

**Bon Secours Richmond
Pharmacy & Therapeutics Committees
Ertapenem (Invanz)
7/2002**

Recommendations: MEC Approved at MPMC/SMH/RCH

- Ertapenem is not recommended for formulary inclusion, as the spectrum is not as complete as piperacillin/tazobactam and imipenem or ceftriaxone when used for intra-abdominal or community acquired pneumonia respectively. Its cost is twenty-five percent lower than piperacillin/tazobactam, seventy-five percent higher than ceftriaxone, and eighty-three percent higher than cefotetan.
- Cefotetan, piperacillin/tazobactam, or ticarcillin/clavulanate is recommended in place of ertapenem when ordered for complicated skin and skin structure, intra-abdominal infections, and acute pelvic infections. (see dosage table below)
- Levaquin or (ceftriaxone plus azithromycin) is recommended in place of ertapenem for community-acquired pneumonia.
- Levaquin is recommended for automatic substitution for ertapenem when ordered for urinary tract infections.
- Ertapenem is not recommended for community-acquired pneumoniae as it has little activity against highly-penicillin-resistant pneumococci and does not cover atypical pathogens.
- *The patent on imipenem will expire this year at which time a less expensive generic form will become available.*

Findings:

- Ertapenem (Invanz®) is a carbapenem antimicrobial with a broad spectrum of activity against both Gram-positive and Gram-negative bacteria. Like meropenem, ertapenem has a 1-β-methyl substituent, and therefore does not require protection with an inhibitor of human renal dehydropeptidase I. Ertapenem has a spectrum of activity broader than that of ceftazidime, but not as broad as meropenem or imipenem.
- Ertapenem is less active than imipenem against gram positive bacteria.
- Ertapenem has similar activity to meropenem against Enterobacteriaceae.
- Ertapenem's antianaerobic is similar to imipenem and piperacillin-tazobactam.
- Ertapenem is not active against Pseudomonas aeruginosa, Pseudomonas spp. or Acinetobacter spp.
- Ertapenem has little activity against highly-penicillin resistant pneumococci, and no activity against MRSA, Enterococcus faecium or faecalis, Stenotrophomonas maltophilia, or atypical respiratory pathogens such as Chlamydia spp., Mycoplasma pneumoniae and Legionella spp. is resistant to ertapenem
- Ertapenem is highly protein bound, 95%.
- Ertapenem is inactivated by hydrolysis of the beta lactam ring and is not hepatically metabolized.
- 38% of ertapenem is excreted unchanged in the urine.
- Ertapenem is not active against Pseudomonas aeruginosa and Acinetobacter and should not be use for empiric treatment of nosocomial infections.
- Clinical studies have general found the following regimen to have similar efficacy in intra-abdominal, pelvic and infections likely to involve multiple organisms including anaerobes: Zosyn, Timentin, Unasyn, and Cefotan all with or without aminoglycosides.
- *Ertapenem should not be mixed with other medications and can not be mixed in dextrose. 0.9% NaCl is the recommended diluent.*
- Seizures occurred in 0.5% of patients studied within 14 days of therapy, most commonly in patient with CNS disorders (brain lesions or history of seizure) and/or comprised renal function. The rate in piperacillin/tazobactam treated patients was 0.3% and 0% for ceftriaxone.
- Ertapenem AUC when co-administered with probenecid, 500mg q6h, was increased by 25%. No other drug interactions have been described.
- Adverse reactions during clinical trials (package insert) show a higher incidence of respiratory distress, dyspnea, altered mental status and death with ertapenem versus Zosyn. *In patients treated for complicated intra-abdominal infections death occurred in 4.7% (15/316) of patients receiving ertapenem and 2.6% (8/307) of patients receiving comparator drug.*

Cost Comparison Chart		
	Usual Dose	Cost per day
Ertapenem	1gm qd	\$36.64
Imipenem	500mg q6h	\$94.63
Zosyn	3.375gm q6h	\$48.30
Rocephin	1 gm q24h	\$20.81
Levaquin	500 mg q24h	\$16.00
Cefotan	1-2gm q12h	\$13.50-27.02

Cost of Conversion of Cefotetan to Invanz							
Cefotetan			Invanz			Excessive Cost of Invanz	
Dose	Number of Doses	Days of therapy	Cost	Dose	Days of therapy	Cost	
1 gm	4370	2185	\$30,096.19	1 gm	2185	\$80,058.40	\$49,962.21
2 gm	3910	1955	\$52,824.10	1 gm	1955	\$71,631.20	\$18,807.10
Totals			\$82,920.29			\$151,689.60	\$68,769.31

Renal Dosing per Package Insert & Sanford Guide						
CrCl (ml/min)	Ertapenem	Cefotetan	CrCl (ml/min)	Imipenem (>70kg)	CrCl (ml/min)	Piperacillin/tazobactam
>30	1g QD	1-2 gm q12h	≥ 71	0.25-1gm q6h	>40-90	3.375gm q6h
10-30	0.5 gm QD	1-2 gm q24h	41-70	0.25-0.75 gm q8h	20-40	2.25gm q6h
< 10	0.5 gm QD	1-2 gm q48h	21-40	0.25-0.5 gm q6-12h	<20	2.25gm q8h
Hemodialysis	0.5 gm QD after Dialysis (Give 150mg supplementary dose if given within 6 hours prior to HD)	25% of dose per above q24h on non-HD days, 50% of dose on HD day	6-20	0.25-0.5 gm q12h	Hemodialysis	2.25gm q8h (MAX) (Give 0.75gm supplementary dose following each HD period)
CAPD	No Data	1 gm QD	≤ 5 or HD	0.125-0.25 gm q12h	-	2.25 gm q8h
CAHV	No Data	750 mg Q12h		0.25 gm q6-12h		-

Clinical Studies

Complicated Intra-Abdominal Infections

Ertapenem had activity comparable to piperacillin/tazobactam in the treatment of complicated intra-abdominal infections in a study enrolling 665 patients with localized complicated appendicitis, and any other complicated intra-abdominal infection including colonic, small intestinal, biliary infections, and generalized peritonitis. Patients received ertapenem 1 g intravenously once daily or piperacillin/tazobactam 3.375 g intravenously every 6 hours for 5 to 14 days. Among microbiologically evaluable subjects at 4 to 6 weeks posttherapy, cure was achieved in 83.6% (163/195) of ertapenem-treated patients and 80.4% (152/189) of piperacillin/tazobactam-treated patients.^(Package Insert)

Complicated Skin and Skin Structure Infections

Ertapenem also had activity comparable to piperacillin/tazobactam in complicated skin and skin structure infections in a double-blind study enrolling 540 patients. Patients were treated with either intravenous ertapenem 1 g once daily or piperacillin/tazobactam 3.375 g every 6 hours. Clinical success at 10 to 21 days posttherapy was reported for 83.9% (141/168) of ertapenem-treated patients and 85.3% (145/170) of piperacillin/tazobactam-treated patients. More than one baseline pathogen was identified in 181 of 540 patients. Clinical outcome was assessable in 127 of 181 (70%) patients from whom a total of 435 pathogens were isolated. The most common diagnoses were deep soft tissue abscess, diabetic lower extremity infections, perineal cellulitis/abscess, post-traumatic wound infection, and complicated cellulitis. Mixed aerobic and anaerobic pathogens were present in 39%, anaerobes only were present in 8%, and aerobes only were present in 53%. The aerobes most commonly isolated were *S. aureus*, *E. coli*, and *S. agalactiae*. The anaerobes most commonly isolated were *Peptostreptococcus* spp., *Prevotella* spp., and *B. fragilis*. The median duration of therapy was 8 days in the ertapenem group and 9 days in the piperacillin/tazobactam group. Clinical response among evaluable patients with polymicrobial infections was achieved in 80.3% of ertapenem-treated patients and 77% of piperacillin/tazobactam-treated patients. Microbiologic response was achieved in 81.8% of ertapenem-treated patients and 77% of piperacillin/tazobactam-treated patients.^(Abstract)

Community-Acquired Pneumonia

Ertapenem was as effective as ceftriaxone in two clinical studies enrolling a total of 866 patients with community-acquired pneumonia. Patients were treated with either ertapenem or ceftriaxone, both at doses of 1 g intravenous or intramuscularly once daily. A switch to oral amoxicillin/clavulanate was allowed after a minimum of 3 days of parenteral therapy. Clinical assessment was available for 76% of patients. Microbiologic assessment was available for 41% of patients. The median duration of therapy was 12 days (4 days parenteral). Oral therapy was administered to 88% of patients. For the first study the primary efficacy parameter was the clinical success rate among clinically evaluable patients. Success rates were 92.3% (168/182) for ertapenem and 91% (183/201) for ceftriaxone at 7 to 14 days. In the second study the primary efficacy parameter was the clinical success rate in microbiologically evaluable patients. Success rates were 91% (91/100) for ertapenem and 91.8% (45/49) for ceftriaxone 7 to 14 days posttherapy. Cure rates for the combined study populations are summarized in Table 1.^{Package Insert,29(Abstract)}

Complicated Urinary Tract Infections

Ertapenem was also as effective as ceftriaxone in two clinical studies enrolling a total of 850 patients with complicated urinary tract infections. Patients received either ertapenem or ceftriaxone at a dose of 1 g once daily. After a minimum of 3 days of parenteral therapy, patients could be switched to oral ciprofloxacin therapy. Assessment was available for 256 of 473 ertapenem-treated patients and 224 of 377 ceftriaxone-treated patients. The median duration of parenteral therapy was 4 days. A follow-up oral agent was administered to 96% of patients. Response rates are summarized below.

Ertapenem and Ceftriaxone in Complicated Urinary Tract Infections:

Assessment	Cure Rates	
	Ertapenem 1 g daily	Ceftriaxone 1 g daily
Overall bacteriologic eradication	89.4%	91.1%
Modified intent-to-treat bacteriologic eradication	90.1%	89%
Bacteriologic eradication - pyelonephritis patients	91.3%	93.4%
Bacteriologic eradication - other patients*	87.6%	89%
E. coli bacteremia eradication	92.1%	92.3%

* included catheter-related infections or lower tract infections with urologic abnormalities

Acute Pelvic Infections

Ertapenem has activity comparable to piperacillin/tazobactam in the treatment of acute pelvic infections in a study enrolling 412 patients. Patients received ertapenem 1 g intravenously once daily or piperacillin/tazobactam 3.375 g intravenously every 6 hours for 3 to 10 days. Clinical success among clinically evaluable patients was achieved in 93.9% (153/163) of ertapenem-treated patients and 91.5% (140/153) of piperacillin/tazobactam-treated patients at 2 to 4 weeks posttherapy.¹

FDA Approved Indications:	Ertapenem	Imipenem	Cefotetan	Piperacillin/tazobactam
Intra-abdominal Infection <i>Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus sp, Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides uniformis</i>	+	+ <i>S. aureus, S. Epidermidis, Citrobacter sp, Clostridium sp., E. faecalis, Enterobacter sp, Klebsiella sp, P. aeruginosa, Peptococcus sp, Proteus sp., Bifidobacterium sp., B. fragilis, Fusobacterium sp</i>	+ Include: <i>Klebsiella sp, Streptococcus sp, Bacteroides sp, Clostridium sp</i> Exclude: <i>Enterococci, B.distasonis, B ovatus, B. thetaiotaomicron, Bacteroides uniformis</i>	
Skin and Skin Structure Infections <i>Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Peptostreptococcus sp</i>	+ (<i>S. aureus</i> methicillin susceptible only)	+ <i>E. faecalis, S.epidermidis, Acinetobacter sp, Citrobacter sp, Enterobacter sp, Klebsiella sp, P.vulgaris, P. aeruginosa, peptococcus sp, Bacteroides sp, Morganella morgani, Serratia sp.</i>	+ <i>S. epidermidis, Streptococcus sp (exclude enterococci), K. pneumoniae</i>	+ piperacillin-resistant, B-lactamase producing strains of <i>S aureus</i>
Community Acquired Pneumonia <i>Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis</i>	+ (<i>S. pneumoniae</i> penicillin susceptible only, <i>H. influenza</i> beta-lactamase negative only)		-	+ piperacillin-resistant, B-lactamase producing strains of <i>H. influenza</i>
Nosocomial pneumonia <i>Staphylococcus aureus</i>			-	+ piperacillin-resistant, B-lactamase producing strains
Urinary Tract Infection <i>Escherichia coli, bacteremia, Klebsiella pneumoniae</i>	+ (complicated)	+ <i>E.faecalis, S. aureus(penicillinase-producing strains), Enterobacter sp, Klebsiella sp, P. aeruginosa</i>	+ <i>Klebsiella sp, Proteus mirabilis, Proteus sp</i>	
Gynecologic infections <i>Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus sp, Prevotella bivia</i>	+	+ <i>E. faecalis, S. aureus(penicillinase-producing strains), S epidermidis, Gardnerella vaginalis, Proteus sp, Bacteroides sp</i> - (<i>Porphyromonas asaccharolytica, Prevotella bivia</i>)	+ <i>S. aureus, S epidermidis, Streptococcus pyogenes, Streptococcus sp(excluding enterococci), P mirabilis, N gonorrhoeae, Peptococcus, Bacteroides sp</i> Exclude: <i>B.distasonis, B ovatus, B thetaiotaomicron</i>	+ piperacillin-resistant, B-lactamase producing strains of <i>E. coli</i> (postpartum endometritis or PID only)
Lower Respiratory tract infections <i>Staphylococcus aureus, Acinetobacter sp, Enterobacter sp, Escherichia coli, Haemophilus influenza, Klebsiella sp, Serratia marcescens</i>	-	+ (<i>S. aureus</i> penicillinase-producing strains)	+ <i>S. pneumoniae, Klebsiella pneumoniae, P. mirabilis</i> Exclude: <i>Acinetobacter sp, Enterobacter sp, S. marcescens</i>	
Endocarditis <i>Staphylococcus aureus</i>	-	+ (<i>S aureus</i> penicillinase-producing strains)	-	
Bone and Joint infections <i>Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, Enterobacter sp, Pseudomonas aeruginosa</i>	-	+ (<i>S. aureus</i> penicillinase-producing strains)	+ <i>S. aureus</i> only	
Bacterial Septicemia <i>Enterococcus faecalis, Staphylococcus aureus, Enterobacter sp, Escherichia coli, Klebsiella sp, Pseudomonas aeruginosa, Bacteroides sp</i>	-	+ (<i>S. aureus</i> penicillinase-producing strains)	-	
Polymicrobial infections <i>S. pneumonia, S. pyogenes, or nonpenicillinase-producing S. aureus (as one of the causative agents)</i>	-	+	-	

Appendicitis(complicated)/peritonitis Escherichia coli, Bacteroides sp (fragilis, ovatus, vulgatus, thetaiotaomicron)	-		-	+ piperacillin-resistant, B-lactamase producing strains
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	Ertapenem	Imipenem	Zosyn	Cefotan
T_{1/2} (hours)	4 (secondary to protein binding)	1	0.7-1.2	3-4.6
Bioavailability Intramuscular	90%		71%	
Vd	8.2	9.8-16	10-16	8-14
Protein Binding	95%	20%	30%	88%
Clearance (L/hr)	1.8	12	8	1.2-1.9
Fraction excreted unchanged in urine	38%	70%	80%	51-81%
Fraction excreted in feces	10%			
Dose & Route	1 gm IV	1 gm	3.375 gm q6h	1gm/2 gm
Peak Single Dose(mcg/ml)	155 (7.8 free)	41-83	242/24.2 _{SS}	158/223
Trough Single Dose (mcg/ml)	1 (0.05 free)	< 1	1/0.5 _{SS}	9/20
Time to trough (hrs)	24	4-6	6	12
AUC			242 ₀₋₆	

MIC Break Points NCCLS Standards				
	Ertapenem	Imipenem	Zosyn	Cefotan
Enterobacteriaceae	S <= 2 I 4 R >= 8	S <=4 I 8 R >=16	S <= 16/4 I 64/4 R >=128/4	S <=16 I 32 R >=64
Haemophilus spp	S <=0.05	S <=4	S <=1/4 R >=2/4	
Staphylococcus spp	S <= 2 I 4 R >= 8		S <=8/4 >=16/4	S <=16 I 32 R >=64
Streptococcus pneumoniae	S <=1	S <=0.12 I 0.25-5 R >=1		
Streptococcus spp.	S <=1			
Anaerobes	S <= 4 I 8 R >= 16	S <=4 I 8 R >=16	S <=16 R >=32	S <=16 I 32 R >= 64
Pseudomonas aeruginosa		S<=4 I 8 R >=16	S<=64/4 R >=128/4	
Non-Enterobacteriaceae		S<=4 I 8 R >=16	S <=16/4 R >=128/4	

Dosage Recommendations per Package Insert				
	Ertapenem	Imipenem	Zosyn	Cefotan
Intra-abdominal Infections	1gm QD 5-14 days	0.25-1gm q6-8h	3.375gm q6h 7-10 days	1g- 2gm q12h 5-10 days
Skin and skin structure infections	1gm QD 7-14 days	0.25-1gm q6-8h	3.375gm q6h 7-10 days	1g -2gm q12-24h 5-10 days
Community Acquired Pneumonia	1gm QD 10-14 days	0.25-1gm q6-8h	3.375gm q6h 7-10 days	-
Nosocomial pneumonia	-	-	3.375gm q4h (+ AG) 7-14 days	-
UTI	1gm QD 10-14 days	0.25-0.5 gm q6h	3.375gm q6h 7-10 days	0.5-2gm q12-24h 5-10 days
Gynecologic Infections	1gm QD 3-10 days	0.25-1gm q6-8h	3.375gm q6h 7-10 days	1-2gm q12h 5-10 days
Lower Respiratory Tract Infections	-	0.25-1gm q6-8h	3.375gm q6h 7-10 days	1- 2gm q12h 5-10 days
Endocarditis	-	0.25-1gm q6-8h	3.375gm q6h 7-10 days	-
Bone and Joint infections	-	0.25-1gm q6-8h	3.375gm q6h 7-10 days	1- 2gm q12h 5-10 days
Bacterial Septicemia	-	0.25-1gm q6-8h	3.375gm q6h 7-10 days	-
Polymicrobial infections	-	0.25-1gm q6-8h	3.375gm q6h 7-10 days	-
Appendicitis/peritonitis	-	-	3.375gm q6h 7-10 days	-

Reference:

1. Hoellman DB. In Vitro Antianaerobic Activity of Ertapenem Compared to Seven Other Compounds. *Antimicrob. Agents Chemother.* 2002;46:220-24
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3. Pankuch GA. Antipneumococcal Activity of Ertapenem Compared to Those of Other Agents. *Antimicrob. Agents Chemother.* 2002;46:42-46.
4. Livermore DM. Activity of Ertapenem versus Enterobacteriaceae with Potent B-Lactamases. *Antimicrob. Agents Chemother.* 2001;45:2831-37

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