National PBM Drug Monograph
Daptomycin (Cubicin™)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

INTRODUCTION

Daptomycin was approved September 2003 for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of *Staphylococcus aureus* (methicillin susceptible and methicillin resistant), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subspecies *equisimilis, and Enterococcus faecalis* (vancomycin susceptible only).

Daptomycin is not approved for treatment of diabetic foot infections due to the small number of patients included in the cSSSI trials.

Daptomycin is the first of a new class of antibiotics known as the cyclic lipopeptides that works by a mechanism that differs from other antibiotics. The mechanism of action of daptomycin is not fully understood. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis resulting in bacterial cell death. Daptomycin exhibits concentration-dependent bactericidal activity with clinical efficacy best correlating with Cmax/MIC or AUC/MIC. Daptomycin also exhibits rapid bactericidal activity as demonstrated in time-kill studies.[1-6, 11]

Calcium is needed for daptomycin to bind to bacterial membranes; as a result, susceptibility testing using Mueller-Hinton broth medium and Mueller-Hinton agar medium requires supplementation with calcium chloride (50mg/L and $\geq$ 28g/L respectively) to provide physiologic levels of free calcium.

Daptomycin is not indicated for treatment of pneumonia. In a phase 3 study of hospitalized community-acquired pneumococcal pneumonia, mortality and serious cardiopulmonary adverse events rates were higher in daptomycin treated patients versus those receiving the ceftriaxone. This negative outcome has been attributed to poor penetration of daptomycin into alveoli.

PHARMACOKINETICS

The pharmacokinetics of daptomycin was determined in a Phase 1 multi-dose trial in 24 healthy volunteers (18 daptomycin, 6 control). Subjects were randomized to receive 4mg/kg, 6mg/kg, 8mg/kg, or control every 24 hours for 7-14 days. Daptomycin exhibits linear pharmacokinetics at the 4mg/kg and 6mg/kg dosages. The 8mg/kg dose exhibited slightly less linearity, as Cmax was 2.2 times higher than the 4mg/kg dose.[7] Pharmacokinetic parameters for daptomycin are presented in Table 1.

Table 1. Pharmacokinetics

	4mg/kg	6mg/kg	8mg/kg
Cmax	57.8 ± 3 mcg/mL	98.6 ± 12mcg/mL	133 ± 13.5mcg/mL
Tmax Median (range)	0.8 hr (0.5, 1.0)	0.5 (0.5, 1.0)	0.5 (0.5, 1.0)
$AUC_{0\text{-}24h}$	494 ± 75 mcg · h/mL	747 ± 91 mcg · h/mL	1130 ± 117 mcg · h/mL
Half-life	8.1 ± 1.0 hr	8.9 ± 1.3 hr	9.0 ± 1.2 hr
Cmin	5.9 ± 1.6 mcg/mL	9.4 ± 2.5mcg/mL	14.9 ± 2.9 mcg/mL
Vd	0.096 ± 0.009 L/kg	0.104 ± 0.013L/kg	0.092 ± 0.012L/kg
Protein binding	~ 92% primarily to serum albumin in a concentration independent fashion. Protein binding decreases with decreasing renal function: • 87.6% - Cr Cl < 30mL/min • 85.9% - hemodialysis patients • 83.5% - CAPD • Child-Pugh B hepatic impairment similar to healthy adults		
Metabolism	Does not appear to induce or inhibit CYP450 enzymes. Unknown if daptomycin is a substrate of the CYP450 enzymes. Inactive metabolites of daptomycin have been found in the urine; however, site of		

	metabolism is unknown.
Excretion	Renal (~ 70% as intact drug)

Mean ± SD, unless otherwise indicated
Pharmacokinetic samples obtained on day 7 except for trough values which were obtained days 4-8

IN VITRO ACTIVITY

Using dilution technique, *Staphylococcus aureus* (methicillin susceptible and methicillin resistant), *Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus dysgalactiae* subspecies *equisimilis* are considered susceptible to daptomycin at MIC ≤ 1mcg/mL. Vancomycin-susceptible Enterococcus faecalis is considered susceptible at MIC ≤ 4 mcg/mL.

A zone of inhibition ≥ 16mm indicates susceptibility of *Staphylococcus aureus* (methicillin susceptible and methicillin resistant), *Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus dysgalactiae* subspecies *equisimilis* to daptomycin and a zone ≥ 11mm for vancomycin-sensitive *E. faecalis*

There are numerous published *in vitro* studies evaluating the susceptibility of gram-positive organisms to daptomycin.[8-15] Broth microdilution method, recommended by NCCLS, was used to determine the in vitro activities of daptomycin and other antibiotics tested. For daptomycin, Mueller-Hinton broth was supplemented with calcium 50mg/L. Some of the organisms tested were considered to be multidrug-resistant (MDR). In the 2 studies by Critchley, approximately 25% of S. aureus were considered to be MDR, with resistance to ciprofloxacin, erythromycin, and oxacillin being the most common MDR phenotype (69.6% U.S. and 10.9% Europe).[8, 9]

Table 2. In vitro activity of daptomycin against organisms studied in the clinical setting

Organism	Reference	# Isolates	MIC_{90}	MIC range
S. aureus (methicillin-susceptible)	Critchley (U.S.) 2003	713	0.25	0.03-0.5
	Critchley 2003	888	0.5	≤ 0.015-1.0
	Richter 2003	306	0.25	0.12-0.5
	Fuchs 2002	25	0.5	0.25-1.0
	Petersen 2002	10	0.5	0.12-0.5
	Barry 2001	375	0.5	0.03-1.0
	King 2001	51	0.25	0.03-0.5
	Wise 2001	50	0.5	0.12-0.5
S. aureus (methicillin-resistant)	Critchley (U.S.) 2003	305	0.5	0.12-0.5
	Critchley 2003	334	0.5	0.12-1.0
	Richter 2003	193	0.5	0.12-1.0
	Fuchs 2002	25	1.0	0.25-1.0
	Petersen 2002	10	0.5	0.23-0.5
	Barry 2001	172	0.5	0.12-2.0
	King 2001	29	0.5	0.125-0.5
	Wise 2001	50	0.5	0.25-0.5
E. faecalis (vancomycin-susceptible)	Critchley (U.S.) 2003	2049	2.0	0.03-4.0
	Critchley 2003	1798	2.0	≤ 0.015-4.0
	Richter 2003	460	2.0	0.06-4.0
	Petersen 2002	10	1.0	0.12-2.0
	Barry 2001	377	2.0	0.06-4.0
Strep agalactiae	Critchely (U.S.) 2003	273	0.25	0.03-0.5
	Critchley 2003	367	0.25	0.06-1.0
	Barry 2001	208	0.25	0.03-0.5
Strep pyogenes	Critchley (U.S.) 2003	484	0.06	≤ 0.015-0.5
	Barry 2001	239	0.06	0.016-0.5

Four studies evaluated susceptibility of MRSA to linezolid with all but 1 study showing 100% susceptibility.[8-11] In this study, the MIC ranged from 2.0-8.0mcg/mL (susceptibility against staphylococci defined as ≤ 4.0mcg/mL per NCCLS guidelines).[11] Both studies by Critchley and Fuchs found 100% of MRSA to be susceptible to quinupristin-dalfopristin whereas Richter found 2.1% and 1.6% of MRSA to be intermediately resistant and resistant respectively.[8-11] Approximately 90% of MRSA were susceptible to trimethoprim-sulfamethoxazole.[8, 9]

Both studies by Critchley found 100% of vancomycin-susceptible E. faecalis susceptible to ampicillin and linezolid.[8, 9] Richter found 0.4% with intermediate susceptibility to linezolid.[10] Approximately 60% of vancomycin-susceptible E. faecalis were susceptible to ciprofloxacin.[8-10]

Other tested organisms

Mean inhibitory concentrations have been determined for the following organisms; however, their clinical significance is unknown at this time. Critchley found that 58.4% and 19.6% of E. faecium were MDR in the U.S. and European studies respectively with over 95% of the strains carrying the ampicillin, ciprofloxacin, and vancomycin MDR phenotype.[8, 9]

Table 3

Organism	Reference	# Isolates	MIC_{90}	MIC range	% Organisms susceptible to other antibiotics
E. faecalis (vancomycin-resistant)	Critchley (U.S.) 2003	40	2.0	≤ 0.015-2.0	100% susceptible to linezolid (Critchley U.S, Critchley, Richter)
	Critchley 2003	40	2.0	0.5-4.0	
	Richter 2003	38	4.0	0.5-4.0	
	Petersen 2002	10	1.0	0.12-2.0	100% susceptible to ampicillin (Critchley U.S., Critchley)
	Barry 2001	10	4.0	0.12-4.0	
E. faecium (vancomycin-susceptible)	Critchley (U.S.) 2003	147	4.0	0.06-8.0	100% susceptible to linezolid (Critchley U.S., Critchley)
	Critchley 2003	333	4.0	0.03-8.0	
	Richter 2003	200	2.0	< 0.015-4.0	
	Petersen 2002	10	2.0	1.0-4.0	6.5% intermediate susceptibility (Richter)
	Barry 2001	50	4.0	0.12-8.0	
	King 2001	32	2.0	0.25-2.0	
E. faecium (vancomycin-resistant)	Critchley (U.S.) 2003	219	4.0	0.25-4.0	99.5% susceptible to linezolid (Critchley U.S.)
	Critchley 2003	114	4.0	0.25-4.0	
	Richter 2003	265	2.0	0.12-4.0	4.2% intermediate-susceptibility (Richter)
	Petersen 2002	10	2.0	1.0-2.0	
	Barry 2001	91	4.0	0.25-8.0	Q-D susceptibility variable (75.4%-97.3%)
	King 2001	18	2.0	0.25-4.0	
Coagulase-negative staphylococci (methicillin-susceptible)	Critchley (Europe)	486	0.5	0.03-1.0	
	Petersen 2002	10	0.25	0.06-0.5	
	Barry 2001	204	0.5	0.016-2.0	
Coagulase-negative staphylococci (methicillin-resistant)	Critchley (Europe)	554	0.5	0.03-1.0	
	Fuchs 2002	40	0.5	0.12-1.0	
	Petersen 2002	10	0.5	0.12-0.5	
	Barry 2001	339	0.5	0.12-2.0	

Streptococcus pneumoniae, including drug-resistant strains, are susceptible to daptomycin (MIC_{90} 0.12 and 0.25mcg/mL).[8, 9, 16, 17] Daptomycin has also been tested against several gram-positive anaerobes and corynebacteria. Daptomycin was active against all tested strains of *Clostridium difficile, Clostridium perfringens, and Corynebacterium jeikeium*. Other Clostridia organisms, Actinomyces group, Eubacterium group, Lactobacillus spp, Propionibacterium spp, Corynebacterium spp, had variable susceptibilities.[18, 19]

Vancomycin-intermediate and vancomycin-resistant S. aureus

With the emergence of vancomycin-intermediate S. aureus and more recently, vancomycin-resistant S. aureus, alternative antibiotic choices are needed. Susceptibility data for daptomycin, linezolid, quinupristin-dalfopristin, and TMP-SMX are presented in table 4.[11,12,20-23]

Table 4. Antibiotic Susceptibility of Vancomycin-resistant and Vancomycin-intermediate S. aureus

Organism	Reference	# Isolates	Daptomycin MIC range / MIC	Linezolid MIC	Quinupristin-dalfopristin MIC	TMP-SMX MIC
VISA	Rybak	3	0.5-1.0	1.0-2.0	0.25-0.25	-
GISA	Fuchs	3	1.0-2.0	0.5-2.0	0.5-0.5	-
GISA*	Petersen	19	0.5-16 4.0	-	-	-
GISA	Cha	2	0.5	-	-	-

VRSA	Bozdogan (HMC3)	1	0.5	1.0	1.0	0.25
VRSA	Chang (DMC83006A)	1	1.0	2.0	≤1.0	2.0

VISA= vancomycin-intermediate *S. aureus*; GISA=glycopeptide-intermediate *S. aureus*; VRSA=vancomycin-resistant *S. aureus*
*GISA obtained from NARSA (Network on Antibiotic Resistance in *Staphylococcus aureus*)

Linezolid and quinupristin-dalfopristin resistant organisms

There have been recent reports linezolid and quinupristin-dalfopristin (Q-D) resistant organisms. Susceptibility of these organisms to other antibiotics is presented.[32]

- Linezolid non-susceptible *S. aureus* was susceptible to daptomycin, vancomycin, and Q-D.
- Linezolid-resistant *E. faecalis* was susceptible to daptomycin and vancomycin.
- Linezolid-resistant *E. faecium* was susceptible to daptomycin and Q-D. Susceptibility to vancomycin was variable (MIC ≤ 0.5-32).
- Q-D resistant *E. faecium* was susceptible to daptomycin and linezolid. Susceptibility to vancomycin was variable (MIC ≤ 0.5-32).

RESISTANCE

Daptomycin is not used in livestock feed or in agriculture and is therefore unlikely to result in the transmission of daptomycin-resistant bacteria from animals to humans.

In vitro tests such as spontaneous resistance testing, serial passage, and chemical mutagenesis have been used to predict the clinical development of bacterial resistance to antimicrobial agents. No spontaneously resistant mutants were obtained when *S. aureus* (n=4), *S. epidermidis* (n=4), *E. faecalis* (n=4), *E. faecium* (n=2), and *S. pneumoniae* (n=2) were tested with daptomycin at 8x MIC. Two separate studies using serial passage and chemical mutagenesis attempted to create daptomycin-resistant S. aureus. After 20 passes (serial passage) and chemical mutagenesis, mutant strains were obtained having MIC values 8-32-fold higher than the parent organism. Some mutant isolates had normal growth rates and were virulent in a mouse model of infection. Other mutants had significant growth defects *in vitro* and were not virulent *in vivo*.[24]

In phase 2/3 studies, the emergence of resistance has been reported in 2 cases. The first case was a resistant S. aureus that emerged during a Phase 2 endocarditis study. In this case, the patient was dosed below the protocol-defined dose. The second case involved a resistant E. faecalis in a patient with a chronic infected decubitus ulcer enrolled in a salvage trial.[33]

POSTANTIBIOTIC EFFECT

The postantibiotic effect (PAE) is defined as the length of time that bacterial growth is suppressed following brief exposure to an antibiotic. The mean PAEs for MSSA (n=2) and MRSA (n=2) were 2.4 and 4.1 hours respectively. For methicillin sensitive (n=2) and methicillin resistant coagulase negative staphylococcus (n=2), the mean PAEs were 1.3 and 2.2 hours respectively. The mean PAE for 6 pneumococcal isolates was 1.7 hours (range 1.0-2.5 hours).[25] Earlier studies have shown PAEs of ranging from 3- 6 hours for S. aureus and E. faecalis.[26, 27]

SYNERGY STUDIES

Synergy studies have been performed with penicillins, cephalosporins, carbapenems, quinolones, and aminoglycosides against S. aureus, S. epidermidis, S. pyogenes, E. faecalis, E. faecium, S. pneumoniae, and viridans streptococcal group. In general, most effects were additive or indifferent and none antagonistic. Synergy was seen most frequently with gentamicin and amikacin, which occurred in 37% and 23% of isolates respectively.[29]

DISTRIBUTION INTO BLISTER FLUID

Daptomycin penetrates well into cantharidin-induced inflammatory blister. The following pharmacokinetic parameters were obtained in 6 healthy males after a 4mg/kg IV dose (Table 5). [28]

Table 5. Blister fluid pharmacokinetics

AUC 0-24 (mcg · h/mL)	Cmax (mcg/ml)	Tmax (h)	T1/2 (h)	% Penetration
318.2 ± 84.9	27.6 ± 9.5	3.67 ± 0.81	17.3 ± 11.3	68.4 ± 19.9

Mean ± SD

CLINICAL TRIALS

Data for the clinical trials were obtained from the FDA web site. [29] There are 2 randomized, investigator-blinded clinical studies comparing daptomycin 4mg/kg once daily to vancomycin 1gm q 12 hours or semi-synthetic penicillin 4-12g/day (oxacillin, nafcillin, cloxacillin, flucoxacillin) in patients with cSSSI. Those with co-infections due to anaerobes and/or gram negatives could also receive metronidazole and/or aztreonam. Adjunctive surgical management such as drainage or debridement was allowed as appropriate. Study 9801 (n=530) was conducted in the U.S. (62 sites) and South Africa (5 sites) and study 9901(n=562) was conducted at non-U.S. sites.

Patients aged 18-85 years who required hospitalization for clinical signs and symptoms of cSSSI that was known or suspected (by gram stain) to be entirely or in part due to gram-positive bacteria were eligible. Patients also had to have $\geq$ 3 of the following: Erythema $\geq$ 1cm beyond wound edge, induration, pain, pus, swelling, temp >37.5°C, tenderness to palpation, WBC 12,000 or $\geq$ 10% bands. Patients with bacteremia at baseline or whose condition required curative surgery were excluded.

Prior to randomization, the investigator evaluated the patient and chose the comparator (vancomycin or semi-synthetic penicillin) should the patient be randomized to the comparator. Those pre-randomized to vancomycin were then randomized to receive vancomycin or daptomycin and those pre-randomized to semi-synthetic penicillin were randomized to the penicillin or daptomycin. Once treatment commenced, patients could be switched from vancomycin to semi-synthetic penicillin or vice versa if deemed appropriate.

After at least 4 days of IV therapy, patients may be switched to oral therapy if clear clinical improvement was noted. Intravenous medication was received exclusively in 92% and 87.5% of daptomycin and comparator-treated patients respectively.

The daptomycin and comparator groups were well matched for type of infection and infecting organisms. Slightly more patients in the comparator group had diabetes and peripheral vascular disease. Study 9901 may have had a less sick population as the incidence of co-morbid conditions and need for adjunctive treatments were lower. Additionally, the incidence of MRSA was lower in study 9901. (Table 6)

Table 6. Patient characteristics

	Study 9801		Study 9901	
	Daptomycin	Comparator	Daptomycin	Comparator
Wound infection	37.5%	43.6%	37.8%	37%
Major abscess	20.8%	16.2%	21.9%	22.3%
Ulcer infection	26.9%	28.2%	19.6%	23.3%
Other infection*	14.8%	12%	20.7%	17.5%
MSSA	49.8%	45.8%	58.2%	54.9%
MRSA	16.3%	16.7%	2.3%	4.3%
Strep pyogenes	15.3%	16.2%	27.7%	26.7%
Strep agalactiae	7.9%	10.6%	6.1%	7.1%
Strep dysgalactiae	3.3%	2.8%	1.9%	3.5%
E. faecalis	11.6%	15.3%	9.4%	11%
% bacteremic	3%	2.2%	2.2%	2.1%
SIRS present	39.8%	45.1%	31.5%	31.2%
Age $\geq$ 65 years	34%	31%	20%	19.2%

Weight (kg) ± SD (Range)	87.6 ± 33.5 (36, 274)	87 ± 27.7 (44, 193)	73.5 ± 19.8 (40, 165)	72.7± 17.4 (40, 130)
Diabetes	40.6%	46.4%	18.5%	23.3%
Peripheral vascular disease	26.2%	30.3%	11.9%	15.8%
Immunocompromised	3-4%	3-4%	~3%	~3%
Adjunctive treatment with aztreonam and/or metronidazole	31.6%	31.8%	17%	22.3%
Adjunctive surgical procedure**	39.8%	39.5%	19.6%	19.9%

*Subsequently categorized as cellulitis, major abscess, or traumatic wound
**Most commonly incision and drainage and wound debridement

The objective of these studies was to demonstrate non-inferiority of daptomycin to the comparator in clinical response using a non-inferiority margin of 10%. Primary efficacy was clinical efficacy in the intent-to-treat group (ITT) defined as those having received at least one dose of study drug and the clinically evaluable group (CE) defined as subjects who met specific protocol criteria. Secondary efficacy variables included the modified intent to treat (MITT) group defined as those patients in the ITT group who had an infecting gram-positive pathogen at baseline and the microbiologically evaluable group (ME) defined as patients in the CE group who had an infecting gram-positive organism at baseline. Study outcomes were based on the post-therapy (test-of-cure visit) conducted 7-12 days post-treatment.

The percent of patients completing study 9801 was 82.6% and 83% for daptomycin and comparator respectively and 93.3% and 95.6% respectively in study 9901. In general, success rates were lower for the U.S./South African study 9801 than for study 9901conducted at non-U.S. sites. This may be attributed to a sicker population with more co-morbitities, concomitant antibiotics, and surgical procedures in study 9801. The success rates demonstrate that daptomycin was not inferior to comparator (Tables 7 and 8). Success rates by infecting organism are presented in table 9.

Table 7. Clinical success rates

	Study 9801			Study 9901		
	Daptomycin	**Comparator**	**95%CI***	**Daptomycin**	**Comparator**	**95%CI***
ITT	62.5%	60.9%	-7.1, 10.3	80.4%	80.5%	-7.0, 6.8
CE	76%	76.7%	-9.4, 7.9	89.9%	90.4%	-6.2, 5.2
MITT	65.1%	64.8%	-9.2, 9.8	84%	83.1%	-6.3, 8.1
ME	76.4%	77.8%	-10.8, 8.0	92.1%	92.3%	-5.8, 5.6

*95% CI around difference in success rate (comparator – daptomycin) per pre-randomized stratification

Table 8. Microbiologic success rates

	Study 9801			Study 9901		
	Daptomycin	**Comparator**	**95%CI***	**Daptomycin**	**Comparator**	**95%CI***
ME	65.1%	64.8%	-11.3, 9.4	80.1%	82.7%	-10.7, 5.4
MITT	57.7%	57.4%	-9.5, 10.1	72.8%	75.3%	-10.9, 5.9

*95% CI around difference in success rate (comparator – daptomycin) per pre-randomized stratification

Table 9. Success rate by infecting organism (MITT/ME population)

	Study 9801		Study 9901	
	Daptomycin	**Comparator**	**Daptomycin**	**Comparator**
MSSA	73/107 (68.2%)	65/99 (65.7%)	103/124 (83.1%)	119/140 (85%)
n/N (%)	69/87 (79.3%)	65/84 (77.4%)	83/111 (74.8%)	99/123 (80.5%)
MRSA	17/35 (48.6%)	17/36 (47.2%)	4/5 (80%)	9/11 (81.8%)
n/N (%)	17/24 (70.8%)	16/27 (59.3%)	3/4 (75%)	8/9 (88.9%)
Strep pyogenes	27/33 (81.8%)	25/35 (71.4%)	53/59 (89.8%)	57/68 (83.8%)
n/N (%)	25/29 (86.2%)	22/29 (75.9%)	52/55 (94.5%)	50/59 (84.7%)
Strep agalactiae	13/17 (76.5%)	14/23 (60.9%)	11/13 (84.6%)	8/18 (44.4%)
n/N (%)	11/15 (73.3%)	12/16 (75%)	10/12 (83.3%)	7/13 (53.8%)
Strep dysgalactiae	7/8 (87.5%)	3/6 (50%)	2/4 (50%)	7/9 (77.8%)

n/N (%)	6/6 (100%)	3/5 (60%)	2/2 (100%)	7/9 (77.8%)
E. faecalis	13/25 (52%)	19/33 (57.6%)	14/20 (70%)	22/28 (78.6%)
n/N (%)	13/21 (61.9%)	19/29 (65.5%)	13/16 (81.3%)	17/24 (70.8%)

The daptomycin group showed greater improvement in clinical signs and symptoms by the third or fourth day than the comparator group. The median duration of therapy was 1 day shorter with daptomycin versus comparator in study 9901.

In both studies, the success rates for those who were switched to oral therapy (MITT population) were approximately 70% for both daptomycin and comparator.

Response rate of daptomycin was lower in patients $\geq$ 65 years old than in those < 65year old. In study 9801, the rates for daptomycin and comparator were 50.5% ($\geq$ 65) vs. 68.8% (< 65) respectively and in study 9901, 83.8% ($\geq$ 65) and 67.7% (< 65) respectively. There was no age-related difference in success rate with the comparator in study 9801. In study 9901, there was approximately a 9% difference favoring those <65years old.

When broken down by primary diagnosis, success rates were similar between daptomycin and comparator. Both daptomycin and the comparator had the highest success rates in those receiving treatment for major abscess. There was a numerically higher success rate with infected non-diabetic ulcers in the comparator arm than with daptomycin. In both studies and in both arms, patients with diabetes had lower cure rates than those who did not have diabetes.

SAFETY

Daptomycin was originally developed in the early 1980s by Lilly; however, it was temporarily shelved due to concerns about skeletal muscle toxicity. At that time, daptomycin was being dosed twice daily. It was later realized that once daily dosing of daptomycin not only improved clinical efficacy, but also minimized the potential for adverse effects on skeletal muscle.

Elevated CPK levels/skeletal muscle toxicity

In phase I studies sponsored by Lilly, 2/102 (2%) had an elevated CPK value. Daptomycin was discontinued in both subjects. In Phase 1 studies by Cubist, 7/240 (2.9%) of daptomycin-treated subjects and 2/109 (1.8%) of comparator-treated subjects had an elevated CPK. Daptomycin was discontinued in 3 of the daptomycin-treated and 1 of the comparator-treated subjects.

In a Cubist sponsored Phase 2 study, 4/47 (5.4%) and 1/24 (4.2%) of patients receiving daptomycin and comparator respectively had increased CPK values with 2 subjects discontinuing therapy in the daptomycin group. In another study, 4/72 (5.6%) of patients receiving daptomycin had an elevated CPK. There was no comparator arm in this study.

In the Phase 3 cSSSI trials, CPK levels were monitored prior to the first dose of drug and on days 3, 5, 7, and daily thereafter while on study medication. Elevated CPK levels were seen in 2.8% and 1.8% of patients receiving daptomycin and comparator agents respectively. According to the manufacturer, the majority of elevations were due to recent surgery, trauma, or intramuscular injections. Discontinuation of daptomycin due to elevated CPK values occurred in 2 patients, 1 of whom who had muscle symptoms. Symptoms rapidly resolved upon discontinuation of study drug.

Nineteen patients receiving daptomycin and 24 receiving comparator had CPK values $\geq$500 at baseline. CPK returned to normal or decreased on therapy in 89.5% and 83.3% of the daptomycin and comparator patients respectively. In the remaining patients, CPK increased while on therapy. No patients developed myopathy.

Symptoms consistent with myopathy (pain in limb, arthralgia, back pain, myalgia, muscle cramps) were reported in 7/534 (1.3%) of patients on daptomycin and 5/558 (0.9%) on comparator. Of those, 3/534 (0.5%) in the daptomycin group was thought to be drug related versus none in the comparator group.

The manufacturer recommends that patients be monitored for muscle pain or weakness, particularly of the distal extremities and to obtain weekly CPK levels while on therapy. Patients developing unexplained CPK elevations should be monitored more frequently; however, those with substantially elevated CPKs ($\geq$ 10 X ULN) should discontinue daptomycin. Daptomycin should also be discontinued in those who have unexplained symptoms of myopathy and elevated CPK. It is suggested that HMG-CoA reductase inhibitors be temporarily discontinued while receiving daptomycin.

Neuropathy

Peripheral nerve toxicity in dogs was seen at 10-25x the human mg/kg dose given for 2 –4 weeks. In humans, motor and sensory neurophysiologic tests were conducted in 120 healthy volunteers receiving daptomycin 6mg/kg x 2 weeks. Median nerve electrophysiology testing, vibratory perception threshold, and a neurologic questionnaire were administered at baseline and days 1, 14, and 28. The only statistically significant difference found was an increase from baseline in the total score on the Symptoms and Functional Deficits Questionnaire on day 28 in the daptomycin group. (Data on file-Cubist)

In Phase 1 Cubist-sponsored studies, 2/240 developed Bell's palsy. In Phase 2 studies by Cubist, 2 patients developed Bell's palsy. There was one case of neuropathy and 1 case of decreased nerve conduction velocity in Phase 2 studies by Lilly. In Phase 3 cSSSI and Community Acquired Pneumonia studies, 0.7% of daptomycin-treated and 0.7% of comparator-treated patients experienced paresthesias. New or worsening peripheral neuropathy was not diagnosed in these patients.

Phase 3 cSSSI studies

Adverse events were reported in 51.3% and 52.5% of patients receiving daptomycin and comparator respectively. Serious adverse events (SAE) occurred in 10.9% receiving daptomycin and in 8.8% receiving comparator. The SAEs were due to cellulitis, urosepsis, hypersensitivity reaction, and diarrhea (aggravated).

The most commonly reported adverse events were gastrointestinal, injection site reactions, and headache. Table 9 lists those adverse events reported in $\geq$ 2% of patients taking either daptomycin or comparator in the Phase 3 cSSSI studies. Shaded areas represent those adverse events occurring more frequently in the daptomycin group.

Table 9. Adverse events occurring in $\geq$ 2% of patients in the Phase 3 cSSSI studies

Adverse event	Daptomycin	Comparator
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhea	5.2%	4.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
Injections site reactions	5.8%	7.7%
Fever	1.9%	2.5%
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.0%
Rash	4.3%	3.8%
Pruritis	2.8%	3.8%
Abnormal liver function tests	3.0%	1.6%
Elevated CPK	2.8%	1.8%
Fungal infections	2.6%	3.2%
Urinary tract infections	2.4%	0.5%
Hypotension	2.4%	1.4%
Hypertension	1.1%	2.0%
Renal failure	2.2%	2.7%

Anemia	2.1%	2.3%
Dyspnea	2.1%	1.6%
Limb pain	1.5%	2.0%
Arthralgia	0.9%	2.2%

DRUG INTERACTIONS

Since daptomycin is not an inhibitor or inducer of the CYP450 enzymes, drug interactions via this system are not expected; however, since it is unknown if daptomycin is a substrate of the CYP450 enzymes, other inducers or inhibitors may affect the metabolism of daptomycin.

Daptomycin has been studied individually with aztreonam, tobramycin, warfarin, simvastatin, and probenecid. The only combination resulting in changes in Cmax and AUC was daptomycin and tobramycin. In this single-dose study, the Cmax and AUC of daptomycin increased by 12.7% and 8.7% respectively while the Cmax and AUC of tobramycin decreased by 10.7% and 6.6% respectively. Significance of this interaction is unknown.

In the daptomycin/warfarin study, INR of warfarin was not significantly altered. Because experience with this drug combination is limited, it is recommended that INR be closely monitored.

There was no increase in the incidence of adverse events when simvastatin 40mg daily was administered with daptomycin 4mg/kg once daily for 14 days. In Phase 3 (cSSSI and Community Acquired Pneumonia) trials, statin use was not allowed; however, a small number of patients (~50 per arm) did receive a statin or fibrate. There was no difference in elevated CPK values or symptoms of myopathy between those receiving a statin and daptomycin versus a statin and comparator. Because of limited experience, it is suggested that HMG-CoA reductase inhibitors be temporarily discontinued while receiving daptomycin.

DOSAGE AND ADMINISTRATION

The dose of daptomycin is 4mg/kg IV once daily for 7-14 days. Patients with CrCl < 30mL/min, including those receiving hemodialysis or continuous ambulatory peritoneal dialysis should receive 4mg/kg IV every 48 hours. Please note that patients with CrCl < 30mL/min were excluded in the Phase 3 cSSSI trials. A Phase 4 commitment has been made to further study this population.

Reconstitute the 250mg vial with 5mL and the 500mg vial with 10mL of 0.9% sodium chloride for injection. Withdraw the desired dose and further dilute in 0.9% sodium chloride for injection and administer by IV infusion over 30 minutes. Daptomycin is not compatible with dextrose-containing solutions. Do not add additives or other drugs to daptomycin IV solution or infuse simultaneously through the IV line delivering other IV fluids/medications. If the same IV line is used for sequential administration of drugs, the line must be flushed with a compatible solution before and after infusing daptomycin. Daptomycin is also compatible with lactated ringers.

Store daptomycin in a refrigerator at 36-46°F. Once reconstituted or in an infusion bag, it is stable at room temperature for 12 hours or for 48 hours if stored under refrigeration. Daptomycin contains no preservatives or bacteriostatic agents; therefore, it is intended for single-use.

OTHER AREAS OF STUDY

Several studies in experimental endocarditis models support evaluating daptomycin for the treatment of endocarditis. There is an ongoing clinical study in the treatment of right-sided endocarditis/bacteremia due to S. aureus using a once daily dose of 6mg/kg for 14-28days. The comparator agents are nafcillin or vancomycin $\pm$ gentamicin.

Studies also support daptomycin for the treatment of experimental osteomyelitis. The manufacturer plans to propose an osteomyelitis study to the FDA using daptomycin 6mg/kg. (Personal communication F. Tally, Cubist)

A study in vancomycin resistant enterococcus was stopped due to slow enrollment. There are plans to present the data on 50 patients who were enrolled in the study. (Personal communication F. Tally, Cubist)

LOOKALIKE/SOUNDALIKE DRUGS

There was a report of a mix-up between daptomycin and the cancer drug dactinomycin (Cosmegen). Both agents are given once daily, supplied as lyophilized powders, and are yellowish solution when reconstituted. Because of differences in dosing, the error was detected before reaching the patient.

COST

The FSS price for a vial of daptomycin 500mg is $100.67. A 250mg vial is available; however, only a price for the 500mg vial has been offered to the government. At 4mg/kg, a 70kg individual would require 280mg once daily. The cost of therapy will depend on whether the remaining drug is used in the preparation of another dose. Since daptomycin comes as a single-use vial, the remaining drug should be prepared at the same time and used within 12 hours if at room temperature or within 48 hours if refrigerated. Cost will also vary depending on whether doses are rounded off. For example, in the 70kg person, some may round off the 280mg dose to 250mg or 300mg.

Table 10 shows how daptomycin pricing compares with the other newer agents. The prices represent drug cost only and do not include cost for IV bags, diluents, IV lines, nursing/pharmacist time, laboratory monitoring, etc. The previous discussion on dosing per weight, rounding off, and use of remaining drug in vials intended for single-use also applies to quinupristin-dalfopristin. Because of these variabilities, cost per day was not calculated.

Table 10. FSS cost per drug vial

	Dose for cSSSI	FSS cost per vial
Daptomycin	4mg/kg q 24 hours	500mg vial = $100.67
Linezolid	600mg q 12 hours	600mg vial= $42.84
Quinupristin-dalfopristin	7.5mg/kg q 12 hours	500mg vial= $63.51

RECOMMENDATION

Daptomycin is a potentially important new antibiotic that has activity against resistant gram-positive organisms. In order to keep daptomycin as a viable treatment option against these organisms, it is important that it is not misused or overused.

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