Public Summary Document

Product: Linezolid, injection, 600 mg per 300 mL, tablet, 600 mg and powder for oral suspension, 20 mg per mL, Zyvox®
Sponsor: Pfizer Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission requested Authority required listings for:

1. Treatment of microbiologically proven, multi-resistant methicillin-resistant Staphylococcus species (MRSS) infection in patients where no other antimicrobial agents can be used;
2. Treatment of microbiologically proven Vancomycin-Resistant Enterococcus species (VRE) infection.

2. Background

This was the second time the PBAC had considered the request to re-instate its September 2002 recommendation.

At the September 2002 meeting, the PBAC recommended listing linezolid 2 mg per mL, 300 mL infusion, 600 mg tablets and granules for oral suspension 20 mg per mL, 150 mL as an Authority required benefit for treatment initiated in a hospital for infections due to microbiologically proven, multi-resistant methicillin-resistant Staphylococcus species, where no other antimicrobial agent can be used, on the basis of an acceptable, but high cost-effectiveness ratio. The PBAC noted that the implication of not achieving an extra cure in this patient group would be a high mortality rate and therefore that this was particularly clinically important.

At its November 2007 meeting, the PBAC rescinded its September 2002 recommendation to list linezolid as the recommendation had not been implemented for more than 5 years, due to unresolved pricing issues.

At the March 2012 meeting, the PBAC rejected a minor submission requesting the reinstatement of the 2002 recommendation to list linezolid (tablet only) for the treatment of multi-resistant methicillin-resistant Staphylococcus species (MRSS) infections in patients meeting certain criteria. The PBAC considered that a major submission would be required to allow a full and contemporary evaluation of the clinical place and cost-effectiveness of linezolid in a tablet formulation only. The VRE listing was not requested in the September 2002 submission.

3. Registration Status

Linezolid was registered by the TGA on 24 September 2001. The current TGA-approved indication is for the treatment of suspected or proven infections due to Gram-positive organisms resistant to multiple classes of antibiotics, including methicillin resistant *Staphylococcus* species and vancomycin resistant *Enterococcus* species.

4. Listing Requested and PBAC's View

Authority required
Treatment of microbiologically proven, multi-resistant MRSS infection in patients where no other antimicrobial agents can be used because of:

1. Demonstrated treatment failure; or
2. Laboratory-confirmed resistance; or
3. Intolerance; or
4. Potential drug interaction; or
5. Toxicity; or
6. Contra-indication.

Note: Application for an increased maximum quantity to allow for up to 1-month of treatment and repeats sufficient for up to 6 months treatment may be authorised.

Authority required
Treatment of microbiologically proven VRE infection.

Note: Application for an increased maximum quantity to allow for up to 1-month of treatment and repeats sufficient for up to 6 months treatment may be authorised.

The PBAC noted the following issues in relation to the restriction wording for the treatment of MRSS:

- The requirement that "…no other antimicrobial agent can be used…" may be interpreted to require that alternative agents, such as teicoplanin, rifampicin (when used as part of a combination) which are not PBS listed for this indication, be trialled and/or considered inappropriate. The PBAC considered that this was not consistent with the submission's proposed place in therapy.
- The criterion for use of linezolid in cases of 'potential drug interaction' may promote the use of linezolid where the infection is susceptible to a combination including rifampicin, which has a number of potential, albeit manageable, drug interactions.
- The proposed restriction does not limit use only to patients with severe infection. The PBAC noted the wide range of severity of MRSS and VRE infections, from mild cystitis to bacteraemia.
- The Committee considered that the inclusion of other staphylococcal species other than *Staphylococcus aureus* could promote the inappropriate use of linezolid in species of low virulence.

In relation to the restriction for first-line use of VRE, the PBAC considered the linezolid listing for VRE should be for patients with severe infection.

The restriction for MRSS as currently presented may result in use of linezolid to avoid manageable clinical issues associated with vancomycin and rifampicin where the causative organism is sensitive to either of these drugs. In particular, linezolid may be used to avoid manageable infusion reactions associated with vancomycin and to avoid manageable drug interactions with rifampicin.

5. Clinical Place for the Proposed Therapy

Multi-resistant Methicillin Resistant Staphylococcus Species (MRSS) infections: First line treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections is hospital-initiated intravenous (IV) vancomycin, followed by oral rifampicin plus fusidate sodium. Some patients may also be discharged on IV vancomycin via hospital in the home

programs. Linezolid is positioned after first-line vancomycin or rifampicin plus fusidate sodium, for the treatment of severe microbiologically proven MRSS infections where alternative antimicrobial therapy is required (e.g. vancomycin-intermediate Staphylococcus aureus). The submission also described linezolid as last-line therapy for multi-resistant MRSS. Cosgrove and Fowler (2008)[1] suggest linezolid can be used as one of a number of salvage therapies including tigecycline and quinupristin with dalfopristin.

Vancomycin-Resistant Enterococcus species (VRE) infections: Linezolid is recommended as a treatment option for microbiologically proven VRE infections, along with quinupristin with dalfopristin, tigecycline, daptomycin, teicoplanin, and nitrofurantoin or norfloxacin (nitrofurantoin or norfloxacin are for VRE urinary tract infections). The sponsor sought PBS-listing of linezolid as first-line therapy for VRE infections. However, Turnidge (2010)[2] describes daptomycin and linezolid as important reserve parenteral drugs for VRE infections.

The PBAC considered that if used appropriately, linezolid would be used after failure of vancomycin or rifampicin+fusidic acid for MRSA. The PBAC considered that the indication should be limited to multi-resistant methicillin-resistant *Staphylococcus aureus* rather than the requested multi-resistant staphylococcus species.

The PBAC considered that in practice the personal choice of the prescriber would influence the use of linezolid in preference to vancomycin or rifampicin+fusidic acid.

The PBAC considered that the place in therapy of linezolid was dependent on the source of bacteraemia, and considered that there is high risk of linezolid use in other indications.

The PBAC noted the high rate of asymptomatic colonisation with VRE, as opposed to true infection. The PBAC considered treatment with linezolid at an earlier stage could potentially drive higher rates of antimicrobial resistance.

6. Comparator

For MRSS and VRE infections, the submission nominated standard therapy, defined as continuation of inadequate, unapproved or no further therapy.

The submission claimed that teicoplanin, quinupristin with dalfopristin, tigecycline, daptomycin, nitrofurantoin and norfloxacin were not appropriate comparators as they are not TGA approved for treatment of VRE infections.

For MRSS infections, the PBAC considered that a mixed comparator of antimicrobials with activity against multi-resistant MRSS (except first-line vancomycin IV and first-line rifampicin plus fusidate sodium) was more appropriate.

For severe VRE infections, the PBAC considered the main treatments likely to be replaced are daptomycin or teicoplanin, noting the susceptibility of the most common cause of VRE, the VanB strain of *E. faecium*, to teicoplanin.

[1] Cosgrove, S.E., & Fowler V.G. (2008). Management of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clinical Infectious Diseases*, 46(suppl 5), S386-93.

[2] Turnidge, J. (2010). Multiresistant organisms at the front line. *Australian Prescriber*, 33(3), 68-71.

The PBAC did not accept the submission's claim that non-TGA registered treatments were not appropriate comparators. The PBAC considered that the therapy most likely to be replaced should be the comparator, irrespective of the regulatory status of the antibiotic.

7. Clinical Trials

The submission presented evidence from:

- Ten non-comparative observational studies using linezolid: Birmingham (2003), Study 025, Moise (2002), Rayner (2004), Antony (2001), Chien (2000), Study 067, Watanabe (2012), Study 082-VRE and Moschovi (2010).
- One linezolid arm extracted from a randomised trial: Study 054A. This appeared to be a subset of patients enrolled in Study 054, due to a protocol amendment.

The PBAC noted that no head-to-head studies were available.

The submission did not include evidence on the safety or efficacy of standard therapy, claiming that randomised controlled trials of linezolid versus standard therapy would be unethical for the requested PBS population.

The economic evaluation relied on data from Birmingham (2003) for the linezolid treatment group. Birmingham (2003) reported on a US compassionate use program conducted between October 1997 and May 2000 (N=796 patients, with 828 infections). Study 025, Moise (2002) and Rayner (2004) appear to overlap with Birmingham (2003); the final report for Study 025 was not provided in the submission.

Details of the published trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Adults ± Children		
Antony SJ et al	Clinical experience with linezolid in the treatment of resistant Gram-positive infections	*Journal of the National Medical Association* (2001); 93:386-91.
Birmingham MC et al	Linezolid for the treatment of multi-drug resistant, Gram-positive infections: experience from a compassionate-use study	*Clinical Infectious Diseases* (2003); 36:15-68.
Chien JW et al	Use of linezolid, an oxazolidinone, in the treatment of multidrug-resistant Gram-positive bacterial infections	*Clinical Infectious Diseases* (2000); 30:146-51.
Moise PA et al	The efficacy and safety of linezolid as treatment for *Staphylococcus aureus* infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin	*Journal of Antimicrobial Chemotherapy* (2002); 50:1017-26.
Rayner CR et al	Linezolid in the treatment of osteomyelitis: results of compassionate use experience	*Infection* (2004); 32:8-14.
Study 025	Linezolid (PNU-100766) given intravenously or orally for compassionate use in patients with significant, resistant bacterial infections	Interim report of the trial M/1260/0025, September 1999.
Study 054A	Linezolid for the treatment of vancomycin-resistant enterococcal infections: a double-blind trial comparing 600mg	Final report of the trial M/1260/0054A, September 1999.

	linezolid every 12 hours with 200mg linezolid every 12 hours	
Study 067	Linezolid (PNU-100766) in the treatment of MRSA infections in patients whose conventional therapy has failed, or who are intolerant to conventional therapy: an open-label, multi-center trial	PhRMA web synopsis for protocol M/126/0067, October 2007.
Watanabe A et al	Usefulness of linezolid in the treatment of hospital-acquired pneumonia caused by MRSA: a prospective observational study	*Journal of Infection and Chemotherapy* (2012); 18:160-8.
Children Only		
Moschovi M et al	Efficacy and safety of linezolid in immunocompromised children with cancer	*Pediatrics International* (2010); 52:694-8.
Study 082-VRE	Linezolid IV/PO for the treatment of vancomycin-resistant *Enterococcus* infections in children	Final report of the study M/1260/0082-VRE (A5951062), December 2004.

8. Results of Trials

The results for clinical outcome at test of cure (TOC) for the all treated population is displayed in the following table. The comparison of data across studies was difficult, due to important differences in definitions of outcomes and methods for assessment of outcomes. The data for Studies 025 and 082-VRE could not be verified during the evaluation. It was unclear whether the results for Birmingham (2003) and Study 025 were for all treated patients ('all treated') rather than an ITT population.

Table 1: Clinical evaluation, overall results for the 'all treated' population

	Clinical outcome at TOC, all treated population n/N (%)				
	Cured	**Failed**	**Indeterminate**	**Non-evaluable**	**Missing**
Adults ± children					
Birmingham 2003	420/828 (50.7)	39/828 (4.7)	114/828 (13.8)	255/828 (30.8)	0/828 (0)
Study 025[a]	75/133 (56.4)[a]	6/133 (4.5)[a]	12/133 (9.0)[a]	NR[a]	40/133 (30.1)[a]
Moise 2002	94/191 (49.2)	18/191 (9.4)	39/191 (20.4)	40/191 (20.9)	NR
Rayner 2004	NR	NR	NR	NR	NR
Antony 2001	NR	NR	NR	NR	NR
Chien 2000	NR	NR	NR	NR	NR
Study 054A (600mg bd arm)	NR	NR	NR	NR	NR
Study 067	NR	NR	NR	NR	NR
Watanabe 2012	NR	NR	NR	NR	NR
Children only					
Study 082-VRE[b]	8/12 (66.7)[b]	2/12 (16.7)[b]	2/12 (16.7)[b]	NR[b]	NR[b]
Moschovi 2010	NR	NR	NR	NR	NR

Abbreviations: NR, not reported; TOC, test of cure

[a] Unable to verify during the evaluation as full CSR not provided. This does not appear to be the all treated population, as 230 patients were enrolled and the CSR does not identify this population for efficacy analyses.

[b] One missing patient not accounted for.

The proportion of patients with clinical cure at the test of cure (TOC) assessment for the 'all treated' population ranged from 49.2% to 56.4% in studies with adults with/without children. The proportion of patients who failed ranged between 4.5% and 9.4%. A large proportion of patients were assessed as indeterminate, non-evaluable or missing (approximately 40%). The economic evaluation applied a linezolid cure rate of 50.7% from Birmingham (2003).

Study 082-VRE in children reported a clinical cure rate of 66.7% at TOC assessment, and a clinical failure rate of 16.7%.

The clinical cure rates for the clinically evaluable population were more favourable than those for the 'all treated' population at TOC, ranging from 62.3% to 81.3% across studies reporting this outcome. The proportion of patients who failed treatment ranged from 6.5% to 20.2% across studies.

The PBAC considered that comparative data of linezolid versus other earlier-line antimicrobials for multi-resistant MRSS would have been informative. The PBAC noted given the body of available evidence for VRE infections, it was unclear whether excluding comparative retrospective studies for this indication is reasonable as they may provide useful information.

The PBAC considered that the studies provided may not represent the full body of available evidence. The PBAC noted the method of inclusion/exclusion of studies was not adequately documented and the inclusion/exclusion criteria may not have been consistently applied. For example, the Watanabe (2012) study presented in submission did not seem to specifically include MRSA patients with treatment failure, resistance intolerance or contraindications to other antimicrobials. In addition, potentially relevant studies may have been excluded (e.g. Raad et al, 2004).

The PBAC considered the overall risk of bias in the studies presented in the submission was high. The ITT analysis in Birmingham (2003) appeared to only include patients who have received linezolid for more than 5 days (i.e. patients had to survive and be treated for at least 5 days to be included).

The PBAC noted the applicability of Birmingham (2003) to current Australian practice is uncertain due to likely differences when compared with US clinical practice during the late 1990s and early 2000s. The PBAC noted ESC did not consider Birmingham (2003) representative of current treatment options as it was conducted in settings where many current therapeutic alternatives such as fusidate (with or without rifampicin), daptomycin, tigecycline and ceftaroline were not available. The PBAC noted ESC expressed concern about whether the clinical cure rate of 50.7% based on Birmingham (2003) was applicable to the PBS population which would be second-line treatment following vancomycin failure or intolerance to vancomycin. Only 25.4% of people receiving linezolid in Birmingham study had failed vancomycin or were intolerant.

The PBAC considered that it was difficult to interpret the results based on the causative pathogens (MRSS versus VRE) presented in the submission, due to differences in assessment time points and definitions across studies. The PBAC noted there were insufficient data by site of infection and causative pathogen to assess any differences in outcomes between these subgroups.

With regard to comparative harms, the submission included safety data from non-randomised studies and reported on all adverse events (054A, 067, 082-VRE) or adverse events considered possibly or probably related to linezolid (Birmingham 2003, Chien 2000, Moise 2002, Rayner 2004), therefore limiting the comparability of the data across studies.

The proportion of deaths ranged from 4.2% to 53.3% and the submission claimed the high death rates seen in some studies were not unexpected due to the serious underlying illness. When reported, no deaths were assessed as causally related to linezolid.

The PBAC noted the major side effects with linezolid were myelosuppression (thrombocytopenia, anaemia, and pancytopenia), lactic acidosis, peripheral neuropathy, optic neuropathy, serotonin syndrome, convulsions and mitochondrial toxicity.

The PBAC noted that the sponsor did not compare safety with standard treatment. The PBAC expressed concern about the potential for antibiotic resistance and possible impact on ability to treat severe infections such as vancomycin-intermediate Staphylococcus aureus (VISA) endocarditis if resistance developed. The PBAC expressed concern about the potential for toxicity with use of linezolid, particularly if used long term.

9. Clinical Claim

The submission described linezolid as superior in terms of comparative effectiveness and inferior in terms of comparative safety compared to standard therapy.

The PBAC did not consider that the submission's claims were supported, as no comparative data was presented. The PBAC considered there were insufficient data to conclude that linezolid was superior in terms of efficacy versus "unapproved" therapy, including antimicrobials that may be effective for MRSS or VRE but are not PBS-listed or not TGA indicated.

The PBAC considered that linezolid was superior to no effective therapy, in terms of comparative effectiveness. In terms of comparative safety, the PBAC expressed concerns about the toxicity and risk of developing antimicrobial resistance with linezolid.

10. Economic Analysis

The submission presented a modelled economic evaluation with a cost effectiveness analysis based on the claim of superior efficacy. The submission presented an ICER in the range $15,000 - $45,000 per extra life year saved based on clinical cure rates and mortality data from a non-randomised linezolid study (Birmingham 2003), mortality data from two non-randomised Australian studies (Turnidge 2009, Cheah 2013), and discussions with key opinion leaders. The 30 day results were extrapolated to 12 months.

The PBAC considered that the economic analysis was consistent with the clinical claim, but not consistent with the clinical evidence as no comparative data were provided.

The PBAC noted that in the March 2002 submission accepted by PBAC there was no economic model presented. The March 2002 submission estimated an incremental cost/extra patient with clinical cure of less than $15,000.

The economic model was a decision analytic Markov model, comparing linezolid with standard therapy. The cycle length was 1 month, with a 12 month time horizon. The base case comprised of both multi-resistant MRSS and VRE infections, as Birmingham (2003) enrolled a mix of patients with serious Gram-positive infections.

The PBAC considered that it was not appropriate to combine MRSS and VRE indications together in one economic model, as linezolid will be used in different lines of treatment in both indications.

The PBAC considered the incremental cost per extra year of life saved was a likely overestimate because mortality rates for bacteraemic patients were applied to the comparator arm.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of $10 – 30 million in Year 5.

12. Recommendation and Reasons

The PBAC rejected the PBS listing of linezolid on the basis of incorrect comparator, and consequent lack of comparative data against the therapies most likely to be replaced.

The PBAC did not consider that the comparator (defined as continuation of inadequate, unapproved or no further therapy) was appropriate. The PBAC did not accept the submission's claim that non-TGA registered treatments were not appropriate comparators. The PBAC considered that the therapy most likely to be replaced should be the comparator, irrespective of the regulatory status of the antibiotic.

For MRSS infections, the PBAC considered that a mixed comparator of antimicrobials with activity against multi-resistant MRSS (except first-line vancomycin IV and first-line rifampicin plus fusidate sodium) was more appropriate.

For severe VRE infections the PBAC considered the main treatments likely to be replaced are daptomycin or teicoplanin , noting the susceptibility of the most common cause of VRE, the VanB strain of *E. faecium*, to teicoplanin.

The PBAC considered the indication should be limited to multi resistant methicillin resistant *Staphylococcus aureus* rather than the proposed multi resistant methicillin resistant staphylococcus *species*.

The PBAC acknowledged that linezolid has a place in the treatment of MRSA and VRE. The PBAC considered that MRSA and VRE are treated in the hospital setting, and the availability of an oral dose form on the PBS may promote overuse.

The PBAC did not consider that linezolid was demonstrably superior to other active therapy. The PBAC agreed that linezolid was superior to no therapy.

The PBAC noted that linezolid was not compared to standard treatment in terms of safety. The PBAC noted known safety concerns with linezolid include myelosuppression, lactic

acidosis, peripheral neuropathy, optic neuropathy, serotonin syndrome and the potential for increased blood pressure (potential to inhibit monoamine oxidase), convulsions and mitochondrial toxicity.

The PBAC expressed concern about the potential for antibiotic resistance and possible impact on ability to treat severe infections such as vancomycin-intermediate Staphylococcus aureus (VISA) endocarditis if resistance developed. The PBAC were also concerned about potential for toxicity with use of linezolid, particularly in long term use.

The PBAC noted the economic evaluation based on a claim of superior efficacy was not consistent with the clinical evidence as no comparative data were provided against effective, albeit unregistered, therapies. The PBAC considered that it was not appropriate to combine MRSS and VRE indications together in one economic model, as linezolid will be used in different lines of treatment in both indications. The PBAC considered that costs for adverse events were inappropriately excluded from the economic evaluation, in light of the claim of inferior comparative safety. The PBAC noted that the 30-day results were extrapolated out to 12 months, and considered that the extrapolation was not justified in the submission.

The PBAC expressed concern about the current lack of effective means to monitor emergence and trends of antimicrobial resistance, despite wide acknowledgement in all healthcare sectors of the importance of these data.

The PBAC considered that the current framework of the PBS did not easily accommodate new antibiotics intended for use against resistant microorganisms. The PBAC considered that it may be appropriate to explore whether a suitable policy construct could be identified which would recognise both the value of development of new antibiotics and the risks of emerging resistance to antimicrobial agents.

Outcome:
Rejected

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Due to the high clinical need for new antibiotics, Pfizer is disappointed with the PBAC's decision to reject linezolid (ZYVOX). The comparator for the MRSS restriction was consistent with the 2002 submission and was, therefore, previously accepted by the PBAC.

The Sponsor is willing to work with the PBAC to develop a PBS framework that can accommodate antibiotics intended for use against resistant microorganisms, such as linezolid.