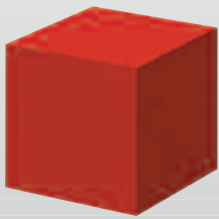


Once-A-Day
■ ■ **CUBICIN**[®]
■ ■ (daptomycin for injection)



Summary of 4 agents for serious *Staphylococcus aureus* infections

CUBICIN[®] (daptomycin for injection)

Vancocin[®] HCl (Vancomycin Injection, USP)

Zyvox[®] (linezolid injection/tablets/oral suspension)

Tygacil[®] (tigecycline for injection)

Indications

Ref 1,
CUBICIN PI,
p 9, ¶3, L1-4, ¶4,
L1,2

Ref 2,
Vancocin PI, p 3,
¶3, L1-6

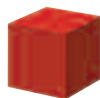
Ref 3,
Zyvox PI,
p 11, ¶2,
L1,2, ¶3, L1,2, ¶4,
L1-3, ¶5, L1,2; p 12,
¶1, L1-3

Ref 4,
Tygacil PI,
p 8, ¶4, L1-5,
¶5, L1,2; p 9, ¶1,
L1-4

Approved Indications	CUBICIN® (daptomycin for injection) ¹	Vancocin® HCl (Vancomycin Injection, USP) ²	Zyvox® (linezolid injection/ tablets/oral suspension) ³	Tygacil® (tigecycline for injection) ⁴
<i>Staphylococcus aureus</i> bacteremia	X			
Non-pathogen-specific septicemia		X		
VREF infections, including concurrent bacteremia			X	
<i>S. aureus</i> right-sided endocarditis	X	X		
Left-sided endocarditis		X		
Complicated skin infections	X	X	X	X
Diabetic foot infections, without concomitant osteomyelitis			X	
Uncomplicated skin infections			X	
Lower respiratory-tract infections		X		
Nosocomial/community-acquired pneumonia			X	
Bone infections		X		
Complicated intra-abdominal infections				X

VREF = vancomycin-resistant *Enterococcus faecium*

For complete information on CUBICIN, refer to the enclosed package insert. For complete information on other products, refer to their respective package inserts.



Safety

	CUBICIN® (daptomycin for injection) ¹	Vancocin® HCl (Vancomycin Injection, USP) ²	Zyvox® (linezolid injection/ tablets/oral suspension) ³	Tygacil® (tigecycline for injection) ⁴
Warnings	<i>Clostridium difficile</i> -associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. CDAD has been reported to occur over 2 months post-antibiotic treatment. If CDAD is suspected, antibiotic treatment may need to be suspended.*	Rapid bolus administration may be associated with exaggerated hypotension; should be administered over period of not less than 60 minutes Ototoxicity Administer with caution in patients with renal insufficiency Pseudomembranous colitis [†]	Zyvox is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections* Mortality imbalance found in patients with catheter-related bloodstream infections, including those with catheter-site infections* <i>Clostridium difficile</i> -associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. CDAD has been reported to occur over 2 months post-antibiotic treatment. If CDAD is suspected, antibiotic treatment may need to be suspended.* Myelosuppression, including anemia, leukopenia, pancytopenia, and thrombocytopenia; CBCs should be monitored weekly	<i>Clostridium difficile</i> -associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. CDAD has been reported to occur over 2 months post-antibiotic treatment. If CDAD is suspected, antibiotic treatment may need to be suspended.* May cause fetal harm in pregnancy (Category D) May permanently discolor developing teeth Administer with caution in patients hypersensitive to tetracyclines May cause life-threatening anaphylaxis/ anaphylactoid reactions
Most common adverse events	Most AEs reported in clinical trials were mild to moderate in intensity Most common AEs: anemia, constipation, diarrhea, nausea, vomiting, injection-site reactions, and headache	Most common AEs not available AEs include infusion-related events, nephrotoxicity, gastrointestinal, ototoxicity, neutropenia	85% of AEs in phase 3 trials were mild to moderate Most common AEs: diarrhea, headache, nausea, vomiting, insomnia	Most common AEs: nausea, vomiting, diarrhea, local reaction to procedure, infection

Ref 1, CUBICIN PI, p 10, ¶15, L1-3; p 15, ¶2, L2,3; p 16, Table 5; pp 17-19 Table 6

Ref 2, Vancocin PI, p 2, C1, ¶16 entire, ¶23, L1, ¶24, L1, ¶25, L1, ¶26, L1, ¶27, L1

Ref 3, Zyvox PI, p 12, ¶4, L1,2,4-8, ¶6, L1,2; p 13, ¶1, L1,2, ¶3, L1-3; p 19, ¶3, L1-7, Table 6

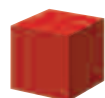
Ref 4, Tygacil PI, p 9, ¶5, L1,2, ¶6, L2,3, ¶7, L1, ¶8, L1-3, ¶9, L1-3; pp 13-15, Table 4

AEs = adverse events; CBCs = complete blood counts

*Highlighted text represents new information added to package inserts in March 2007.

[†]*C. difficile* warning was not added to Vancocin package insert as of August 2007.

For complete information on CUBICIN, refer to the enclosed package insert. For complete information on other products, refer to their respective package inserts.



Safety (cont'd)

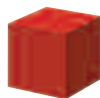
Ref 1,
CUBICIN PI,
p 11, ¶12 (entire),
¶18, L1-6;
p 12, ¶14 entire;
p 13, ¶1, L4-6
Ref 2,
Vancocin PI,
p 2, C1,
¶10 entire, ¶11,
L1-3, ¶12 entire,
¶16, L1,2, ¶17, L1-3
Ref 3,
Zyvox PI,
p 13, ¶7, L1, ¶8, L1-3,
p 14, ¶2, L1, ¶4,
L1,2; p 15, ¶3,
L1-5
Ref 4,
Tygacil PI,
p 10, ¶3,
L1-3, ¶4,
L1-5; p 11, ¶2, L1,2,
¶3, L1,2

	CUBICIN® (daptomycin for injection) ¹	Vancocin® HCl (Vancomycin Injection, USP) ²	Zyvox® (linezolid injection/ tablets/oral suspension) ³	Tygacil® (tigecycline for injection) ⁴
Precautions, including drug interactions	<p>Patients with persisting or relapsing <i>S. aureus</i> infection or poor clinical response should have repeat blood cultures. If a culture is positive for <i>S. aureus</i>, MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection. Appropriate surgical intervention (eg, debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibiotic regimen may be required</p> <p>Patients should be monitored for development of muscle pain or weakness, particularly of the distal extremities; CPK levels should be monitored weekly or more frequently in patients with renal insufficiency or unexplained CPK elevations and in those who received prior or concomitant therapy with HMG-CoA inhibitors*</p> <p>Warfarin: no significant pharmacokinetic effect; monitor anticoagulant activity</p> <p>Consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors</p>	<p>Nephrotoxicity; renal function should be monitored</p> <p>Ototoxicity; auditory monitoring may be helpful</p> <p>Neutropenia; leukocyte counts should be monitored</p> <p>Infusion-related events, including inadvertent extravasation, phlebitis, erythema, histamine-like flushing (increased with the administration of anesthetic agents)</p> <p>Neurotoxic/nephrotoxic drugs necessitate monitoring</p>	<p>Lactic acidosis</p> <p>Serotonin syndrome: spontaneous reports associated with the coadministration of Zyvox and serotonergic agents, including antidepressants (eg, SSRIs)</p> <p>Peripheral and optic neuropathy</p> <p>Adrenergic agents: pressor response to indirect-acting sympathomimetic, vasopressor, or dopaminergic agents may be enhanced; initial doses of adrenergic agents should be reduced</p> <p>Convulsions: a history of seizures or risk factors for seizures were associated with most of these cases</p>	<p>May produce adverse effects similar to those of tetracyclines: photosensitivity, pseudomotor cerebri, pancreatitis, and antianabolic action</p> <p>Warfarin: prothrombin time or other suitable anticoagulation test should be monitored or performed</p> <p>Oral contraceptives may be less effective when used concomitantly with antibacterial drugs</p> <p>Exercise caution when considering Tygacil monotherapy for CIAI secondary to clinically apparent intestinal perforation</p>

CIAI = complicated intra-abdominal infections; CPK = creatine phosphokinase; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-Coenzyme A; SSRIs = selective serotonin reuptake inhibitors

*CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1000 U/L (~5X ULN), or in patients without reported symptoms who have marked elevations in CPK >2000 U/L (≥10X ULN).

For complete information on CUBICIN, refer to the enclosed package insert. For complete information on other products, refer to their respective package inserts.



Administration, Dosing, and Monitoring in Adults

	CUBICIN® (daptomycin for injection) ¹	Vancocin® HCl (Vancomycin Injection, USP) ²	Zyvox® (linezolid injection/ tablets/oral suspension) ³	Tygitil® (tigecycline for injection) ⁴
Administration				
Dosing interval	Once-daily*	Twice-daily	Twice-daily	Twice-daily
Infusion time	30 min	No more than 10 mg/min or 60 min, whichever is longer	30–120 min	~30–60 min
Infusion volume	50 mL	100 or 200 mL	100, 200, or 300 mL	100 mL
Dosing	cSSSIs 4 mg/kg IV q24h* for 7–14 d <i>S. aureus</i> bloodstream infections (bacteremia), including right-sided endocarditis 6 mg/kg IV q24h* for a minimum of 2 to 6 weeks	Skin and skin structure infections/endocarditis/ septicemia/bone infections/LRTIs† 500 mg IV q6h or 1 g IV q12h	cSSSIs, including diabetic foot infections, without concomitant osteomyelitis Nosocomial pneumonia and CAP 600 mg IV/PO q12h for 10–14 d Uncomplicated SSSIs 400 mg PO q12h for 10–14 d VREF infections, including concurrent bacteremia 600 mg IV/PO q12h for 14–28 d	cSSSIs/complicated intra-abdominal infections Initial dose of 100 mg IV, then 50 mg q12h for 5–14 d†
Monitoring	CPK Anticoagulant activity in patients receiving concomitant warfarin therapy	Serum vancomycin levels Renal function Auditory function Leukocyte levels	CBCs Visual function in all patients receiving therapy for extended period and reporting new visual symptoms	Anticoagulant activity in patients receiving concomitant warfarin therapy

cSSSIs = complicated skin and skin structure infections; LRTIs = lower respiratory tract infections; CAP = community-acquired pneumonia; VREF = vancomycin-resistant *E. faecium*; CPK = creatine phosphokinase; CBCs = complete blood counts.

*In patients with creatinine clearance <30 mL/min, including those undergoing hemodialysis or continuous ambulatory peritoneal dialysis, 4 mg/kg q48h for cSSSI and 6 mg/kg q48h for *S. aureus* bacteremia, including right-sided endocarditis.

† Dosage adjustment must be made in patients with impaired renal function.

‡ Dosage adjustment necessary in patients with severe hepatic impairment (Child Pugh C).

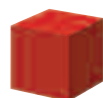
For complete information on CUBICIN, refer to the enclosed package insert. For complete information on other products, refer to their respective package inserts.

Ref 1,
CUBICIN PI,
p 9, ¶3, L1-4, ¶4,
L1,2; p 11, ¶8,
L1-6; p 12, ¶4, L3-5
p 21, ¶4, L1,2, ¶5,
L1,2; p 22, Table 9

Ref 2,
Vancocin PI, p 1, C2,
¶17 entire; p 2, C1,
¶10, L1,2,4, ¶11, L3,
C2, ¶4, L1-3, ¶5, L1,
¶6, L1-3, ¶7, L1

Ref 3,
Zyvox PI,
p 11, ¶1, L1,2, ¶2,
L1,2, ¶3, L1, ¶4,
L1,2, ¶5, L1; p 12,
¶1, L1 p 12, ¶4,
L4-8; p 14, ¶3, L3-5;
p 25, Table 14 +
footnote; p 26, ¶1,
¶6, L1,2; p 27, ¶3,
L1-6

Ref 4,
Tygitil PI,
p 8, ¶3, L1,2, ¶4,
L1-5, ¶5, L1; p 11,
¶2, L1,2, p 16, ¶5,
L1-3, ¶6, L1,2, ¶7,
L2-4



Microbiology

Ref 1,
CUBICIN PI,
p 1, ¶12, L1;
p 6, ¶13, L1-3,
¶14, L1,2,
¶15, L2
Ref 2,
Vancocin PI,
p 1, C1, ¶12,
L1,2, ¶10, L1
Ref 3,
Zyvox PI,
p 1, ¶12, L2;
p 8, ¶11, L1,2,6-11
Ref 4,
Tygacil PI,
p 1, ¶12, L1;
p 4, ¶17, L1,2; p 5,
¶11, L1,11,12, ¶13,
L1, ¶14, L1, ¶15, L1;
p 6, ¶14 entire
Ref 5,
Akins 2001,
p 456, C1, ¶13,
L17, C2, ¶11, L1,2
Ref 6,
Pankuch 2003,
p 446, C1, ¶12,
L14-17
Ref 7,
Watanakunakorn
1982, p 915, C1, ¶1,
L1,2

Ref 1,
CUBICIN PI,
p 7, ¶14-7 entire
Ref 2,
Vancocin PI,
p 2, ¶13, L6-21
Ref 3,
Zyvox PI,
p 8, ¶14, L1,2;
p 9, ¶11-3 entire
Ref 4,
Tygacil PI,
p 5, ¶12 entire, ¶13
entire, ¶16 entire;
p 6, ¶11 entire

	CUBICIN® (daptomycin for injection) ¹	Vancocin® HCl (Vancomycin Injection, USP) ²	Zyvox® (linezolid injection/ tablets/oral suspension) ³	Tygacil® (tigecycline for injection) ⁴
Class of antibiotic	Lipopeptide	Glycopeptide	Oxazolidinone	Glycylcycline
In vitro activity	Bactericidal*	Not listed†	Mixed†	Bacteriostatic [§]
Spectrum	Gram positive	Gram positive	Gram positive	Gram positive Gram negative
Location of activity	Cell membrane	Cell wall	Ribosomal RNA subunit	Ribosomal subunit

*Bactericidal activity against Gram-positive pathogens.

†In general, exhibits bacteriostatic activity against enterococci and bactericidal activity against streptococci and staphylococci.⁵⁻⁷

‡Bacteriostatic against enterococci and staphylococci. Bactericidal against most streptococci.

§In general, bacteriostatic against aerobic and facultative Gram-positive and -negative pathogens, anaerobic microorganisms, and *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium fortuitum in vitro*.

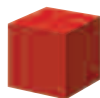
Susceptibility

	CUBICIN ¹	Vancocin HCl ²	Zyvox ³	Tygacil ⁴
MSSA	X	X	X	X
MRSA	X	X	X	X
<i>Streptococcus agalactiae</i>	X	<i>In vitro</i> only	X	X
<i>Streptococcus dysgalactiae</i> subspecies <i>equisimilis</i>	X			
<i>Streptococcus pyogenes</i>	X	<i>In vitro</i> only	X	X
<i>Enterococcus faecalis</i> (vancomycin-susceptible)	X	X	<i>In vitro</i> only	X
<i>Enterococcus faecalis</i> (vancomycin-resistant)	<i>In vitro</i> only		<i>In vitro</i> only	<i>In vitro</i> only
<i>Enterococcus faecium</i> (vancomycin-susceptible)	<i>In vitro</i> only	X	<i>In vitro</i> only	<i>In vitro</i> only
<i>Enterococcus faecium</i> (vancomycin-resistant)	<i>In vitro</i> only		X	<i>In vitro</i> only
<i>Streptococcus pneumoniae</i>		<i>In vitro</i> only	X	
<i>Staphylococcus epidermidis</i> (including methicillin-susceptible and methicillin-resistant strains)	<i>In vitro</i> only	X	<i>In vitro</i> only	<i>In vitro</i> only
<i>Staphylococcus haemolyticus</i>	<i>In vitro</i> only		<i>In vitro</i> only	<i>In vitro</i> only
Viridans group streptococci		X	<i>In vitro</i> only	
<i>Corynebacterium jeikeium</i>	<i>In vitro</i> only			
<i>Streptococcus bovis</i>		X		
<i>Listeria monocytogenes</i>		<i>In vitro</i> only		<i>In vitro</i> only
Diphtheroids		X		
<i>Streptococcus anginosus</i> group				X
Other <i>Enterococcus</i> species*				<i>In vitro</i> only

MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*; X = active both *in vitro* and in clinical infections; *In vitro* only = active *in vitro*, but clinical significance is unknown

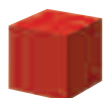
*Including *avium*, *casseliflavus*, and *gallinarum*.

For complete information on CUBICIN, refer to the enclosed package insert. For complete information on other products, refer to their respective package inserts.



References

1. CUBICIN® [package insert]. Lexington, MA: Cubist Pharmaceuticals, Inc.; 2007.
2. Vancocin® HCl [package insert]. Deerfield, IL: Baxter International Inc.; 2003.
3. Zyvox® [package insert]. New York, NY: Pfizer Inc; 2007.
4. Tygacil® [package insert]. Madison, NJ; Wyeth; 2007.
5. Akins RL, Rybak MJ. Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus* isolates in an in vitro pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother.* 2001;45:454-459.
6. Pankuch GA, Jacobs MR, Appelbaum PC. Bactericidal activity of daptomycin against *Streptococcus pneumoniae* compared with eight other antimicrobials. *J Antimicrob Chemother.* 2003;51:443-446.
7. Watanakunakorn C, Tisone JC. Effects of a vancomycin-rifampin combination on enterococci. *Antimicrob Agents Chemother.* 1982;22:915-916.



Acquisition Cost*

Ref 1, Cubicin PI, p 21, ¶14, L1,2, ¶15, L1,2; p 22, ¶13, L1-8, Table 9

Ref 2, Vancocin PI, p 6, ¶9, L1-6, ¶10, L1,2, ¶13, L1,2

Ref 3, Zyvox PI, p 25, Table 14

Ref 4, Tygacil PI, p 16, ¶16, L1,2, ¶18, L2-4

	CUBICIN® (daptomycin for injection)^{1,‡}	Vancocin® HCl (Vancomycin Injection, USP)^{2,§}	Zyvox® (linezolid injection/ tablets/oral suspension)³	Tygacil® (tigecycline for injection)⁴
Cost (WAC)[†] per day for adults with cSSSI				
Cost per day in patients without renal impairment Creatinine clearance ≥30 mL/min	\$96	\$21	\$159 (injection) \$124 (oral)	\$100
Cost per day in patients with renal impairment Creatinine clearance <30 mL/min	\$48	Variable	\$159 (injection) \$124 (oral)	\$100
Cost (WAC) per day for adults with <i>S. aureus</i> bacteremia, including right-sided endocarditis				
Cost per day in patients without renal impairment Creatinine clearance 30 mL/min	\$144	\$21	Not indicated— see Warnings	Not indicated
Cost per day in patients with renal impairment Creatinine clearance <30 mL/min	\$72	Variable	Not indicated— see Warnings	Not indicated

*Cost per day calculated using wholesale acquisition cost as listed in Thomson Micromedex Red Book™ ReadyPrice® System (March 2007 release) and assuming a 70-kg patient dosed according to the applicable package insert.

[†]WAC = wholesale acquisition cost, the list price to wholesalers without regard to prompt payment terms, discounts, rebates, or chargebacks.

[‡]Assumes no product wastage. Less frequent dosing needed for patients with renal impairment. In patients with creatinine clearance <30 mL/min, CUBICIN should be dosed at 4 mg/kg q48h or 6 mg/kg q48h.

[§]Vancomycin cost is approximated using a weighted average WAC of all generic formulations weighted by sales volume per IMS (Q105). Recommended vancomycin dosing for patients with creatinine clearance <30 mL/min varies based on several clinical variables referenced in the Vancocin package insert.

^{||}100 mg loading dose followed by 50 mg BID. Cost of loading dose averaged over assumed average 10 day course of therapy.

**CUBICIN® and Cubist are registered trademarks of Cubist Pharmaceuticals, Inc.
All other trademarks are the property of their respective owners.**

Please see enclosed full prescribing information.



www.cubist.com
©2007 Cubist Pharmaceuticals, Inc.
4003081307 August 2007
CUBICIN is a registered trademark
of Cubist Pharmaceuticals, Inc.

