

NEW MEDICINES ON THE MARKET

Evaluated information for the NHS

LINEZOLID

Summary

- Linezolid is the first of a new class of antimicrobial agents, the oxazolidinones, whose mechanism of action differs from that of existing agents. Cross-resistance to other antimicrobials is therefore less likely and has not been shown to date. It is active against a wide range of Gram-positive bacteria including MRSA, vancomycin-resistant enterococci (VRE) and penicillin-resistant pneumococci, but not against Gram-negative pathogens
- It is currently licensed for nosocomial pneumonia, community acquired pneumonia and skin and soft-tissue infections. Use of linezolid in pneumonia demands confirmation of a Gram-positive pathogen or combination with a Gram-negative agent. Its spectrum of activity makes it particularly appropriate for treating complicated skin and soft-tissue infections, where multiresistant enterococci or staphylococci are documented or likely.
- Two randomised controlled trials have been published. They showed that linezolid was equivalent to vancomycin in the treatment of hospitalised patients with nosocomial pneumonia and to oxacillin-dicloxacillin in the treatment of complicated skin and soft tissue infections. In a trial published in abstract form, linezolid produced >85% clinical/microbiological cure in VRE infections
- Plasma levels do not require monitoring and it has 100% oral bioavailability enabling early switch to oral therapy. A trial showing higher first week discharge rates with oral and IV linezolid compared with vancomycin in the treatment of complicated skin and soft tissue infections, pneumonia, UTI and bacteraemia, has been published. Differences in discharge rates during the first week of therapy were most marked for patients with skin and soft tissue infections. Further comparative clinical data are needed to assess the potential economic benefits of linezolid
- It has few adverse effects, but cases of myelosuppression following long-term (>14days) therapy have been noted
- Given that current available evidence suggests similar effectiveness to other antibiotics, and because of concerns about emerging resistance, linezolid should be reserved for specialist recommendation in situations where other antibiotics have failed or are inappropriate due to bacterial resistance

Date Published: June 2001

Monograph Number: 4/01/05

Marketed: January 2001

Region of origin to whom queries should be directed: South West (Bristol)

The information contained in this document will be superseded in due course.

Not to be used for commercial purposes

Copyright MIPG 2001

Web site <http://www.ukdipg.org.uk/stage4.htm>

LINEZOLID

Approved Name:	Linezolid
Brand Name (Manufacturer):	Zyvox (Pharmacia)
Presentation:	Tablets,linezolid 600mg; solution for infusion, linezolid 600mg in 300ml (2mg/ml)
BNF therapeutic class:	Oxazolidinone antibacterial agent
Licensed Indication:	<ul style="list-style-type: none"> • Treatment of nosocomial pneumonia, community acquired pneumonia, skin and soft tissue infections when known or suspected to be caused by susceptible micro-organisms which include aerobic Gram positive bacteria, certain Gram negative aerobes and certain Gram positive anaerobes • In combination with other antimicrobials if a concomitant Gram negative pathogen is documented or suspected
Dosage and Administration:	<p>Pneumonia - 600mg IV or orally twice daily</p> <p>Skin and soft tissue infections - 400mg to 600mg orally or 600mg IV twice daily depending on clinical severity. Duration of treatment is 10-14 consecutive days and is dependent on the pathogen, the site of the infection and its severity, and on the patient's clinical response.</p>
Sector of Use:	Hospital [Y] Primary Care [N]

Therapeutic Comment:	<p>Linezolid is the first of a new antibiotic class active against strains of Gram-positive bacteria resistant to other antibiotics, including MRSA and VRE. No cross-resistance to other antimicrobial agents has yet been shown. It is likely to be particularly useful for skin and soft tissue infections in hospital where multi-resistant enterococci or staphylococci are known or likely to be present. Oral administration may allow early discharge and more appropriate use of resources</p>
-----------------------------	---

Cost and Course Details:	<p>Cost of 10 days treatment at 600mg bd:-</p> <table style="margin-left: 40px;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Hospital cost</u></th> <th style="text-align: center;"><u>Basic NHS cost</u></th> </tr> </thead> <tbody> <tr> <td>Linezolid infusion</td> <td style="text-align: center;">£670</td> <td style="text-align: center;">£890</td> </tr> <tr> <td>Linezolid tablets</td> <td style="text-align: center;">£670</td> <td style="text-align: center;">£890</td> </tr> </tbody> </table>		<u>Hospital cost</u>	<u>Basic NHS cost</u>	Linezolid infusion	£670	£890	Linezolid tablets	£670	£890
	<u>Hospital cost</u>	<u>Basic NHS cost</u>								
Linezolid infusion	£670	£890								
Linezolid tablets	£670	£890								

Treatment Alternatives:	<table style="margin-left: 40px;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Basic NHS cost</u></th> </tr> </thead> <tbody> <tr> <td>Cost of 10 days treatment</td> <td></td> </tr> <tr> <td>Vancomycin 1g bd</td> <td style="text-align: center;">£346.40</td> </tr> <tr> <td>Quinupristin/dalfopristin 500mg (1 vial) tds</td> <td style="text-align: center;">£1110</td> </tr> <tr> <td>Teicoplanin (see SPC)</td> <td style="text-align: center;">£ 208.40 - 572.5</td> </tr> </tbody> </table>		<u>Basic NHS cost</u>	Cost of 10 days treatment		Vancomycin 1g bd	£346.40	Quinupristin/dalfopristin 500mg (1 vial) tds	£1110	Teicoplanin (see SPC)	£ 208.40 - 572.5
	<u>Basic NHS cost</u>										
Cost of 10 days treatment											
Vancomycin 1g bd	£346.40										
Quinupristin/dalfopristin 500mg (1 vial) tds	£1110										
Teicoplanin (see SPC)	£ 208.40 - 572.5										

INTRODUCTION

There are growing concerns about the increasing problem of antimicrobial resistance [1-3]. In the 1980s Gram negative bacteria were a major clinical problem, whereas the 1990s saw the emergence of penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [4]. The latter are of particular concern as several strains are resistant to all currently available antibiotics [5]. In addition, cases of clinically significant bacteraemia in England and Wales, reported to the Communicable Disease Surveillance Centre, increased from 31,763 in 1990, to 51,232 in 1998 [6]. Analysis of trends in this data showed a substantial increase in reports of MRSA and VRE, as well as *Streptococcus pneumoniae* resistant to both penicillin and erythromycin.

These problems have given added impetus to the search for new antimicrobial agents. Oxazolidinones are a new class of antimicrobials unrelated to other agents in current use, with a novel mechanism of action.

PHARMACOLOGY

Linezolid selectively inhibits bacterial protein synthesis by binding to a site on the bacterial ribosome and preventing the formation of the functional initiation complex which is an essential component of the translation process [7,8]. This mechanism of action may reduce the likelihood of bacteria developing cross-resistance to this agent, although clinicians must still expect resistance to linezolid and ensure it is used appropriately.

PHARMACOKINETICS

Linezolid is rapidly and completely absorbed after oral administration reaching peak plasma concentration after 2 hours; it has a mean absolute bioavailability of approximately 100% [7,9]. Absorption is not significantly affected by food [9]. There is rapid distribution into body tissues. At steady state after twice daily oral administration of linezolid 375 and 625mg minimum plasma concentrations (C_{min}) were equal to or greater than 4 mg/L (i.e. above the MIC_{90} for the most resistant pathogens) for both doses. After twice daily IV administration of linezolid 500mg and 625mg, at steady state C_{min} values were 3.51 and 3.84 mg/L respectively. Time in excess of the the MIC_{90} for more common pathogens was 9-10 hours of the 12 hour dosing interval [10]. Linezolid is metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive metabolites. Approximately 30% of linezolid is excreted as active drug in the urine and elimination half-life is 5-7 hours [7]. The pharmacokinetic properties of a single oral dose were similar in young (18-40) and

elderly (mean age 70) volunteers. Although clearance was lower in women compared with men, half-lives were similar [11]. A single oral dose study in 7 patients with mild to moderate hepatic impairment found that pharmacokinetic parameters were comparable to those in the control group [12]. Dose adjustment for age or gender or in patients with mild to moderate hepatic impairment is therefore not required [7,11,12]. Although studies of linezolid kinetics in children and adolescents aged 3 months to 17 years have been carried out [7,13] there are insufficient safety and efficacy data to establish dosage recommendations for patients under 18 years [7]. A single oral dose study in 24 subjects with varying degrees of renal impairment showed that there was little effect of renal function on the overall clearance of linezolid [14]. However the two primary metabolites will accumulate in patients with severe renal insufficiency including patients on dialysis. The clinical significance of this is unknown [7]. Approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis, therefore the dose should be given after dialysis (see SPC).

EFFICACY

In vitro studies

Linezolid is active chiefly against Gram-positive organisms. In-vitro bacteriostatic activity has been shown against staphylococci (including MRSA) [15], enterococci (including VRE), penicillin-resistant pneumococci [15,16,17] and group C and G streptococci (including vancomycin tolerant species)[18]. Bactericidal activity has also been shown against many streptococci [8]. Linezolid has a narrow range of MICs (0.5-4mg/L) against a wide range of strains of multi-resistant Gram-positive cocci [19].

Cross-resistance between linezolid and other antimicrobials, including chloramphenicol, fusidic acid, macrolides and tetracyclines has not been shown to date [20]. A study of the prevalence of antibiotic resistance amongst Gram-positive cocci from 25 UK hospitals over an 8 month period found that all the organisms tested, including multi-resistant strains, were susceptible to linezolid with MICs in the range 0.12-4mg/L. These included penicillin- and erythromycin-resistant *Strep. Pneumoniae*, VRE, MRSA and coagulase negative staphylococci resistant to vancomycin and teicoplanin [21].

Clinical studies

Phase I and Phase II. Open label non-comparative, non-randomised phase I and phase II studies have reported on the use of IV and oral linezolid for skin and soft tissue infections, community-acquired pneumonia and bacteraemia; doses were 200-1270mg daily for periods of 3-28 days [22]

In an open-label, compassionate use trial pts aged at least 28 days with a significant infection due to a resistant Gram-positive organism, or intolerance or non-responsiveness to other agents received oral or IV linezolid 600mg bd (10mg/kg/bd for children). Duration of treatment was 5 to 21 days. Preliminary results showed clinical cure in 75.3% of 271 pts and microbiological cure in 74.5% of 157 pts. Infections included bacteraemia, endocarditis, intra-abdominal abscess and peritonitis, skin and soft tissue infections and osteomyelitis. Causative organisms included MRSA and VRE [23].

In another open-label phase II study 273 hospitalised pts with skin/soft-tissue infections predominantly caused by *S. aureus* were given IV followed by oral linezolid low-dose (250mg tds or 375mg bd) or high-dose (375mg tds or 625mg bd) for a mean of 10 days. At 15 - 28 days follow-up clinical success rates were 83.3% and 87.7% for the low and high dose groups respectively. Microbiological cure was achieved in 82.5-90% of pts [24].

In a study in hospitalised pts with community-acquired pneumonia using a similar dosage and treatment protocol, at follow-up (15 to 28 days after the end of treatment) 93.2% and 94.4% of pts in the low-dose group (n=44) achieved clinical and microbiological success, respectively. In the high dose group (n=76), success rates were 94.4% and 97.4% [25].

Phase III. Several phase III trials with linezolid involving over 4000 pts are complete, but are awaiting full publication [26-29,32,33]. Two have been fully published [30,31]. In all studies the primary efficacy variables were clinical and microbiological outcome. Clinical outcome was assessed at the long-term 'test of cure' follow-up visit (up to 28 days). In the pneumonia studies clinical cure was defined as resolution of baseline clinical signs and symptoms of infection (e.g. fever, changes in WBC) and improvement or lack of progression of infection-related radiographic abnormalities.

In all the studies the numbers of clinically evaluable (CE) pts were much smaller than the ITT population. CE pts included those who were assessed during the follow-up period, who did not receive other antibiotics, who completed at least 7 days of treatment (unless the pt discontinued the study for any reason other than lack of efficacy), or did not miss two or more consecutive doses and took at least 80% of prescribed study medication.

In CE pts clinical and microbiological cure rates of around 90% have been achieved in skin and soft tissue infections and in community acquired pneumonia. In hospital acquired pneumonias linezolid plus aztreonam achieved clinical cure rates of 66%-67%, similar to those seen with vancomycin/aztreonam. Against MRSA infections, linezolid achieved a clinical cure rate of 63%, compared with 66% for vancomycin; hospital

discharge was often earlier in the linezolid arm, owing to the facility to switch to oral therapy [26]. When looking at these results it should be remembered that treatments seem more effective when looking at results in CE pts rather than ITT pts.

For a summary of the studies see table.

Resistance. During the phase III trials and the US compassionate use program the development of resistance to linezolid was reported in 15 pts treated for enterococcal infections [34, 35]. In these patients there was a four-fold increase in MIC. Factors shown to be implicated in the development of resistance in enterococcal species include: prolonged and/or subtherapeutic dosing, complex concurrent disease and non-removal of infected prosthetic devices. Two of these cases have been reported [36]. Five more cases of infections due to vancomycin-resistant *E. faecium* resistant to linezolid have been reported recently, all of these pts receiving prolonged therapy and having complex underlying problems [37].

PROMOTIONAL DATA

The manufacturer is promoting linezolid for use in hospitals to treat severe infections caused by multiresistant Gram-positive cocci. Use in the community is being discouraged.

- ◆ Linezolid is being promoted for ease of switching to oral therapy - the oral and IV dosage forms are bioequivalent (see above). Oral administration allows earlier discharge of patients, reducing exposure to nosocomial pathogens and allowing more efficient use of resources. In an intention to treat analysis of data from a phase III study comparing linezolid (IV/oral) with vancomycin (IV) for the treatment of infections due to MRSA [33], patients treated with linezolid had a median length of stay (LOS) (95% CI) of 14 days (9-17) vs 15 days (13-17) in the vancomycin group. In the clinically evaluable sample (linezolid n=124, vancomycin n=130) the corresponding LOS was 14 (9-18) and 16 (14-19) days respectively [38]. LOS was calculated as the number of days between a patient's first dose of study medication and the discharge date. However, the number of patients discharged during the first week differed significantly between the groups (ITT sample, 30% in the linezolid group vs. 19% in the vancomycin group (p=0.005) and in the clinically evaluable sample, 31% vs. 12%, respectively [p=0.001])
- ◆ Linezolid is well-tolerated. In clinical trials approximately 22% of pts experienced adverse events. About 3% of pts discontinued treatment because they experienced a drug-related adverse event [7] (see below).
- ◆ Linezolid is effective in treating infections caused by resistant pathogens. Two

randomised phase III clinical trials published in abstract form have evaluated the use of two doses of linezolid in the treatment of VRE [39] and compared linezolid with vancomycin in MRSA infections [33,40]. The clinical cure rate in CE pts with VRE infections receiving linezolid 600mg IV or oral bd was 94% [39,41]. Clinical cure rates in the CE pts with MRSA infections were similar in the linezolid (600mg IV bd) and vancomycin (1g IV bd) groups [33,40,41]. Data is available from the compassionate use programme in patients with significant infections caused by a cultured Gram-positive organism not able to be treated otherwise (i.e. due to resistance to, or poor tolerability of other therapies). Up to January 2000, 671 pts had been enrolled in the USA [41].

ADVERSE EFFECTS

Information on adverse reactions is based on data from clinical studies involving over 2,000 adult patients who received the recommended doses of linezolid for up to 28 days [7]. Approximately 22% of patients experienced adverse reactions; those most commonly reported were headache, diarrhoea, nausea, vomiting, metallic taste, abnormal liver function tests and vaginal and oral candidiasis. In phase II trials the incidence of adverse events was as follows: nausea (5.4%), diarrhoea (5.2%), tongue discoloration (2.5%), oral thrush (2.3%), headache (2.3%), taste alteration (2.3%) [41]. The most commonly reported drug-related adverse events which led to discontinuation of treatment were headache, diarrhoea, nausea and vomiting. About 3% of patients discontinued treatment because they experienced an adverse event. The SPC has a table of common and uncommon adverse events [7,8,42].

Reversible myelosuppression (including anaemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported when linezolid has been used for longer than 10-14 days. A decrease in platelet count may occur more commonly in patients with severe renal insufficiency. Platelet counts and haemoglobin levels should be monitored in these patients and in those with pre-existing anaemia or thrombocytopenia, or those who receive more than 10-14 days of therapy or who are receiving concomitant medications that may decrease haemoglobin levels, platelet count or function [7,42]. Following reports to the FDA of myelosuppression in patients on linezolid, Pharmacia recently issued a warning in the USA about this adverse effect recommending that complete blood counts should be monitored weekly in patients receiving linezolid, particularly in those whose course of treatment exceeds two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or

concomitant antibiotic therapy [43]. Three cases of reversible myelosuppression with red cell hypoplasia, resembling reversible chloramphenicol bone marrow toxicity have been reported. Duration of therapy with linezolid was 2 weeks, 6 weeks and 4 months [44].

CONTRAINDICATIONS/ PRECAUTIONS (See SPC)

Linezolid is a weak, reversible, non-selective inhibitor of monoamine oxidase (MAOI) [7,8]. There are limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAOI inhibition [7]. In view of the limited data, linezolid is contraindicated in patients on MAOI and caution is advised with a number of other drugs and medical conditions (see SPC). Ingestion of excessive amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extract, soy sauce) should also be avoided [7]. No CYP450 interactions are expected as linezolid is not metabolised by cytochrome P450 and it does not inhibit any of the clinically significant human CYP isoforms [7]. For other interactions/warnings/ precautions/monitoring requirements see SPC and 'Adverse Effects'.

Use in renal insufficiency
Use in hepatic insufficiency See SPC
Pregnancy and lactation

REFERENCES

1. Science and Technology Committee of the House of Lords. Science and Technology - Seventh Report. Resistance to Antibiotics and other Antimicrobial Agents, 17 March 1998
2. Sub-group on Antimicrobial Resistance, Standing Medical Advisory Committee, Dept. of Health. The Path of Least Resistance, 1998
3. Chief Medical Officer, Dept of Health. Antimicrobial Resistance PL/CMO/98/6
4. Chambers ST. Resistance to antimicrobial agents: can we make a difference? *Adverse Drug React.Toxicol.Rev.* 2000; **19**: 207-221
5. Moellering RC Jr. Vancomycin-resistant enterococci. *Clin.Infect.Dis.* 1998; **26**: 1196-1199
6. Reacher MH et al. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* 2000; **320**: 213-216
7. Zyvox. Summary of Product Characteristics. Pharmacia & Upjohn Limited January 2001
8. Clemett D & Markham A Linezolid *Drugs* 2000; **59**: 815-827
9. Welshman IR et al. Assessment of absolute bioavailability and evaluation of the effect of food on oral bioavailability of linezolid [abstract]. *Antiinfect. Drugs Chemother.* 1998; **16** Suppl. 1: 54
10. Stalker DJ et al. Linezolid safety, tolerance and pharmacokinetics after intravenous dosing twice daily for 7.5 days [abstract]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 September 28-October 1; Toronto. Abstract A-116

11. Lasher Sisson T et al. Effect of age and gender on the single-dose pharmacokinetics of linezolid. Proceedings of the 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 September 27; San Francisco. Abstract 1194
12. Hendershot PE et al. Pharmacokinetics of linezolid in patients with liver disease [abstract]. *J. Antimicrob. Chemother.* 1999; **44** Suppl. A: 55
13. Stalker DJ et al. Pharmacokinetics of linezolid in paediatric patients [abstract]. *Clin.Infect.Dis.* 1998; **27**: 1061
14. Brier ME et al. Pharmacokinetics of linezolid in subjects with varying degrees of renal function and on dialysis [abstract]. *J.Invest.Med.* 1998; **46**: 276A
15. Piper KE et al. In-vitro activity of linezolid against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant pneumococci [abstract]. 38th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 September 24-27; San Diego
16. Jones RN et al. Antimicrobial activity of linezolid (Formerly U-100766) tested against 3,808 strains of Gram-positive organisms having resistance to various drugs (Poster). 37th Annual Meeting of the Infectious Diseases Society of America; 1999 November 18-21; Philadelphia
17. Patel R et al. In vitro activity of linezolid against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn.Microbiol.Infect.Dis.* 1999; **34**: 119-122
18. Zaoutis T et al. In vitro activity of linezolid (U-100766) and quinupristin/dalfopristin against vancomycin-tolerant Group C and Group G streptococci (Poster). 37th Annual Meeting of the Infectious Diseases Society of America; 1999 November 18-21; Philadelphia
19. Johnson AP et al. Activity of linezolid against multi-resistant Gram-positive bacteria from diverse hospitals in the United Kingdom. *J.Antimicrob.Chemother.* 2000; **45**: 225-230
20. Fines M and Leclercq R. Influence of mechanisms of resistance to antibiotics that bind to the 50S ribosomal subunit on the activity of linezolid against gram-positive organisms. Proceedings of the 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 September 26-29; San Francisco, C183
21. Henwood CJ et al. Susceptibility of Gram-positive cocci from 25 UK hospitals to antimicrobial agents including linezolid *J.Antimicrob.Chemother.* 2000; **46**: 931-940
22. Anon. Linezolid. *New Drugs In Clinical Development UKDIPG/NPC* May 2000 3/00/03 Birmingham MC et al. Outcomes with linezolid from an ongoing compassionate use trial of patients with significant, resistant, gram-positive infections (Poster). 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 September 24-27; San Francisco
23. Cammarata SK et al. Efficacy of linezolid in skin and soft tissue infections [abstract]. *Clin.Microbiol.Infect.* 1999; **5** Suppl. 3: 133
24. Cammarata SK et al. Efficacy of linezolid in community-acquired *S.pneumoniae* pneumonia. *Am.J.Respir.Crit.Care Med* 1999;**159** Suppl. Pt 2 (3): A844
25. Livermore DM. Quinupristin/dalfopristin and linezolid: where, when, which and whether to use? *J.Antimicrob.Chemother.* 2000; **46**: 347-350
26. Plouffe JF. Emerging therapies for serious Gram-positive bacterial infections: a focus on linezolid. *Clin.Infect.Dis.* 2000; **31** (Suppl 4): S144-149
27. Cammarata SK et al. Oral linezolid in the treatment of community-acquired pneumonia:a phase III trial [abstract E73]. In: Program and abstracts of the American Thoracic Society International Conference (Toronto). New York: American Thoracic Society, 2000: 654
28. Cammarata SK et al. Comparison of linezolid versus ceftriaxone/cefepodoxime in the treatment of hospitalized community-acquired pneumonia (Poster) 9th International Congress on Infectious Diseases; 2000 April 10-13; Buenos Aires
29. Rubinstein E et al. Linezolid (PNU_100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin.Infect.Dis.* 2001; **32**: 402-412
30. Stevens DL et al. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. *Antimicrob.Ag.Chemoth.* 2000; **44**: 3408-3413
31. Duvall SE et al. Comparison of oral linezolid to oral clarithromycin in the treatment of uncomplicated skin infections: results from a multinational phase III trial (Poster). 9th International Congress on Infectious Diseases; 2000 April 10-13; Buenos Aires
32. Hafkin B et al. Linezolid for the treatment of methicillin-resistant *Staphylococcus* species (MRSS) infections: a randomized, open-label trial comparing linezolid IV/PO and vancomycin IV. **M/1260/0031** 22 September 1999. Pharmacia & Upjohn Data on file.
33. Anon. FDA panel backs P&U's Zyvox. *SCRIP* No 2526 March 29th 2000 p.18
34. www.zyvox.com/pdfs/zyvox_full_prescribe_012001.pdf (accessed 19.04.01)
35. Zurenko G et al. Development of linezolid-resistant *Enterococcus faecium* in two compassionate use program patients treated with linezolid (Poster). 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 September 26-29; San Francisco
36. Gonzales RD et al. Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid. *Lancet* 2001; **357**: 1179
37. Li J et al. Comparison of length of hospital stay for patients with known or suspected methicillin-resistant *Staphylococcus* species infections treated with linezolid or vancomycin: a randomized, multicenter trial *Pharmacotherapy* 2001; **21**: 263-274 Hartman CS et al. Linezolid in the treatment of vancomycin-resistant enterococcus: a dose comparative, multicenter phase III trial (Abstract) 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 September; Toronto
38. Leach TS et al. Linezolid vs vancomycin for the treatment of MRSA infections: results of a randomized phase III trial (Abstract). 9th International Congress on Infectious Diseases (ICID). 2000 April 10-13; Buenos Aires
39. Perry CM and Jarvis B. Linezolid. *Drugs* 2001; **61**: 525-551
40. Wilks NE et al. Safety and tolerance of linezolid in phase II trials (Poster). 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 September 26-29; San Francisco
41. Zyvox. Clinical Information Pack. Pharmacia & Upjohn. January 2001
42. Peterson J. Important drug warning. March 2001. Pharmacia Corporation. New Jersey.
43. Green SL et al. Linezolid and reversible myelosuppression. *JAMA* 2001; **285**: 1291

LINEZOLID

Ref No	Design of Study	Treatments Assessed	Major Outcome Measures	Results and Comments																														
28 abstr	Randomised, single-blind, multicentre study in 540 adult outpatients with community-acquired pneumonia (clinical symptoms e.g. cough, purulent sputum, fever; chest X-ray)	Linezolid 600mg PO bd (n=272) vs cefpodoxime 200mg PO bd (n=268) for 7-14d	Clinical cure and microbiological eradication rates assessed at 15-21 d after the end of therapy	<table style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">Linezolid</td> <td style="text-align: center;">Cefpodoxime</td> <td></td> </tr> <tr> <td>Clinical cure</td> <td style="text-align: center;">180/201 (90%)</td> <td style="text-align: center;">187/206 (91%)</td> <td style="text-align: center;">(p=0.68)</td> </tr> <tr> <td>Microbiological cure</td> <td style="text-align: center;">43/49 (88%)</td> <td style="text-align: center;">42/47 (89%)</td> <td style="text-align: center;">CI not stated</td> </tr> </table> <p>133 pts non-evaluable. <i>S. pneumoniae</i> predominant organism isolated Linezolid equivalent to cefpodoxime. Similar incidence of ADRs</p>		Linezolid	Cefpodoxime		Clinical cure	180/201 (90%)	187/206 (91%)	(p=0.68)	Microbiological cure	43/49 (88%)	42/47 (89%)	CI not stated																		
	Linezolid	Cefpodoxime																																
Clinical cure	180/201 (90%)	187/206 (91%)	(p=0.68)																															
Microbiological cure	43/49 (88%)	42/47 (89%)	CI not stated																															
29 abstr	Randomised, multinational, open-label study in 747 hospitalised pts aged >13 with community acquired pneumonia (clinical signs and symptoms; chest X-ray)	Linezolid 600mg bd IV followed by PO (n=381) vs ceftriaxone 1g IV bd followed by cefpodoxime 200mg PO bd (n=366) for 7-14d	Clinical cure and microbiological eradication rates (<i>S.pneumoniae</i> and <i>S.aureus</i>) assessed at 15-21 days after the end of therapy	<table style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">Linezolid</td> <td style="text-align: center;">Ceftriaxone/cefpodoxime</td> <td></td> </tr> <tr> <td>Clinical cure</td> <td style="text-align: center;">247/272 (91%)</td> <td style="text-align: center;">225/254 (89%)</td> <td style="text-align: center;">(p=0.4)</td> </tr> <tr> <td>Microbiological cure *</td> <td></td> <td></td> <td style="text-align: center;">CI not stated</td> </tr> <tr> <td><i>S.pneumoniae</i></td> <td style="text-align: center;">63/71 (89%)</td> <td style="text-align: center;">62/69 (90%)</td> <td style="text-align: center;">*data on file</td> </tr> <tr> <td><i>S.aureus</i></td> <td style="text-align: center;">18/20 (90%)</td> <td style="text-align: center;">13/17 (77%)</td> <td></td> </tr> </table> <p>221 pts non-evaluable Linezolid equivalent to ceftriaxone/cefpodoxime. Similar incidence of ADRs</p>		Linezolid	Ceftriaxone/cefpodoxime		Clinical cure	247/272 (91%)	225/254 (89%)	(p=0.4)	Microbiological cure *			CI not stated	<i>S.pneumoniae</i>	63/71 (89%)	62/69 (90%)	*data on file	<i>S.aureus</i>	18/20 (90%)	13/17 (77%)											
	Linezolid	Ceftriaxone/cefpodoxime																																
Clinical cure	247/272 (91%)	225/254 (89%)	(p=0.4)																															
Microbiological cure *			CI not stated																															
<i>S.pneumoniae</i>	63/71 (89%)	62/69 (90%)	*data on file																															
<i>S.aureus</i>	18/20 (90%)	13/17 (77%)																																
30 publ. study	Randomised, multinational, multicentre, double-blind trial in 396 hospitalised pts aged >18 with nosocomial pneumonia (clinical signs and symptoms; chest X-ray)	Linezolid 600mg bd IV plus aztreonam 1-2g IV tds (n=203) vs vancomycin 1g IV bd plus aztreonam 1-2g IV tds (n=193) for 7-21 d	Clinical cure and microbiological outcomes evaluated at 12-28 d after the end of therapy The primary reasons for clinical nonevaluability in the ITT population were absence of follow-up within the specified time period, insufficient therapy, or non-compliance	<table style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">Linezolid /Aztreonam</td> <td style="text-align: center;">Vancomycin/Aztreonam</td> <td></td> </tr> <tr> <td>Clinical cure</td> <td style="text-align: center;">71/107 (66%)</td> <td style="text-align: center;">62/91 (68%)</td> <td style="text-align: center;">95% CI¹, (-15% to 11%)</td> </tr> <tr> <td>Microbiological cure</td> <td style="text-align: center;">36/53 (68%)</td> <td style="text-align: center;">28/39 (72%)</td> <td style="text-align: center;">95% CI¹, (-23% to 15%)</td> </tr> </table> <p>In the ITT population 75/203 (37%) of linezolid and 68/193 (35%) of vancomycin pts were clinical failures. Most common causes for clinical failure in the ITT linezolid gp were Gram-negative pathogen only identified at baseline or no baseline or follow-up pathogens identified. Microbiological eradication rates for all <i>S.aureus</i>, MRSA and <i>S.pneumoniae</i> were similar in both groups. No resistance or significant ADRs were noted. Linezolid and vancomycin were equally effective <i>*for difference</i></p>		Linezolid /Aztreonam	Vancomycin/Aztreonam		Clinical cure	71/107 (66%)	62/91 (68%)	95% CI ¹ , (-15% to 11%)	Microbiological cure	36/53 (68%)	28/39 (72%)	95% CI ¹ , (-23% to 15%)																		
	Linezolid /Aztreonam	Vancomycin/Aztreonam																																
Clinical cure	71/107 (66%)	62/91 (68%)	95% CI ¹ , (-15% to 11%)																															
Microbiological cure	36/53 (68%)	28/39 (72%)	95% CI ¹ , (-23% to 15%)																															
31 publ. study	Randomised, multinational multicentre, double-blind trial in 826 hospitalised pts aged >18 with complicated skin and soft tissue infections (most commonly cellulitis and skin abscess)	Linezolid 600mg IV bd followed by linezolid 600 mg PO (n=400) vs oxacillin 2g IV qds bd followed by dicloxacillin 500mg PO qds (n=419) for 10 to 21d	Clinical cure rates in the intention-to-treat (ITT) and clinically evaluable pts (CE); microbiological success rate in microbiologically evaluable (ME) pts	<table style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;"><u>Clinical cure</u></td> <td></td> <td style="text-align: center;"><u>95%CI for difference</u></td> <td style="text-align: center;"><u>p</u></td> </tr> <tr> <td></td> <td style="text-align: center;">Linezolid</td> <td style="text-align: center;">Oxacillin/dicloxacillin</td> <td></td> <td></td> </tr> <tr> <td>ITT</td> <td style="text-align: center;">279/400 (70%)</td> <td style="text-align: center;">272/419 (65%)</td> <td style="text-align: center;">-1.58 to 11.25</td> <td style="text-align: center;">0.141</td> </tr> <tr> <td>CE</td> <td style="text-align: center;">264/298 (89%)</td> <td style="text-align: center;">259/302 (86%)</td> <td style="text-align: center;">-2.5 to 8.2</td> <td style="text-align: center;">0.3</td> </tr> <tr> <td></td> <td style="text-align: center;"><u>Microbiological cure</u></td> <td></td> <td></td> <td></td> </tr> <tr> <td>ME</td> <td style="text-align: center;">26/143 (88%)</td> <td style="text-align: center;">130/151 (86%)</td> <td style="text-align: center;">(95% CI, -5.6 to 9.7)</td> <td style="text-align: center;">p=0.6</td> </tr> </table> <p>Linezolid and oxacillin/dicloxacillin equally effective. In the majority of pts infecting organisms isolated were <i>S.aureus</i> and <i>S.pyogenes</i> Pts with MRSA were excluded</p>		<u>Clinical cure</u>		<u>95%CI for difference</u>	<u>p</u>		Linezolid	Oxacillin/dicloxacillin			ITT	279/400 (70%)	272/419 (65%)	-1.58 to 11.25	0.141	CE	264/298 (89%)	259/302 (86%)	-2.5 to 8.2	0.3		<u>Microbiological cure</u>				ME	26/143 (88%)	130/151 (86%)	(95% CI, -5.6 to 9.7)	p=0.6
	<u>Clinical cure</u>		<u>95%CI for difference</u>	<u>p</u>																														
	Linezolid	Oxacillin/dicloxacillin																																
ITT	279/400 (70%)	272/419 (65%)	-1.58 to 11.25	0.141																														
CE	264/298 (89%)	259/302 (86%)	-2.5 to 8.2	0.3																														
	<u>Microbiological cure</u>																																	
ME	26/143 (88%)	130/151 (86%)	(95% CI, -5.6 to 9.7)	p=0.6																														
32 abstr data on file	Randomised, multinational, multicentre double-blind trial in 332 adult pts with uncomplicated skin and skin-structure infections	Linezolid 400mg PO bd (n=166) vs clarithromycin 250mg PO bd (n=166) for 7-14 days	Clinical cure and microbiological outcomes at follow-up 7-21 days after the end of treatment	<table style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">Linezolid (CE)</td> <td style="text-align: center;">Clarithromycin (CE)</td> <td></td> </tr> <tr> <td>Clinical cure</td> <td style="text-align: center;">113/124 (91%)</td> <td style="text-align: center;">114/123 (93%)</td> <td style="text-align: center;">(p=0.65)</td> </tr> <tr> <td>Microbiological cure *</td> <td style="text-align: center;">98%</td> <td style="text-align: center;">97%</td> <td style="text-align: center;">CI not stated</td> </tr> <tr> <td>Eradication rates for <i>S. aureus</i></td> <td style="text-align: center;">38/39 (97%)</td> <td style="text-align: center;">51/53 (96%)</td> <td style="text-align: center;">*data on file</td> </tr> </table> <p>Most common pathogens <i>S.aureus</i> & <i>S.pyogenes</i></p>		Linezolid (CE)	Clarithromycin (CE)		Clinical cure	113/124 (91%)	114/123 (93%)	(p=0.65)	Microbiological cure *	98%	97%	CI not stated	Eradication rates for <i>S. aureus</i>	38/39 (97%)	51/53 (96%)	*data on file														
	Linezolid (CE)	Clarithromycin (CE)																																
Clinical cure	113/124 (91%)	114/123 (93%)	(p=0.65)																															
Microbiological cure *	98%	97%	CI not stated																															
Eradication rates for <i>S. aureus</i>	38/39 (97%)	51/53 (96%)	*data on file																															
33 data on file	Randomised, multinational, multicentre open-label trial in 529 pts aged >13 with known or suspected methicillin-resistant <i>Staphylococcus</i> species (MRSS) infections	Linezolid 600mg IV bd followed by optional oral, (n=240) vs vancomycin 1g IV bd (n=220) for 1 to 4 weeks	Resolution of clinical and microbiological signs and symptoms at up to 4 weeks post-treatment observation Separate analyses carried out for intention-to-treat, clinically evaluable and microbiologically evaluable pts	<table style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">Linezolid (CE)</td> <td style="text-align: center;">Vancomycin (CE)</td> <td></td> </tr> <tr> <td>Clinical cure</td> <td style="text-align: center;">97/103 (94%)</td> <td style="text-align: center;">96/110 (87%)</td> <td style="text-align: center;">CI not stated</td> </tr> <tr> <td>Microbiological cure</td> <td style="text-align: center;">38/64 (60%)</td> <td style="text-align: center;">43/67 (64%)</td> <td></td> </tr> </table> <p>Both treatments were equally effective in eradicating <i>S. aureus</i> and coagulase negative <i>Staphylococcus</i> regardless of primary source of MRSS infection. Incidence of ADRs leading to discontinuation, similar in both gps. Most ADR were mild-to-moderate</p>		Linezolid (CE)	Vancomycin (CE)		Clinical cure	97/103 (94%)	96/110 (87%)	CI not stated	Microbiological cure	38/64 (60%)	43/67 (64%)																			
	Linezolid (CE)	Vancomycin (CE)																																
Clinical cure	97/103 (94%)	96/110 (87%)	CI not stated																															
Microbiological cure	38/64 (60%)	43/67 (64%)																																