LLN	< 75% of BL (if BL > ULN) < 90% of BL (if BL < LLN)
Hematocrit	< 75% of LLN	< 75% of BL (if BL > ULN) < 90% of BL (if BL < LLN)
Red Blood Count	< 75% of LLN	< 75% of BL (if BL > ULN) < 90% of BL (if BL < LLN)
*Platelet Count	< 75% of LLN	< 75% of BL (if BL < LLN)
*White Blood Count	< 75% of LLN	< 75% of BL (if BL < LLN)
*Neutrophils, Absolute Count	< 0.5 x LLN	< 0.5 x BL (if BL < LLN)
*Total Bilirubin	> 2 x ULN	> 1.5 x BL (if BL > ULN)
*ALT/SGPT	> 2 x ULN	> 2 x BL (if BL > ULN)
*Creatinine	> 2 x ULN	> 2 x BL (if BL > ULN)
Sodium	>1.05 x ULN or < 0.95 x LLN	>1.05 x BL (if BL > ULN) or <0.95 x BL (if BL < LLN)
Potassium	>1.1 x ULN or < 0.90 x LLN	>1.10 x BL (if BL > ULN) or <0.90 x BL (if BL < LLN)
Chloride	>1.1 x ULN or < 0.90 x LLN	>1.10 x BL (if BL > ULN) or <0.90 x BL (if BL < LLN)
Bicarbonate	>1.1 x ULN or < 0.90 x LLN	>1.10 x BL (if BL > ULN) or <0.90 x BL (if BL < LLN)
*Amylase	> 2 x ULN	> 2 x BL (if BL > ULN)

Abbreviations: BL = baseline; LLN = lower limit of laboratory normal range;

ULN = upper limit of laboratory normal range

A value was considered abnormal at baseline if it was outside the laboratory reference range, except for those tests marked with an *. For these one-directional evaluations, baseline values were considered abnormal only when they deviated from the normal range in the same direction as criteria 2. For example, baseline values of *Amylase were considered abnormal only if they were above the upper limit of normal.

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Appendix 4A: Grading Criteria for Selected Hematology and Chemistry Laboratory Tests (Study 0065)*

Laboratory Test by Age Group	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/dL)	> 9.4	8.0- 9.4	7.0 - 7.9	6.5 - 6.9	< 6.5
Platelets (x10 ³ /μL)	> 99	75 - 99	50 - 74.9	20 - 49.9	< 20
Neutrophils (x10 ³ /μL)	> 1500	1000 - 1500	750 - 999	500 - 749	< 500
ALT	<1.25 x ULN	≥1.25 - <2.5 x ULN	≥2.5 - <5. x ULN	≥5.0 - <10.0 x ULN	≥10.0 x ULN
AST	<1.25 x ULN	≥ 1.25 - <2.5 x ULN	≥2.5 - <5.0 x ULN	≥5.0 <10.0 x ULN	≥ 10.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of laboratory normal range
 Pediatric ACTG criteria (<http://pactg.s-3.com>).

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Appendix 4B: Grading Criteria for Selected Hematology and Chemistry Laboratory Tests (Study 0082)*

Laboratory Test by Age Group	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/dL)					
8 days-90 days	≥ 10.0	9.0 - 9.9	7.0 - 8.9	6.5 - 6.9	< 6.5
91 days - <1 year	≥ 10.0	9.0 - 9.9	7.0 - 8.9	6.5 - 6.9	< 6.5
1 year - 4 years	≥ 10.0	9.0 - 9.9	7.0 - 8.9	6.5 - 6.9	< 6.5
5 years-11 years	≥ 10.0	9.0 - 9.9	7.0 - 8.9	6.5 - 6.9	< 6.5
Platelets (x10³ L)					
8 days - 90 days	≥ 100	75 - 99.9	50 - 74.9	25 - 49.9	< 25
91 days - <1 year	≥ 100	75 - 99.9	50 - 74.9	25 - 49.9	< 25
1 year - 4 years	≥ 100	75 - 99.9	50 - 74.9	25 - 49.9	< 25
5 years -11 years	≥ 100	75 - 99.9	50 - 74.9	25 - 49.9	< 25
Neutrophils (μL)					
8 days - 90 days	≥ 1200	750 - 1199	400 - 749	250 - 399	< 250
91 days - <1 year	≥ 1200	750 - 1199	400 - 749	250 - 399	< 250
1 year - 4 years	≥ 1200	750 - 1199	400 - 749	250 - 399	< 250
5 years -11 years	≥ 1200	750 - 1199	400 - 749	250 - 399	< 250
ALT					
8 days - 90 days	≤ ULN	1.1- 4.9 x ULN	5.0- 9.9 x ULN	10.0 - 14.9 x ULN	≥ 15.0 x ULN
91 days-<1 year	≤ ULN	1.1- 4.9 x ULN	5.0 - 9.9 x ULN	10.0 - 14.9 x ULN	≥ 15.0 x ULN
1 year - 4 years	≤ ULN	1.1- 4.9 x ULN	5.0 - 9.9 x ULN	10.0 - 14.9 x ULN	≥ 15.0 x ULN
5 years - 11 years	≤ ULN	1.1- 4.9 x ULN	5.0 - 9.9 x ULN	10.0 - 14.9 x ULN	≥ 15.0 x ULN
Bilirubin					
8 days - 90 days	≤ ULN	1.1- 1.9 x ULN	2.0 - 2.9 x ULN	3.0 - 7.4 x ULN	≥ 7.5 x ULN
91 days - <1 year	≤ ULN	1.1- 1.9 x ULN	2.0 - 2.9 x ULN	3.0 - 7.4 x ULN	≥ 7.5 x ULN
1 year - 4 years	≤ ULN	1.1- 1.9 x ULN	2.0 - 2.9 x ULN	3.0 - 7.4 x ULN	≥ 7.5 x ULN
5 years -11 years	≤ ULN	1.1- 1.9 x ULN	2.0 - 2.9 x ULN	3.0 - 7.4 x ULN	≥ 7.5 x ULN

Modified from pediatric ACTG criteria (<http://pactg.s-3.com>) to fit age group classifications for this study

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/s/

Sumathi Nambiar
2/11/03 08:03:20 AM
MEDICAL OFFICER

Susan Thompson
2/13/03 04:30:34 PM
MEDICAL OFFICER

Janice Soreth
2/19/03 09:35:14 AM
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