National PBM Drug Monograph
Ertapenem sodium (Invanz™)
June 2002

Introduction

For decades we have been engaged in a continuing battle of bugs (pathogenic microorganisms) vs. drugs (antibiotics). Ertapenem is the third carbapenem to arrive on the antimicrobial front lines; the first being imipenem (Primaxin™, in combination with cilastatin) and the second being meropenem (Merem™). Invanz™ was approved by the FDA in November, 2001. It is the purpose of the monograph to succinctly review the utility and safety of ertapenem in reasonable use within the Department of Veterans Affairs HealthCare System.

Clinical Pharmacology

Ertapenem sodium is a synthetic, parenteral, 1-β methyl carbapenem antibiotic, formerly known as MK-0826. It is provided as a lyophilized powder for both intravenous and intramuscular use. It is soluble in water and 0.9% sodium chloride (NS), but nearly insoluble in ethanol. It is likewise soluble in 1% lidocaine as an intramuscular (IM) injection.
Each gram of ertapenem provides 137mg (approximately 6 mEq) of sodium.[1]

Antimicrobial activity. Ertapenem has antimicrobial activity against a broad range of microorganisms, including most anaerobes (notable exception of Lactobacillus)[2-4], streptococcal spp.[5-6], *Streptococcus pneumoniae*[5,7] *Staphylococcus* (except methicillin-resistant strains)[5-6], many enteric gram-negative bacilli (except *Pseudomonas*)[5,8-10]. It is highly resistant to degradation by a wide variety of beta-lactamases, including the extended spectrum beta-lactamases. It is, however, quite susceptible to carbapenemases (the metallo-beta-lactamases).[8,10]

Pharmacokinetics[1]

Preliminarily, there appears to be no substantial difference in the adult pharmacokinetic parameters that can be directly attributed to differences in gender or age, other than the inherent decrease in renal function with age.
Absorption. The bioavailability of an IM dose (reconstituted with 1% lidocaine) is approximately 90%. The peak serum concentrations occur approximately 2.3 hours after an IM injection of 1g ertapenem.
Distribution. Ertapenem appears to have saturable protein binding, ranging from 85-95% at serum concentrations between 300mcg/ml and less than 100mcg/ml, respectively, resulting in nonlinear pharmacokinetics. Steady state volume of distribution is approximately 8.2 liters
Metabolism. Ertapenem appears not to undergo hepatic metabolism based on *in vitro* studies. However, hydrolysis does occur of the beta-lactam ring in human studies, leading to its major metabolite.
Elimination. Ertapenem is principally eliminated via the kidneys, accounting for 80% of an administered dose; 38% being unchanged drug, the rest being the hydrolytic metabolite. Approximately 10% of the dose can be recovered in feces. Accumulation does not appear to occur after multiple doses. In 5 patients, 4-hour hemodialysis appeared to remove approximately 30% of a 1g dose administered immediately beforehand.

FDA Approved Indications[1]

- Complicated Intra-abdominal Infections due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron* or *Bacteroides uniformis*.
- Complicated Skin and Skin Structure Infections due *Staphylococcus aureus* (methicillin-sensitive strains only), *Streptococcus pyogenes, Escherichia coli, Peptostreptococcus* species.
- Community Acquired Pneumonia due *Streptococcus pneumoniae* (penicillin susceptible strains only) including those with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative strains only), or *Moraxella catarrhalis*.
- Complicated Urinary Tract Infections, including pyelonephritis due to *Escherichia coli*, including those with concurrent bacteremia, or *Klebsiella pneumoniae*.

- Acute pelvic Infections, including postpartum endomyometritis, septic abortion and post surgical gynecologic infections due to *Streptococcus agalactiae*, *Escherichia coli*, *Bacteroides fragilis*, *Porphyromonas asaccharolytica*, *Peptostreptococcus* species, or *Prevotella bivia*

Current VA National Formulary Status

Ertapenem is not currently on VA National Formulary; as is true of meropenem.

Dosage and Administration[1]

Dose. The recommended dosing of ertapenem, unlike most beta-lactams, is quite straightforward; it is the duration that varies. For all indications the recommended dose from the manufacturer is 1g once daily for creatinine clearances of >30 ml/min/1.73m^2. For those patients with creatinine clearances ≤ 30 ml/min/1.73m^2 , half of the dose (500 mg daily) is recommended. If the dose of ertapenem is given within 6 hours prior to hemodialysis, the manufacturer recommends a supplementary dose of 150 mg. A summary of ertapenem dosing is listed below:

Table 1. Ertapenem dosing guidelines for adults with normal renal function and body weight

Infection	Daily Dose	Recommended Total Duration
Complicated Intra-abdominal Infections	1g	5-14 days
Complicated Skin and Skin Structure Infections	1g	7-14 days
Community Acquired Pneumonia	1g	10-14 days
Complicated Urinary Tract Infections	1g	10-14 days
Acute pelvic Infections (as listed above)	1g	3-10 days

Preparation/Administration. Each dose for IV administration reconstituted with 10 ml of sterile water for injection or NS. It should be further diluted with 50 ml NS (NOT Dextrose) and infused over 30 minutes. Doses for IM injection should be reconstituted with 3.2 ml of 1% lidocaine and injected (into gluteus or lateral thigh) within 1 hour of preparation.

Similar to other carbapenems, the reconstituted solutions of ertapenem are relatively unstable. The manufacturer states that the IM reconstituted solutions (with 1% lidocaine) should be used within 1 hour of preparation. Solutions for IV infusion may be reconstituted with sterile water for injection with or without 0.9% benzyl alcohol, or 0.9% sodium chloride for injection, with stability at room temperature and under refrigeration of 2 hours and 6 hours, respectively. Diluted solutions should be infused within 6 hours of preparation unless refrigerated. If refrigerated immediately upon preparation and dilution, ertapenem is stable for 24 hours if infused within 4 hours of removal from refrigeration. Solutions of ertapenem should not be frozen.

Ertapenem demonstrates Y-site or in-line compatibility with heparin flush or solutions containing 5% dextrose, potassium chloride.[11]

Adverse Effects[1]

Reporting of incidences for adverse effects associated with a relatively new antibiotic should be construed as preliminary, if our experience with other drugs in the past years is instructive. That said, it would appear that trends in adverse drug event reporting for ertapenem appear comparable to other β-lactams (ceftriaxone and piperacillin/tazobactam being the comparators).

Table 2. Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-day Follow-up in ≥ 2% of Patients Treated with INVANZ in Clinical Studies[1]

Adverse Events	INVANZ 1g daily (N=802)	Piperacillin/ Tazobactam* 3.375 g q6h (N=774)	INVANZ 1g daily (N=1152)	Ceftriaxone 1 or 2 g daily (N=942)
Local:				
Infused vein complication	7.1	7.9	5.4	6.7
Systemic:				
Death	2.5	1.6	1.3	1.6
Edema/swelling	3.4	2.5	2.9	3.3
Fever	5.0	6.6	2.3	3.4

Abdominal pain	3.6	4.8	4.3	3.9
Hypotension	2.0	1.4	1.0	1.2
Constipation	4.0	5.4	3.3	3.1
Diarrhea	10.3	12.1	9.2	9.8
Nausea	8.5	8.7	6.4	7.4
Vomiting	3.7	5.3	4.0	4.0
Altered mental status	5.1	3.4	3.3	2.5
Dizziness	2.1	3.0	1.5	2.1
Headache	5.6	5.4	6.8	6.9
Insomnia	3.2	5.2	3.0	4.1
Dyspnea	2.6	1.8	1.0	2.4
Pruritis	2.0	2.6	1.0	1.9
Rash	2.5	3.1	2.3	1.5
Vaginitis	1.4	1.0	3.3	3.7

Table 3. Incidence (%) of Specific Laboratory Adverse Experiences Reported During Study Therapy Plus 14-day Follow-up in ≥ 2% of Patients Treated with INVANZ in Clinical Studies[1]

Adverse laboratory experiences	INVANZ 1g daily (N=766)	Piperacillin/ Tazobactam* 3.375 g q6h (N=755)	INVANZ 1g daily (N=1122)	Ceftriaxone 1 or 2 g daily (N=920)
ALT increased	8.8	7.3	8.3	6.9
AST increased	8.4	8.3	7.1	6.5
Serum alkaline phosphatase increased	6.6	7.2	4.3	2.8
Hematocrit decreased	3.0	2.9	3.4	2.4
Hemoglobin decreased	4.9	4.7	4.5	3.5
Platelet count increased	6.5	6.3	4.3	3.5
Urine RBCs increased	2.5	2.9	1.1	1.0
Urine WBCs increased	2.5	3.2	1.6	1.1

Precautions and Contraindications[1]

As with all beta-lactam antibiotics, allergic reactions may be serious and even fatal. Use of ertapenem should be approached with caution in patients known to have hypersensitivity to beta-lactam antibiotics.
At this time ertapenem is considered a Category B entity for pregnancy.

Drug Interactions[1]

- Probenecid. While the co-administration of probenecid with ertapenem increases the latter's AUC by 25% and decreases its renal clearance by 30%, the net effect on ertapenem's half-life is minimal; an increase to 4.8 hours from 4.0 hours. The manufacturer does not recommend the addition of probenecid for the purpose of increasing ertapenem's half-life.
- No other specific drug-drug interaction studies have been published involving ertapenem.
- Cytochrome P-450. Study of human liver microsomes demonstrates that ertapenem does not inhibit the following isoforms: 1A2, 2C9, 2C19, 2D6, 2E1, 3A4. A drug-drug interaction involving this system is believed to be very unlikely.
- P-glycoprotein-mediated transport. Ertapenem appears to be neither a substrate nor an inhibitor of this metabolic pathway.

Clinical Trials [12-13]

Published human clinical trials involving the use of ertapenem are limited in both scope and number. To date only two human studies have been published: in community acquired pneumonia and in soft tissue infections. Others are either in press or in review.

Citation	Ortiz-Ruiz G, Caballero-Lopez J, Friedland IR, et al. A Study Evaluating the Efficacy, Safety, and Tolerability of Ertapenem versus Ceftriaxone for the Treatment of Community-Acquired Pneumonia in Adults. Clin Inf Dis 2002 15 April;34:1076-1083.
Study Goals	To compare ertapenem and ceftriaxone in the treatment of community-acquired pneumonia (CAP) requiring parenteral therapy.
Methods	**Design**: international, randomized, double-blind multi-center trial conducted from July 1998 through December 1999 All patients received blinded 1g doses of either ceftriaxone or ertapenem daily. For patients with creatinine clearances < 30 ml/min 500 mg ertapenem daily was allowed. After 3 days of this therapy and sufficient clinical response, patients were allowed to switch to oral amoxicillin 875mg/clavulanate 125mg twice daily to complete a 10-14 day total course. Patients were also stratified into 4 groups utilizing two parameters: age >65 or ≤ 65, and by a pneumonia severity index: 1-3 (mild to moderate) and 4-5 (severe). Antimicrobial susceptibility testing was performed on all baseline pathogens isolated from sputum or blood utilizing a standardized methods (disk diffusion, with oxacillin disk and E-strip for pneumococcal susceptibility to penicillin). Following completion of therapy, assessment of cure was made at 1-2 weeks, and assessment for relapse was made at 3-4 weeks. The study was designed to test non-inferiority.
Criteria	**Inclusionary**: adults ≥18 years of age, diagnosis of pneumonia utilizing commonly accepted constellation of signs and symptoms, with attempts at minimizing enrolling patients with high likelihood of atypical pathogens (e.g. *Mycoplasma*, *Legionella*, etc). **Exclusionary**: presence of empyema, underlying structural lung abnormalities, lung malignancy, nosocomial pneumonia, mechanical ventilation, active tuberculosis, rapidly progressive or terminal illness, immunocompromising disease or receipt of immunosuppressive therapy, successful antibiotic treatment for ≥24 hours during the 72-hour pretreatment period. Presence of any of the following, unless thought to be directly due to the acute infection: elevated liver enzymes, neutropenia (ANC<1000), thrombocytopenia (<75,000), anticoagulated to >1.5 x upper limit of normal
Results	502 patients enrolled, with 383 (76%) of these clinically evaluable. Both groups had clinical responses of over 90%.
Conclusions	Ertapenem is safe and equally as effective as ceftriaxone, in 1g daily doses, in the treatment of CAP, including those with penicillin-intermediately sensitive pneumococci.
Critique	The use of ertapenem to treat CAP complicated by compromised pathophysiology should be discouraged at this time since these were excluded from study. No atypical coverage was provided since this study preceded the inclusion of such therapy in the guidelines. However, the high success rates would argue that not all hospitalized CAP requires coverage against such organisms, despite CAP guidelines.

Citation	Graham DR, Lucasti C, Malafaia O, et al, Ertapenem Once Daily Versus Piperacillin-Tazobactam 4 Times per Day for Treatment of Complicated Skin and Skin-Structure Infections in Adults: Results of a Prospective, Randomized, Double-Blind Multicenter Study. Clin Infect Dis 2002 1 June;34:1460-1468.
Study Goals	To compare ertapenem and piperacillin/tazobactam in the treatment of complicated soft tissue infections in adults ≥18 years of age.
Methods	**Design**: international, randomized, double-blind multi-center trial conducted from April 1998 through November 1999.

	All patients were randomly assigned to receive 7-14 days of piperacillin/tazobactam 3.37g every 6 hours or 1g ertapenem daily with subsequent saline placebo infusions every 6 hours. Therapy was begun in the hospital but could be completed in the home. Patients were also stratified into 2 groups: 1)those with underlying diabetes mellitis, decubitus ulcers, or other neuropathic conditions and 2) all other types complicated skin conditions. Antimicrobial susceptibility testing was performed on all baseline pathogens isolated from sputum or blood utilizing standardized methods . Following completion of therapy, assessment of cure was made at 10-21days (TOC). The study was designed to test equivalence.
Criteria	**Inclusionary**: Adults ≥18 years of age with a diagnosis of complicated skin or skin-structure infection (CSSSI) requiring parenteral therapy. Patients had to have signs and symptoms of acute infection listed in the protocol such as purulence, fever, leukocytosis, erythema or fluctuance. Surgical drainage or debridement of the area had to have been completed with 48 hours of starting antibiotics. **Exclusionary**: pregnancy, lactating women, serious allergy to or intolerance of any β-lactam, rapidly progressive or terminal illness, receipt of long-term immunosuppressants, AIDS, infected burns, necrotizing fasciitis, osteomyelitis, septic arthritis, gangrene, need for amputation, DVT, additional concurrent systemic antibiotics, concurrent infection which could interfere with assessments, dialysis, successful antibiotic treatment for ≥24 hours during the 72-hour pretreatment period. Presence of any of the following: elevated liver enzymes, thrombocytopenia (<75,000), anticoagulated to >1.5 x upper limit of normal.
Results	540 patients were randomized with only 359 (66%) clinically evaluable. Of these 85% were microbiologically evaluable. S. aureus was the most frequently isolated pathogen but approximately 40% of cases with pathogens isolated were polymicrobial. Bacterial eradication and clinical cure were similar in both groups, exceeding 80%. Patients with diabetes or similar debilitating disorder had a lower cure rate. Ertapenem (n=185) — Piperacillin/tazobactam (n=714) Stratum I, Diabetes Group: 28/42, 66.7(52.2-81.1) — 27/36, 75.0(60.7-89.3) Stratum II: 124/143, 86.7(81.1-92.3) — 120/138, 87.0(81.3-92.6)
Conclusions	In the treatment of CSSSI, ertapenem is equivalent to piperacillin/tazobactam in the above stated doses. In addition ertapenem is generally well tolerated with a safety profile comparable to piperacillin/tazobactam.
Critique	This study does not provide evidence that either ertapenem or piperacillin/tazobactam is the therapy of choice for CSSSI infections, just equally effective. However, given the polymicrobial nature of such infections, ertapenem remains an intriguing alternative. Patients with osteomyelitis and other deep infections were excluded from the study, which should discourage the extrapolation of therapy to such infections without more study.

Acquisition Costs*

Table 4.

Drug	Dose	Cost/Day/Patient ($)	Cost/14-day Course/Patient ($)
ertapenem	1g daily	28.44	398.16
ampicillin/sulbactam	3g every 6 hours	34.44	482.16

piperacillin/tazobactam	3.375g every 6 hours	35.00	490.00
ticarcillin/clavulanate	3.1g every 6 hours	29.48	412.72
cefotetan	2g every 12 hours	24.90	348.60
ceftriaxone	1g every 24 hours	17.75	248.50
ceftriaxone	2g every 24 hours	36.04	504.56
imipenem/cilastatin	500 mg every 6 hours	58.68	821.52
meropenem	1g every 8 hours	63.99	895.86

*includes cost of 50-100 ml IVPB

Cost Analysis

Frequently, acquisition costs associated with parenteral therapies are the only costs considered when comparing different drugs. It could be argued that other costs (e.g. nursing labor, pharmacy preparation time, IV administration supplies) should be considered in such comparisons as well. Vander Linde, et al[14] calculated the monetary value of such costs and while dated, provide an estimate of the impact of dosing frequency on the cost antibiotic administration. For once daily administration these costs were reported as $6/day and for each additional dose given, the incremental cost was approximately $2/dose. Applying such costs to the chart above yields the following total cost estimates.

Table 5.

Drug	Dose	ApproximateCost/ Day/Patient ($)#	Approximate Cost/14-day Course/Patient ($)#
ertapenem	1g daily	34	476
ampicillin/sulbactam	3g every 6 hours	46	644
piperacillin/tazobactam	3.375g every 6 hours	47	658
ticarcillin/clavulanate	3.1g every 6 hours	41	574
cefotetan	2g every 12 hours	33	462
ceftriaxone	1g every 24 hours	24	336
ceftriaxone	2g every 24 hours	42	588
imipenem/cilastatin	500 mg every 6 hours	71	994
meropenem	1g every 8 hours	74	1036

#includes cost of 50-100ml IVPB + estimate of per/dose non-drug costs

Conclusions

Ertapenem is a recent addition to the parenteral antibiotic armamentarium that offers the convenience of once daily dosing. Its relative stability against many of the beta-lactamases that inactivate our antibiotic mainstays provides another avenue of treatment in the beta-lactam category. But, it is this very characteristic that should cause the most concern if ertapenem is used routinely. Medical centers could find an increasing problem of carbapenemase-producing Gram-negative bacteria, effectively eliminating one of the last choices in multi-drug resistant pathogens; the other two available carbapenems. Current microbiological susceptibility testing panels (e.g. Microscan™) do not specifically test for ertapenem at this time, and are not anticipated to do so any time soon. There remains the potential for selected susceptibility testing using the E-Strip or Kirby-Bauer methods, albeit somewhat more labor intensive than the automated systems. In general, we must rely on class representation, such as penicillin for streptococci and oxacillin for staphylococci to guide any routine use of ertapenem.

The relative lack of activity against *Pseudomonas aeruginosa*, enterococci, and MRSA continues to limit our treatment choices for our most problematic bacteria; ertapenem offers nothing new in this regard. In addition, a lack of efficacy data in the treatment of osteomyelitis, should instill a sense of caution when considering the positive attributes of Invanz™ in managing this common infection, especially if using the standard dosing guideline.

Those institutions availing themselves of the cost-containment advantages of hospital-based outpatient infusion therapy and/or those who are trying to minimize infusion-related nursing expenses, will no doubt be attracted to the once-daily regimens offered by ertapenem. For home infusion, on-site preparation will be necessary.

Judicious and informed use of ertapenem (Invanz™) within the VA HealthCare System could offer limited cost savings.

Recommendations

Add to National Formulary, restricted to Infectious Diseases Section or prudent local criteria.
Ertapenem does not appear to be cost-effective for the treatment of most community-acquired pneumonias.
For patients receiving ertapenem on hemodialysis, simplify dosing by scheduling the daily dose for after dialysis.

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