

Bon Secours Richmond
Pharmacy and Therapeutics Committee
Linezolid (Zyvox®)
11/2000

Recommendations : All MEC approved 1/8/2001

- Linezolid (Zyvox®) is recommended for addition to the formulary as a **restricted** antibiotic for treatment of documented serious vancomycin resistant Enterococcus faecium infections when no other alternative is available.
- Doxycycline and nitrofurantoin are recommended for susceptible VRE lower urinary tract infections.
- Linezolid is not recommended for treatment of other documented infections unless the patient is allergic/intolerant to all other antibiotics demonstrating activity against the pathogen.
- Synercid is recommended for removal from the formulary due to its adverse reaction and drug interaction profile.

Findings:

- Linezolid is a oxazolidinone antibiotic with gram (+) spectrum. It is bacteriostatic against enterococci and staphylococci. It is bacteriocidal against most strains of streptococci. Linezolid is active against vancomycin sensitive/resistant Enterococcus faecalis, but not FDA approved for their treatment.

FDA Approved Indications			
	Linezolid	Synercid®	Vancomycin
Community Acquired Pneumonia	+ (Strep pneumoniae-PCN sensitive, MSSA)	-	+
Noscomial pneumonia	+ (MSSA/MRSA, Strep. pneumoniae- PCN sensitive)	-	+
Complicated Skin & Skin Structure	+(MSSA/MRSA, Strep. Agalactiae, pyogenes)	+ (MSSA, Strep. pyogenes)	+
Vancomycin Resistant Enterococcus faecium	+	+	-

Selected Pharmacokinetics			
	Linezolid	Synercid	Vancomycin
Metabolism	65%	Bile 75%	0%
Fraction excreted unchanged in urine	30%	<5%	100%
Oral Bioavailability	100%	ND/NA	0%
Half-life	5.5 Hours	3 hr Quinupristin 1 hr Dalfopristin	8 hours
Renal Failure Adjustment	No But metabolites accumulate	No	Yes
Hemodialysis	Administer After Dialysis		No Change

- Currently the lab reports the following drugs for enterococcus species: ampicillin, ciprofloxacin, erythromycin, penicillin, rifampin, tetracycline, vancomycin, levofloxacin, and nitrofurantoin. For species that appear to be vancomycin resistant, a vancomycin E-test and a doxycycline disk are dropped.

Efficacy/Cost Comparison

- Linezolid cure rates are similar to vancomycin for nosocomial pneumonia, complicated skin and skin structure infections, but is substantially more expensive.

Efficacy and Cost Comparison for the treatment of MRSA/E infections.							
Drug	Dose (mg)	Route	Frequency	Duration (days)	% Cure Rate	Cost per Dose	Treatment Cost

Vancomycin	1000	IV	BID	14	75	\$4.29	\$120.12
Linezolid	600	IV/PO	BID	14 (7 IV/7 PO)	78	\$56.35 IV/41.56 oral	\$1372.00
Synercid	500	IV	BID	14	70	\$84.36	\$2334.64

- Head-to-head comparative studies of linezolid and vancomycin showed no apparent difference in the treatment of MRSA. There are no head-to-head clinical studies published comparing either vancomycin or linezolid versus Synercid®. However, one can compare the relative cure rates from individual studies and conclude that no efficacy difference has been identified between the three agents for the treatment of MRSA. All provide between 70 and 80% cure rate over an average treatment period of 14 days.

Efficacy comparison for treatment of VRE infections.							
Drug	Comments	Dose (mg)	Route	Frequency	Duration (days)	Response Rate (%)	Cost
Linezolid	Package Insert	600	IV/PO	BID	14 (7IV/7PO)	66%	\$1,372.00
Synercid	Package Insert	500	IV	TID	14	52%	\$3,501.96
Chloramphenicol	Serious Systemic Infection	500 – 1000	IV/PO	TID–QID	14	57%	\$175.14
Nitrofurantoin	UTI	100	PO	QID	14	100.0**	\$27.44
Doxycycline	UTI	100	PO	BID	14	100.0**	\$2.52

** Small # of patients where the removal of a catheter may have been responsible for the cure rate.

- The acquisition cost of vancomycin is 10-fold smaller than linezolid and 20-fold smaller than Synercid®.
- Linezolid is 65% metabolized. Approximately 30% is excreted unchanged in the urine. The metabolites of linezolid accumulate in patients with renal insufficiency, and the clinical significance is unknown. Linezolid is not an inducer/inhibitor of cytochrome P450.
- Linezolid's most common ADRs are GI tract related (diarrhea, nausea, and vomiting).
- Linezolid is associated with thrombocytopenia 1.5% (0.3-10%).
- Synercid's predominate ADRs are infusion site related, including pain, inflammation, edema and thrombophlebitis, occurring in 75% of patients when Synercid was given through a peripheral line. Infusion related ADRs are dose and concentration dependent. Approximately 5% of patients have discontinued Synercid due to infusion site reactions. Central line infusion is preferred. Arthralgias and myalgias are common and may be severe. Other ADRs include HA, GI disturbances, non-local skin reactions, and LFT and bilirubin elevations up to 5 times the upper limit of normal.
- Synercid is a potent inhibitor of CYP3A4, increasing serum concentrations of nifedipine, midazolam, and cyclosporine (levels doubled). Concurrent use of cisapride should be avoided. Concomitant administration of drugs that can prolong the QTc interval should be avoided.
- Linezolid is a reversible nonselective inhibitor of monoamine oxidase and may interact with tyramine, adrenergic, and serotonergic agents. Blood pressure and heart rate response to phenylpropranolamine and pseudoephedrine is increased.
- Linezolid is rated pregnancy Category C.

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