PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] ERTAPENEM FOR INJECTION

Ertapenem for Injection

Powder for Solution, 1 g/vial ertapenem (as ertapenem monosodium), for Intravenous or Intramuscular Use

Antibiotic

Auro Pharma Inc.
3700 Steeles Avenue West, Suite # 402
Woodbridge, Ontario, L4L 8K8,
Canada.

Date of Initial Authorization:
September 11, 2019

Date of Revision:
January 17, 2023

Submission Control Number: 266851

RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Skin	01/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Treatment

ERTAPENEM FOR INJECTION (ertapenem monosodium) is indicated for the treatment of patients with the following moderate to severe infections caused by susceptible strains of the designated microorganisms (see 4 DOSAGE AND ADMINISTRATION).

- **Complicated intra-abdominal infections** due to *Escherichia coli, Clostridium clostridioforme, Eubacteriumlentum, Peptostreptococcus species, Bacteroidesfragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides uniformis, or Bacteroides thetaiotaomicron.*

- **Complicated skin and skin structure infections** due to *Staphylococcus aureus* (methicillin- susceptible strain only), *Streptococcus pyogenes, Escherichia coli* and *Peptostreptococcus species*, as well as, diabetic foot infections due to *Staphylococcus aureus* (methicillin-susceptible strain only) and *Peptostreptococcus species*. Ertapenem has not been studied in diabetic foot infections with concomitant osteomyelitis or severe ischemia (see 14 CLINICAL TRIALS).

- **Community acquired pneumonia** due to *Streptococcus pneumoniae* (penicillin-susceptible strain only), *Haemophilus influenzae* (β-lactamase negative strain only), or *Moraxella catarrhalis*.

- **Complicated urinary tract infections including pyelonephritis** due to *Escherichia coli, Klebsiella pneumoniae* or *Proteusmirabilis.*

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

Prevention

ERTAPENEM FOR INJECTION is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERTAPENEM FOR INJECTION and other antibacterial drugs, ERTAPENEM FOR INJECTION should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should

be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to ertapenem. Initial therapy with ERTAPENEM FOR INJECTION may be instituted empirically for the treatment of bacterial infections, including mixed infections, while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

1.1 Pediatrics

Pediatrics (3 months - 17 years of age): Safety and effectiveness of ertapenem in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from comparator-controlled studies in pediatric patients 3 months to 17 years of age with the following infections (see 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics and 14 CLINICAL TRIALS, Pediatric Patients):

- Complicated Intra-Abdominal Infections
- Complicated Skin and Skin Structure Infections
- Community Acquired Pneumonia
- Complicated Urinary Tract Infections
- Acute Pelvic Infections

ERTAPENEM FOR INJECTION is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient cerebrospinal fluid (CSF) penetration.

Pediatrics (< 3 months of age): ERTAPENEM FOR INJECTION is not recommended in infants under 3 months of age as no data are available. Therefore, Health Canada has not authorized an indication for this population.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): In clinical studies, the efficacy and safety of ertapenem in the elderly (≥ 65 years) was comparable to that seen in younger patients (< 65 years).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

ERTAPENEM FOR INJECTION (ertapenem monosodium) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Due to the use of lidocaine HCl as a diluent, ERTAPENEM FOR INJECTION administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block (refer to the Product Monograph for lidocaine HCl).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) AND OTHER
  SERIOUS SKIN REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS, INCLUDING ERTAPENEM (see 7 WARNINGS AND PRECAUTIONS, Immune and 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions

- Seizures and other CNS (Central Nervous System) adverse experiences, have been reported during treatment with ertapenem. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Renal and 8 ADVERSE REACTIONS).

- Case reports in the literature have shown that co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or divalproex sodium results in a reduction in serum valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. In some cases of co-administration of ertapenem with valproic acid, breakthrough seizures have occurred. Increasing the dose of valproic acidor divalproex sodium may not be sufficient to overcome this interaction.

- The concomitant use of ertapenem and valproic acid/divalproex sodium is generally not recommended. Anti-bacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of ERTAPENEM FOR INJECTION is necessary, supplemental anti-convulsant therapy should be considered (see 9 DRUG INTERACTIONS).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of ERTAPENEM FOR INJECTION (ertapenem) in patients 13 years of age and older is 1 gram (g) given once a day. The recommended dose of ERTAPENEM FOR INJECTION in patients 3 months to 12 years of age is 15 mg/kg twice daily (not to exceed 1 g/day).

Table 1 presents treatment guidelines for ERTAPENEM FOR INJECTION.

Table 1: Daily Treatment Guidelines for Adult and Pediatric Patients with Normal Renal Function*

Infection†	Patients 13 years of age and older	Patients 3 months to 12 years of age	Recommended Duration of Total Antimicrobial Treatment
Complicated Intra-abdominal Infections	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	5 to 14 days
Complicated Skin and Skin Structure Infections	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	7 to 14 days
Diabetic foot infections	1 g daily (patients ≥ 18 years old only)	not applicable	5 to 28 days‡
Community Acquired Pneumonia	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	10 to 14 days‡
Complicated Urinary Tract Infections including pyelonephritis	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	10 to 14 days‡
Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post-surgical gynecologic infections	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	3 to 10 days

* Defined as creatinine clearance > 90 mL/min/1.73 m2.
† Due to the designated pathogens (see 1 INDICATIONS).
‡ Duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated.
§ Not to exceed 1 g/day.

Special Populations

Patients with Renal Insufficiency

ERTAPENEM FOR INJECTION may be used for the treatment of infections in adult patients with renal insufficiency. In patients whose creatinine clearance is> 30 mL/min/1.73 m^2 (International System of Units (SI) = > 0.5 mL/s/1.73 m^2), no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1.73 m^2 (SI = ≤ 0.5 mL/s/1.73 m^2)), and end-stage renal insufficiency on hemodialysis (creatinine clearance ≤ 10 mL/min/1.73 m^2 (SI = ≤ 0.17 mL/s/1.73 m^2)) should receive 500 mg daily. There are no data in pediatric patients with renal insufficiency. This recommended dosage reduction is based on pharmacokinetic modeling of data collected from a clinical safety and pharmacokinetic study in adult patients with varying degrees of renal insufficiency (including those with creatinine clearance < 30 mL/min/1.73 m^2 (SI = < 0.5 mL/s/1.73 m^2)) receiving a single 1 g IV dose of ertapenem (see 10 CLINICAL PHARMACOLOGY, Renal Insufficiency). The efficacy of the recommended adjusted dose (500 mg) for adult patients with advanced or end-stage renal insufficiency has not been established.

Patients on Hemodialysis

When adult patients on hemodialysis are given the recommended daily dose of 500 mg of ERTAPENEM FOR INJECTION within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session. If ERTAPENEM FOR INJECTION is given at least 6 hours prior to hemodialysis, no supplementary dose is recommended. There are no data in patients undergoing peritoneal dialysis or hemofiltration. There are no data in pediatric patients on hemodialysis.

When only the serum creatinine is available, the following formula** may be used to estimate creatinine clearance (mL/min). The serum creatinine should represent a steady state of renal function.

Males: $\frac{\text{(weight in kg) x (140 − age in years)}}{\text{(72) x serum creatinine (mg/100 mL)}}$

Females: (0.85) x (value calculated for males)

When using the International System of units (SI), the estimated creatinine clearance (mL/s) can be calculated as follows:

Males: $\frac{\text{(weight in kg) x (140 − age in years) x 1.4736}}{\text{(72) x serum creatinine (μ mol/L)}}$

Females: (0.85) x (value calculated for males)

Patients with Hepatic Impairment

** *Cockcroft and Gault equation: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976.

No dosage adjustment recommendation can be made in patients with impaired hepatic function (see 10 CLINICAL PHARMACOLOGY, Hepatic Insufficiency and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Age/Gender

No dosage adjustment is recommended based on age (**13 years of age and older**) or gender. Dosing adjustment is needed based on age **3 months to 12 years of age** (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions and 7.1.3 Pediatrics).

Prevention

Table 2 presents prophylaxis guidelines for ERTAPENEM FOR INJECTION.

Table 2: Prophylaxis Guidelines for Adults

Indication	Daily Dose (IV) Adults	Recommended Duration of Total Antimicrobial Treatment
Prophylaxis of surgical site infection following elective colorectal surgery*	1 g	Single intravenous dose given 1 hour prior to the surgical incision

* Limited data are available in patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1.73 m^2 [SI = ≤ 0.5 mL/s/1.73 m^2]) (see 8 ADVERSE REACTIONS, Prevention, Patients with Renal Insufficiency).

4.3 Reconstitution

Parenteral Products:

Patients 13 years of age and older

Preparation for Intravenous Administration:

DO NOT MIX OR CO-INFUSE ERTAPENEM FOR INJECTION WITH OTHER MEDICATIONS.

DO NOT USE DILUENTS CONTAINING DEXTROSE (α D-GLUCOSE).

ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

- Reconstitute the contents of a 1 g vial of ERTAPENEM FOR INJECTION with 10 mL Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection to yield a reconstituted solution of approximately 100 mg/mL. Shake well to dissolve.
- To withdraw a 1 gram dose, immediately withdraw 9.8 mL of the reconstituted vial and transfer to 50 mL of 0.9% Sodium Chloride Injection.
- The reconstituted IV solution should be used within 6 hours after preparation.

Preparation for Intramuscular Administration:

ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

- Reconstitute the contents of a 1 g vial of ERTAPENEM FOR INJECTION with 3.2 mL of 1.0% lidocaine HCl injection* ** (**without epinephrine**) to yield a reconstituted solution of approximately 280 mg/mL. Shake vial thoroughly to form solution. To withdraw a 1 gram dose, the contents of the reconstituted vial should be withdrawn as completely as possible.
- Immediately withdraw the contents of the vial and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
- The reconstituted IM solution should be used within 1 hour after preparation.
  Note: The reconstituted solution should not be administered intravenously.

Pediatric patients 3 months to 12 years of age

Preparation for Intravenous Administration:

DO NOT MIX OR CO-INFUSE ERTAPENEM FOR INJECTION WITH OTHER MEDICATIONS.

DO NOT USE DILUENTS CONTAINING DEXTROSE (α D-GLUCOSE).

ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

- Reconstitute the contents of a 1 g vial of ERTAPENEM FOR INJECTION with 10 mL Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection to yield a reconstituted solution of approximately 100 mg/mL. Shake well to dissolve.
- Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 500 mg per dose) and dilute in 0.9% Sodium Chloride Injection to a final concentration of 20 mg/mL or less (not to exceed 1g/day).
- The reconstituted IV solution should be used within 6 hours after preparation. Discard unused portion of the vial.

Preparation for Intramuscular Administration:
ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

- Reconstitute the contents of a 1 g vial of ERTAPENEM FOR INJECTION with 3.2 mL of 1.0% lidocaine HCl injection*** (**without epinephrine**) to yield a reconstituted solution of approximately 280 mg/mL. Shake vial thoroughly to form solution.
- Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 500 mg per dose and 1g/day) and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
- The reconstituted IM solution should be used within 1 hour after preparation.

* ** Refer to the prescribing information for lidocaine HCl

Note: The reconstituted solution should not be administered intravenously. Discard unused portion of the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion. Solutions of ERTAPENEM FOR INJECTION range from colorless to pale yellow. Variations of color within this range do not affect the potency of the product.

The vials are for single use only. Unused portions should be discarded.

4.4 Administration

ERTAPENEM FOR INJECTION may be administered by intravenous infusion or intramuscular injection. When administered intravenously, ERTAPENEM FOR INJECTION should be infused over a period of 30 minutes.

Intramuscular administration of ERTAPENEM FOR INJECTION may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate.

4.5 Missed Dose

The injection schedule will be set by the physician, who will monitor the response and condition to determine what treatment is needed.

5 OVERDOSAGE

No specific information is available on the treatment of over dosage with ERTAPENEM FOR INJECTION (ertapenem monosodium). Intentional overdosing of ERTAPENEM FOR INJECTION is unlikely. Intravenous administration of ERTAPENEM FOR INJECTION at a 3 g daily dose for 8 days to healthy adult volunteers did not result in significant toxicity. In clinical studies in adults, inadvertent administration of up to 3 g in a day did not result in clinically important adverse experiences. In pediatric clinical studies, a single IV dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity.

In the event of an overdose, ERTAPENEM FOR INJECTION should be discontinued and general supportive treatment given until renal elimination takes place.

ERTAPENEM FOR INJECTION can be removed by hemodialysis; however, no information is available on the use of hemodialysis to treat over dosage.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous Intramuscular	Powder for Solution 1 g ertapenem/vial (as ertapenem monosodium)	Sodium hydrogen carbonate and sodium hydroxide.

ERTAPENEM FOR INJECTION (ertapenem) is supplied as a sterile lyophilized powder in single dose glass vials. Each vial contains 1.046 grams Ertapenem Monosodium equivalent to 1 gram Ertapenem.

Each vial of ERTAPENEM FOR INJECTION contains the following non- medicinal ingredients: sodium hydrogen carbonate and sodium hydroxide. The sodium content is 130.15 mg - 178.1 mg.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

As with other antibiotics, prolonged use of ERTAPENEM FOR INJECTION may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If super infection occurs during therapy, appropriate measures should be taken.

Caution should be taken when administering ERTAPENEM FOR INJECTION intramuscularly to avoid inadvertent injection into a blood vessel (see 4 DOSAGE AND ADMINISTRATION, 4.4 Administration)

Lidocaine HCl is the diluent for intramuscular administration of ERTAPENEM FOR INJECTION Refer to the Product Monograph for lidocaine HCl for additional precautions.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including ertapenem. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic mega colon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. Clostridium difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see 8 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. Of the total number of patients in clinical studies, 37 patients receiving ertapenem 1 g daily and 36 patients receiving comparator drugs were considered to have Child-Pugh Class A, B or C liver impairment. The incidence of adverse experiences in patients with hepatic impairment was similar between the ertapenem group and the comparator groups.

Immune

Hypersensitivity

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) AND OTHER SERIOUS SKIN REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBIOTICS, INCLUDING ERTAPENEM. HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. CROSS-REACTIVITIES BETWEEN BETA- LACTAM ANTIBIOTICS HAVE BEEN CLEARLY DOCUMENTED. BEFORE INITIATING THERAPY WITH ERTAPENEM FOR INJECTION (ertapenem) CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO ERTAPENEM FOR INJECTION OCCURS, DISCONTINUE THE DRUG IMMEDIATELY. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED** (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Monitoring and Laboratory Tests

While ertapenem possesses toxicity similar to the beta-lactam group of antibiotics, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Neurologic
During clinical investigations in adult patients treated with ertapenem (1 g once a day), seizures, irrespective of drug relationship, occurred in 0.5% of patients during study therapy plus 14-day follow-up period (see 8 ADVERSE REACTIONS). These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Close adherence to the recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of ERTAPENEM FOR INJECTION re-examined to determine whether it should be decreased or the antibiotic discontinued (see 8 ADVERSE REACTIONS).

Renal
Dosage adjustment of ERTAPENEM FOR INJECTION is recommended in patients with reduced renal function (see 4 DOSAGE AND ADMINISTRATION). A supplementary dose may be recommended in patients following hemodialysis (see 4 DOSAGE AND ADMINISTRATION, Patients on Hemodialysis).

Reproductive Health: Female and Male Potential

- **Fertility**
  Insufficient clinical data are available to inform on drug-associated risks to fertility. Fertility studies were performed in rats. In the female fertility study in rats, there were no treatment-related effects on mating, fertility, or fecundity indices, or embryonic/fetal survival. In the male fertility study in rats, there were no treatment-related effects on mating index, fertility index, fecundity index, embryonic/fetal survival, sperm count and motility, and testicular/epididymal organ weights or histology (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- **Function**
  Insufficient data are available to inform on drug-associated risks to sexual desire, erection, orgasm or ejaculation.

- **Teratogenic Risk**
  Available data from a small number of post-marketing cases with ertapenem use in pregnancy are insufficient to inform any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes (see 7.1.1 Pregnant Women). Developmental toxicity studies were performed in rats and mice. There were no drug-related effects in rats at any dose level tested. In mice, the developmental toxicity study showed slight decreases in average fetal weight and an associated decrease in the number of ossified sacrocaudal vertebrae at 700 mg/kg/day. The no-effect level in mice for developmental toxicity was 350 mg/kg/day, which is approximately 1.5-fold the typical human dose based on body surface area (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology)

Sensitivity/Resistance

Development of Drug Resistant Bacteria

Prescribing ERTAPENEM FOR INJECTION in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Skin

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, ERTAPENEM FOR INJECTION should be discontinued and appropriate therapy and/or measures should be taken.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. ERTAPENEM FOR INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

7.1.2 Breast-feeding

Ertapenem is excreted in human milk. ERTAPENEM FOR INJECTION should be administered to nursing mothers only when the potential benefit outweighs the potential risk (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

7.1.3 Pediatrics

Pediatrics (3 months - 17 years of age): Safety and effectiveness of ertapenem in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from comparator-controlled studies in pediatric patients 3 months to 17 years of age with the following infections (see 1 INDICATIONS, 4 DOSAGE AND ADMINISTRATION and 14 CLINICAL TRIALS, Pediatric Patients):

- Complicated Intra-Abdominal Infections
- Complicated Skin and Skin Structure Infections
- Community Acquired Pneumonia
- Complicated Urinary Tract Infections
- Acute Pelvic Infections

ERTAPENEM FOR INJECTION is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient cerebrospinal fluid (CSF) penetration.

Pediatrics (< 3 months of age): ERTAPENEM FOR INJECTION is not recommended in infants under 3 months of age as no data are available. Therefore, Health Canada has not authorized

an indication for this population.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): In clinical studies, the efficacy and safety of ertapenem in the elderly (≥ 65 years) was comparable to that seen in younger patients (< 65 years).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adult Patients

The total number of patients treated with ertapenem in clinical studies was over 1900 of which over 1850 received a 1 g dose of ertapenem. Most adverse experiences reported in these clinical studies were described as mild to moderate in severity. Drug-related adverse experiences were reported in approximately 20% of patients treated with ertapenem. Ertapenem was discontinued due to adverse experiences thought to be drug-related in 1.3% of patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adult Patients

Table 4 shows the incidence of drug-related adverse experiences reported during parenteral therapy.

Table 4: Incidence (%) of Drug-Related Adverse Experiences* Reported During Parenteral Therapy in ≥ 1.0% of Adult Patients Treated with Ertapenem in Clinical Studies

Adverse Events	Ertapenem 1 g daily (N=1866)	Piperacillin/ Tazobactam 3.375 g q6h (N=775)	Ceftriaxone 1 or 2 g daily (N=912)

Gastrointestinal disorders:			
Diarrhea	4.3	6.6	3.7
Nausea	2.9	3.2	2.6
Vomiting	1.0	1.5	0.9
General disorders and administration site conditions:			
Infused vein complication	3.9	5.5	4.3
Nervous system disorders:			
Headache	2.1	1.0	2.2
Vascular disorders:			
Phlebitis/thrombophlebitis	1.3	1.3	1.4

* Determined by the investigator to be possibly, probably, or definitely drug-related.

In clinical studies, seizure was reported during parenteral therapy in 0.2% of patients treated with ertapenem, 0.3% of patients treated with piperacillin/tazobactam and 0% of patients treated with ceftriaxone.

Prevention (prophylaxis of surgical site infection following elective colorectal surgery)

In a clinical study for the prophylaxis of surgical site infections following elective colorectal surgery in which 476 adult patients received a 1 g dose of ertapenem and 476 adult patients received a 2 g dose of cefotetan prior to surgery, the following additional (i.e., in addition to Adverse Experiences listed in Table 4) drug-related adverse experience was reported with an incidence of ≥ 1.0% (common): wound infection (1.7% for patients treated with ertapenem and 2.1% for patients treated with cefotetan).

Patients with Renal Insufficiency

There are limited data in adults patients with renal insufficiency from the study of prophylaxis of surgical site infection following elective colorectal surgery. In a clinical study in which 476 treated patients received a 1 g dose of ertapenem 1 hour prior to surgery, the AE profile observed in five patients with creatinine clearance ≤ 30 mL/min/1.73 m2 is consistent with their underlying renal condition and/or having just undergone major elective colorectal surgery.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The total number of pediatric patients treated with ertapenem in clinical studies was 384. The overall safety profile is comparable to that in adult patients. In clinical trials, the most common drug-related clinical adverse experiences reported during parenteral therapy were diarrhea (5.5%), infusion site pain (5.5%) and infusion site erythema (2.6%).

Table 5 shows the incidence of drug-related adverse experiences reported during parenteral therapy.

Table 5: Incidence (%) of Drug-Related Adverse Experiences* Reported During Parenteral Therapy in ≥ 1.0% of Pediatric Patients Treated with Ertapenem in Clinical Studies

Adverse Events	Ertapenem (N=384)	Ceftriaxone (N=100)	Ticarcillin/clavulanate (N=24)
Gastrointestinal disorders:			
Diarrhea	5.5	10.0	4.2
Vomiting	1.6	2.0	0.0
General disorders and administration site conditions:			
Infusion site erythema	2.6	2.0	0.0
Infusion site pain	5.5	1.0	12.5
Infusion site phlebitis	1.8	3.0	0.0
Infusion site swelling	1.0	0.0	0.0
Skin and subcutaneous tissue disorders:			
Rash	1.3	1.0	4.2

* Determined by the investigator to be possibly, probably or definitely drug-related.

In the pediatric clinical studies, the majority of the patients had parenteral therapy followed by a switch to an appropriate oral antimicrobial (see 14 CLINICAL TRIALS). During the entire treatment period and a 14 day post-treatment follow-up period, drug-related adverse experiences reported with an incidence of ≥ 1.0% in patients treated with ertapenem were no different than those listed in Table 5.

8.3 Less Common Clinical Trial Adverse Reactions

Adults

Table 6 lists the less common drug-related adverse experiences that were reported during parenteral therapy with ertapenem within each body system.

Table 6: Less Common Clinical Trial Adverse Drug Reactions (< 1%) in Adult Patients

System Organ Class	Uncommon Clinical Trial Adverse Drug Reactions (≥ 0.1% but < 1.0%) Ertapenem (N=1866)	Rare Clinical Trial Adverse Drug Reactions (< 0.1%) Ertapenem (N=1866)
Blood and lymphatic system disorders		eosinophilia, neutropenia, thrombocytopenia
Cardiac disorders		arrhythmia, tachycardia
Gastrointestinal disorders	Acid regurgitation, constipation, *C. difficile*-associated diarrhea, dry mouth, dyspepsia	colitis, dysphagia, tongue edema, flatulence, gastritis, gastric ulcer, fecal incontinence, mouth ulcer, pelvic peritonitis
General disorders and administration site conditions	Asthenia/fatigue, edema/swelling, fever, pain, abdominal pain, chest pain, extravasation, candidiasis, taste perversion	chills, cold extremities, facial edema, injection site induration, injection site stinging, malaise, thirst, warm sensation

Hepatobiliary disorders		cholecystitis, jaundice, liver disorder
Immune system disorders		Allergy
Infections and infestations	Oral candidiasis	cellulitis, dermatomycosis, fungal infection, herpes simplex, postoperative wound infection, urinary tract infection
Injury, poisoning and procedural complications		drug overdose
Investigations		increased blood pressure
Metabolism and nutrition disorders	Anorexia	hypoglycemia
Musculoskeletal and connective tissue disorders		muscle cramps, elbow pain, shoulder pain
Nervous system disorders	Confusion, dizziness, insomnia, somnolence, seizures	restless leg syndrome, grand mal seizure, parasthesia, tremor
Pregnancy, puerperium and perinatal conditions		abortion
Psychiatric disorders		agitation, anxiety, depression, hallucinations, syncope
Renal and urinary disorders		acute renal insufficiency, renal insufficiency
Reproductive system and breast disorders	Vaginal pruritus	genital bleeding, vaginal dryness
Respiratory, thoracic and mediastinal disorders	Dyspnea	nasal congestion, cough, epistaxis, pharyngeal discomfort, pneumonia, rales/rhonchi, wheezing
Skin and subcutaneous tissue disorders	Erythema, pruritus	dermatitis, desquamation
Vascular disorders	Hypotension	flushing, hot flashes, vasculitis

Prevention (prophylaxis of surgical site infection following elective colorectal surgery)

The following additional (i.e., in addition to Adverse Experiences listed in Table 6) drug-related adverse experiences were reported with an incidence of < 1.0% (uncommon) as listed below:

Cardiac disorders: Sinus bradycardia
Infections and infestations: Cellulitis, clostridial infection, Clostridium colitis, postoperative infection.

Injury and poisoning: Wound complication.

Skin and sub cutaneous tissue disorders: Erythematous rash, urticaria.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Additional drug-related adverse experiences that were reported during parenteral therapy with ertapenem with an incidence of > 0.2% but < 1% in pediatric studies within each body system are listed below in Table 7:

Table 7: Less Common Clinical Trial Adverse Drug Reactions (> 0.2% but < 1%) in Pediatric Patients

System Organ Class	Ertapenem (N=384)
Gastrointestinal	abdominal pain, enteritis, flatulence, loose stools, nausea, toothache
General disorders and administration site conditions	chest pain, hypothermia, infusion site burning, infusion site induration, infusion site oedema, infusion site pruritus, infusion site reaction, infusion site warmth, injection site bruising, injection site erythema
Infections and infestations	oral candidiasis
Metabolism and nutritional	decreased appetite
Nervous system	headache
Reproductive system and breast disorders	genital rash
Respiratory, thoracic and mediastinal disorders	wheezing
Skin and subcutaneous tissue disorders	Dermatitis diaper, erythema, petechiae, pruritus, rash erythematous, rash macular
Vascular disorders	hot flash, hypertension, phlebitis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Adult Patients

Table 8 shows the most frequently observed drug-related laboratory abnormalities during parenteral therapy in patients receiving ertapenem.

Table 8: Incidence* (%) of Specific Drug-Related Laboratory Adverse Experiences Reported During Parenteral Therapy in ≥ 1.0% of Adult Patients Treated With Ertapenem in Clinical Studies

Laboratory adverse experiences	Ertapenem 1 g daily n†=1766	Piperacillin/Tazobactam 3.375 g q6h n†=750	Ceftriaxone 1 or 2 g daily n†=870
Chemistry:			
ALT ↑	5.5	4.4	4.9

AST ↑	4.8	4.5	4.2
Alkaline phosphatase ↑	2.9	3.9	1.4
Hematology:			
Platelet count ↑	2.0	3.9	0.4

* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test; where at least 1516 patients had the test.
† Number of patients with one or more laboratory tests.

Other drug-related laboratory abnormalities that were reported during parenteral therapy in > 0.1% but < 1.0% of patients treated with ertapenem in clinical studies included the following:

Chemistry: increases in direct serum bilirubin, total serum bilirubin, indirect serum bilirubin, BUN, serum creatinine, serum glucose.

Hematology: increases in eosinophils, PTT, monocytes; decreases in segmented neutrophils, white blood cells, hematocrit, hemoglobin and platelet count.

Urinalysis: increases in urine bacteria, urine epithelial cells, urine red blood cells.

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial (see 14 CLINICAL TRIALS). During the entire treatment period and a 14-day post- treatment follow-up period, drug-related laboratory abnormalities in patients treated with ertapenem were no different than those listed in Table 8.

Prevention (prophylaxis of surgical site infection following elective colorectal surgery)
The following additional (i.e., in addition to adverse experiences listed in the Abnormal Laboratory Findings Section) drug related laboratory adverse experiences were reported with an incidence of < 1.0% (uncommon): increases in white blood cells and prothrombin time (PT).
Pediatrics

Table 9 shows the most frequently observed drug-related laboratory abnormality during parenteral therapy in patients receiving ertapenem.

Table 9: Incidence* (%) of Specific Drug-Related Laboratory Adverse Experiences Reported During Parenteral Therapy in ≥ 1.0% of Pediatric Patients Treated With Ertapenem in Clinical Studies

Laboratory adverse experiences	Ertapenem (N†=384)	Ceftriaxone (N†=100)	Ticarcillin/clavulanate (N†=24)
Chemistry:			
ALT ↑	1.9	0.0	4.3
AST ↑	1.9	0.0	4.3
Hematology:			
Neutrophil count ↓	2.5	1.1	0.0

* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test; where at

least 300 patients had the test.
† Number of patients with one or more laboratory tests.

Additional drug-related laboratory adverse experiences that were reported during parenteral therapy in > 0.5% but < 1.0% of pediatric patients treated with ertapenem in clinical studies include: increase in eosinophils.

Post-Market Findings
Not applicable.

8.5 Post-Market Adverse Reactions

The following additional post-marketing adverse experiences have been reported:

Gastrointestinal Disorders: teeth staining.

Immune System: anaphylaxis including anaphylactoid reactions.

Musculoskeletal and Connective Tissue Disorders: muscular weakness.

Nervous System Disorders: depressed level of consciousness, dyskinesia, gait disturbance, myoclonus, tremor, encephalopathy (recovery was prolonged in patients with renal impairment).

Psychiatric Disorders: altered mental status (e.g., aggression, agitation, confusion/confusional state, delirium, disorientation, mental status changes), hallucinations.
Skin and Subcutaneous Tissue Disorders: Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), hypersensitivity vasculitis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview
In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. *In vitro* studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the following six cytochrome P450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Drug interactions caused by inhibition of P-glycoprotein-mediated drug clearance or CYP-mediated drug clearance with the listed isoforms are unlikely (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). In vitro studies indicate that ertapenem, over its therapeutic concentration range, has little effect on the unbound fraction of warfarin in human plasma.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies were conducted with ertapenem.

9.4 Drug-Drug Interactions

Probenecid

When ertapenem is administered with probenecid (500 mg of probenecid every 6 hours), probenecid competes for active tubular secretion and reduces the renal excretion of ertapenem. This leads to small but statistically significant increases in the elimination half-life (19%, mean half-life with probenecid is 4.8 hours and mean half-life without probenecid is 4.0 hours) and in the extent of systemic exposure (25%, mean AUC0-∞ of total ertapenem with probenecid is 767.6 µg•hr/mL and mean AUC0-∞ of total ertapenem without probenecid is 616.2 µg•hr/mL). The coadministration of ertapenem with probenecid is not recommended, unless clinically necessary, due to the small effect on half-life. No dosage adjustment is recommended when patients receive probenecid concomitantly with ertapenem.

Valproic Acid

Case reports in the literature have shown that co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or divalproex sodium results in a reduction of serum valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. In some cases of co- administration of ertapenem with valproic acid, breakthrough seizures have occurred. The mechanism of this interaction is unknown (see 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ertapenem is a sterile, synthetic, parenteral, 1-ß methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins, with in vitro activity against a range of gram-positive and gram-negative aerobic and anaerobic bacteria.

The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In Escherichia coli, it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3.

Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases. Ertapenem is hydrolyzed by metallo-beta- lactamases (see 15 MICROBIOLOGY).

10.2 Pharmacodynamics

See 15 MICROBIOLOGY.

10.3 Pharmacokinetics

Overall, ertapenem pharmacokinetics were approximately linear. The plasma concentration of total ertapenem declines in a poly-exponential fashion following single 30-minute intravenous infusion. Area under the plasma concentration curve (AUC) of ertapenem increased slightly less than dose- proportionally based on total ertapenem concentrations over the 0.5 to 2 g dose range and that the AUC increased slightly greater than dose proportionally based on unbound ertapenem concentrations over the 0.5 to 2 g dose range. The slight deviations from strict dose proportionality are thought to be due to concentration-dependent plasma protein binding at the proposed therapeutic dose. The departure from dose-proportionality is very slight and, given the apparent wide therapeutic index of ertapenem, is not considered clinically relevant. The apparent volume of distribution of ertapenem at steady state is approximately 8.2 liters. The major metabolite of ertapenem is the bacteriologically inactive ring-opened derivative formed predominantly by the kidney by hydrolysis of the beta-lactam ring. Ertapenem is eliminated primarily by the kidneys. Plasma radioactivity consists predominantly (94%) of ertapenem. The mean plasma half-life of ertapenem in healthy young adults and patients 13 to 17 years of age is approximately 4 hours and approximately 2.5 hours in pediatric patients 3 months to 12 years of age. The mean bioavailability of 1 g IM dose is approximately 92%. There is no accumulation of ertapenem following multiple IV doses ranging from 0.5 to 2 g daily or IM doses of 1 g daily.

Average plasma concentrations (µg/mL) and mean $AUC_{0-\infty}$ of total ertapenem following a single 30-minute IV infusion of a 1 or 2 g dose and IM administration of a single 1 g dose in healthy young adults are presented in Table 10.

Table 10: Plasma Concentrations and Mean $AUC_{0-\infty}$ of Total Ertapenem After Single Dose Administration in Healthy Young Adults

Route/Dose	Average Plasma Concentrations (µg/mL)									$AUC_{0-\infty}$ (µg·hr/mL)
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr	
IV 1 g*	155	115	83	48	31	20	9	3	1	572
IV 2 g*	283	202	145	86	58	36	16	5	2	1011
IM 1 g	33	53	67	57	40	27	13	4	2	555

* IV doses were infused at a constant rate over 30 minutes.

Mean AUC0-∞ values (µg·hr/mL) of unbound ertapenem for intravenous doses of 1 g and 2 g

are 33.2 and 76.6, respectively.
Average plasma concentrations (μg/mL) of ertapenem in pediatric patients are presented in Table 11.

Table 11: Plasma Concentrations of Ertapenem in Pediatric Patients After Single IV* Dose Administration

Age Group	Average Plasma Concentrations (μg/mL)							
(Dose)	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
3 to 23 months								
(15 mg/kg)†	103.8	57.3	43.6	23.7	13.5	8.2	2.5	-
(20 mg/kg)†	126.8	87.6	58.7	28.4	-	12.0	3.4	0.4
(40 mg/kg)‡	199.1	144.1	95.7	58.0	-	20.2	7.7	0.6
2 to 12 years								
(15 mg/kg)†	113.2	63.9	42.1	21.9	12.8	7.6	3.0	-
(20 mg/kg)†	147.6	97.6	63.2	34.5	-	12.3	4.9	0.5
(40 mg/kg)‡	241.7	152.7	96.3	55.6	-	18.8	7.2	0.6
13 to 17 years								
(20 mg/kg)†	170.4	98.3	67.8	40.4	-	16.0	7.0	1.1
(1 g)§	155.9	110.9	74.8	-	24.0	-	6.2	-
(40 mg/kg)‡	255.0	188.7	127.9	76.2	-	31.0	15.3	2.1

* IV doses were infused at a constant rate over 30 minutes
† up to a maximum dose of 1g/day
‡ up to a maximum dose of 2 g/day
§ Based on three patients receiving 1 g ertapenem who volunteered for pharmacokinetic assessment in one of the two safety and efficacy studies

Absorption
Ertapenem, reconstituted with 1% lidocaine HCl injection, USP (in saline without epinephrine), is well absorbed following IM administration at the recommended dose of 1 g. The mean bioavailability is approximately 92%. Following 1 g daily IM administration, mean peak plasma concentrations (mean C_{max} = 70.6 μg/mL) are reached in approximately 2 hours (mean T_{max} = 2.2 hours) (see Table 10).

Distribution
Ertapenem is highly bound to human plasma proteins. In healthy young adults, the proportion of protein binding of ertapenem decreases as plasma concentrations of total ertapenem increase, from approximately 95% bound at an approximate plasma concentration of < 100 micrograms (μg)/mL to approximately 85% protein bound at an approximate plasma concentration of 300 μg/mL.

The apparent volume of distribution (V_{dss}) of ertapenem in adults at steady state is approximately 8.2 liters (0.12 liter/kg), approximately 0.2 liter/kg in pediatric patients 3 months to 12 years of age and approximately 0.16 liter/kg in pediatric patients 13 to 17 years of age.

Concentrations of ertapenem achieved in skin blister fluid at each sampling point on the third

day of 1 g once daily IV doses are presented in Table 12. The ratio of AUC0-24hr of total ertapenem in skin blister fluid to AUC0-24hr of total ertapenem in plasma is 0.61.

Table 12: Concentrations (µg/mL) of Total Ertapenem in Adult Skin Blister Fluid at Each Sampling Point on the Third Day of 1 g Once Daily IV Doses

0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
7	12	17	24	24	21	8

The concentration of ertapenem in breast milk of 5 lactating women was measured at random time points daily for 5 consecutive days following the last 1 g dose of a 3- to 6-day, once daily intravenous therapy. The measured concentration of ertapenem in breast milk on the last day of therapy (5 to 14 days postpartum) in all 5 women was < 0.38 µg/mL; peak concentrations were not assessed. By Day 5 after discontinuation of therapy, the level of ertapenem was undetectable in the breast milk of 4 women and was detected at trace levels (<0.13 µg/mL) in 1 woman.

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport (see 9 DRUG INTERACTIONS).

Metabolism

In healthy young adults, after IV infusion of radiolabeled 1 g ertapenem, the plasma radioactivity consists predominantly (94%) of ertapenem. The major metabolite of ertapenem is the bacteriologically inactive ring-opened derivative formed predominantly by the kidney by hydrolysis of the beta-lactam ring. This metabolite is found in urine (approximately 37% of the administered dose).

In vitro studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the six major cytochrome P450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (see 9 DRUG INTERACTIONS). In vitro studies in human liver microsomes indicate that ertapenem is a poor substrate of cytochrome P450 (CYP) isoforms.

Coadministration of cilastatin (renal dehydropeptidase-1 inhibitor) significantly reduced the plasma clearance of ertapenem and increased the urinary excretion of ertapenem in rats and mice consistent with the view that dehydropeptidase-1 catalyzed the metabolism of ertapenem.

Elimination

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults and patients 13 to 17 years of age is approximately 4 hours and approximately 2.5 hours in pediatric patients 3 months to 12 years of age.

Following administration of a 1 g radiolabeled IV dose of ertapenem to healthy young adults, approximately 80% is recovered in urine and 10% in feces. Of the 80% recovered in urine, approximately 38% is excreted as unchanged drug and approximately 37% as the bacteriologically inactive ring-opened metabolite.

In healthy young adults given a 1 g IV dose, average concentrations of ertapenem in urine exceed 984 µg/mL during the period 0 to 2 hours post dose and exceed 52 µg/mL during the period 12 to 24 hours post dose.

Special Populations and Conditions

- **Pediatrics:** Plasma concentrations of ertapenem are comparable in pediatric patients 13 to 17 years of age and adults following a 1 g once daily IV dose.

  Following the 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13 to 17 years of age were generally comparable to those in healthy young adults. Three out of six patients 13 to 17 years of age received less than a 1 g dose. To provide an estimate of the pharmacokinetic data if all patients in this age group were to receive a 1 g dose, the pharmacokinetic data were calculated adjusting for a 1 g dose, assuming linearity. A comparison of results shows that a 1 g once daily dose of ertapenem achieves a pharmacokinetic profile in patients 13 to 17 years of age comparable to that of adults. The ratios (13 to 17 years/Adults) for AUC, the end of infusion concentration and the concentration at the midpoint of the dosing interval were 0.99, 1.20, and 0.84 respectively.
  Plasma concentrations at the midpoint of the dosing interval following a single 15 mg/kg IV dose of ertapenem in patients 3 months to 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1 g once daily IV dose in adults (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Distribution). The plasma clearance (mL/min/kg) of ertapenem in patients 3 months to 12 years of age is approximately 2-fold higher as compared to that in adults. At the 15 mg/kg dose, the AUC value (doubled to model a twice daily dosing regimen, i.e., 30 mg/kg/day exposure) in patients 3 months to 12 years of age was comparable to the AUC value in young healthy adults receiving a 1g IV dose of ertapenem.

  Geriatrics: Plasma concentrations (AUC) following a 1 g and 2 g IV dose of ertapenem are slightly higher (approximately 39% and 22% for total ertapenem, respectively, and approximately 71% and 65% for unbound ertapenem, respectively) in elderly adults (≥ 65 years) relative to young adults (< 65 years). These differences could be attributed partly to age-related changes in renal function. No dosage adjustment is necessary for elderly patients with normal (for their age) renal function.

- **Sex:** The plasma concentration profiles of ertapenem are comparable in healthy men and women when body weight differences are taken into consideration. No dosage

adjustment is recommended based on gender.

- **Hepatic Insufficiency:** The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. *In vitro* studies indicate that ertapenem is metabolically stable in human liver microsomes. Following administration of a 1 g radiolabeled IV dose of ertapenem to healthy young adults, only 10% of ^{14}C-ertapenem was recovered in feces(see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Metabolism and Elimination). Due to the limited extent of hepatic metabolism of ertapenem, its pharmacokinetics are not expected to be affected by hepatic impairment. No dosage adjustment recommendations can be made in patients with hepatic impairment.

- **Renal Insufficiency:** Single 1 g IV doses of ertapenem were administered to 26 adult subjects with varying degrees of renal impairment, AUC was similar in patients with mild renal insufficiency (Clcr 60–90 mL/min/1.73 m^2 (when using International System of Units(SI), SI = 1.0–1.5 mL/s/1.73m^2)) compared with healthy subjects(ages 25 to 82 years). AUC was increased in patients with moderate renal insufficiency (Clcr 31–59 mL/min/1.73 m^2 (SI = 0.52–0.98 mL/s/1.73m^2)) approximately 1.5-fold compared with healthy subjects. AUC was increased in patients with advanced renal insufficiency (Clcr 5–30 mL/min/1.73 m^2 (SI = 0.08–0.50 mL/s/1.73m^2)) approximately 2.6 fold compared with healthy subjects. AUC was increased in patients with end-stage renal insufficiency (Clcr < 10 mL/min/1.73 m^2 (SI= < 0.17 mL/s/1.73 m2)) approximately 2.9 fold compared with healthy subjects. There are no data in pediatric patients with renal insufficiency. A dosage adjustment (500 mg once daily) is recommended for adult patients with advanced or end-stage renal insufficiency (see 4 DOSAGE AND ADMINISTRATION). The recommended dosage reduction is based on pharmacokinetic modeling of data collected from the clinical safety and pharmacokinetic study in patients with varying degrees of renal insufficiency (including those with creatinine clearance < 30 mL/min/1.73 m^2 (SI = < 0.5 mL/s/1.73 m^2)) receiving a single 1 g IV dose of ertapenem. Pharmacokinetic modeling was used to determine a dosing regimen, which would provide equivalent drug exposure for which clinical efficacy has been demonstrated.

  Following a single 1 g IV dose in 5 patients with end-stage renal insufficiency given immediately prior to a 4-hour hemodialysis session, approximately 30% of the dose was recovered in the dialysate. When patients on hemodialysis are given the recommended daily dose of 500 mg of ERTAPENEM FOR INJECTION within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session (see 4 DOSAGE AND ADMINISTRATION).

  Table 13 displays the mean plasma AUCs and the geometric mean AUC ratios (RI/Pooled Control) for total and unbound ertapenem in adult patients with varying degrees of renal insufficiency (RI).

Table 13: Mean Plasma AUCs and Geometric Mean Ratios (GMR) for Total and Unbound

Ertapenem Following a 1 g Intravenous Dose of Ertapenem in Adult Patients with Varying Degrees of Renal Insufficiency (RI) Versus the Pooled Control Group

Pharmacokinetic Parameter	Pooled Control*	Mild RI†	Moderate RI†	Advanced RI†	End-Stage RI
Total drug					
$AUC_{0-\infty}$ (µg•hr/mL)	665.9	712.2	1016.5	1719.9	1941.5
GMR‡	--	1.1	1.5	2.6	2.9
Unbound drug					
$AUC_{0-\infty}$ (µg•hr/mL)	42.5	44.2	76.1	144.6	252.7
GMR	--	1.0	1.8	3.4	6.0

* Pooled Control: Healthy young adult and healthy elderly subjects.
† Mild RI = Cl_{cr} 60–90 mL/min/1.73 m^2; Moderate RI = Cl_{cr} 31–59 mL/min/1.73 m^2; Advanced RI = Cl_{cr} 5–30 mL/min/1.73 m^2; End-Stage RI = Cl_{cr} < 10 mL/min/1.73 m^2.
‡ GMR = Geometric Mean Ratio of RI/Pooled Control.

Human Pharmacology
***In Vivo* Pharmacokinetics**

Table 14: Clinical Pharmacology and Bio pharmaceutics Studies

Study	Dose (n Analyzed)	Number Entered†/ Analyzed (Gender/Race)‡	Results and Conclusions
A 2-part, double-blind, placebo-controlled study in healthy men and women to determine the safety, tolerability, and preliminary pharmacokinetic profile of ertapenem after single (Part I) and multiple (Part II) dose intravenous (IV) infusions. Part I was a 2- panel, 4-period, single- rising IV dose study. Part II was a sequential 5- panel, multiple IV dose study.	<u>Part I</u> Panel A (n=6 M) 0.04, 0.25, 1, and 2 g (n=6 F) 1 g Panel B 0.1, 0.5, 1.5, and 3 g <u>Part II</u> Panel A (n=6) 0.25 g Panel B (n=6) 0.5 g Panel C (n=6) 1 g Panel D (n=6) 2 g Panel E (n=6) 3 g	50/49 S (6F, 43M/1A, 6B, 42C)	The mean plasma concentration of total ertapenem at 12 hours following a 1g IV dose is sufficient to suggest once-daily dosing in clinical trials with patients. No accumulation of ertapenem is observed with multiple daily doses up to 3 g. Intact drug accounts for the biological activity of ertapenem and no active metabolites are present. Following a 1 g IV dose, the pharmacokinetics of ertapenem are generally similar between men and women based on area under the curve (AUC).

An open-label, randomized, 4-period, crossover study in healthy subjects to investigate single-dose pharmacokinetics and dose proportionality of ertapenem at 0.5, 1, 2, and 3 g doses.	0.5, 1, 2, and 3 g (n=16)	16/16 S (8F, 8M/16C)	Ertapenem, based upon $AUC_{0-\infty}$ of total and unbound drug, is nearly dose proportional over the 0.5 to 2 g dose range, with a slight deviation from dose proportionality at the 3 g dose. No clinically meaningful difference in the pharmacokinetics of ertapenem is observed between men and women.
An open-label, 2-period, fixed-sequence study in healthy elderly subjects who received ertapenem 1 g IV once daily for 7 days in Period 1 and a single IV dose of 2 g in Period 2.	Period 1 1 g (n=14) Period 2 2 g (n=14)	15/14 S (6F, 8M/14C)	Plasma concentrations of total ertapenem are somewhat higher following a 1 g single IV dose ($AUC_{0-\infty}$ approximately 39% higher) and following a 2 g single IV dose ($AUC_{0-\infty}$ approximately 22% higher) in elderly relative to young adults. Renal clearance of ertapenem at the 1 g and 2 g doses is moderately lower in the elderly than in young adults, but this does not fully account for the increases in AUC in the elderly. Ertapenem does not accumulate with multiple dosing in elderly adults. Plasma concentrations of total and unbound ertapenem (based on $AUC_{0-\infty}$ are similar in elderly men and women). No dosage adjustment is recommended for elderly adults.
A randomized, placebo-controlled, single- ascending-dose study to investigate the safety, tolerability, and single-dose pharmacokinetics of intramuscular (IM) ertapenem at the 0.25, 0.5, and 1 g doses. Subjects in Panel A received a single dose of 0.25 g (or placebo) in Period 1 and a 1 g dose (or placebo) in Period 2. Subjects in Panel B received a single dose of 0.5 g (or placebo) in Period 1 and a 1 g dose (or placebo) in Period 2.	0.25, 0.5, and 1 g (n=8)	11/8 S (4F, 4 M/2A, 5C, 1H)	Compared with historical data, the plasma profiles following a 1 g dose of ertapenem are similar after 3 hours post dose whether administered intramuscularly or intravenously and the bioavailability for the IM dose appears to be nearly 100%.

An open-label, single IV dose study in healthy male and female subjects. Subjects received 1 g 14C-ertapenem IV, followed by the collection of blood samples for up to 48 hours post dose and urine samples for up to 168 hours post dose, for the measurement of ertapenem and radioactivity. Stool samples were also collected at specified times up to 168 hours post dose for the recovery of radioactivity.	1g ^{14}C-ertapenem Approximately 104 µCi of radioactivity per dose 20 mg/mL ^{14}C-ertapenem (n=7)	7/7 S (3F, 4 M/4B, 2C, 1H)	The plasma radioactivity consists predominantly of ertapenem (approximately 94%) after IV infusion of radiolabeled 1 g ertapenem. The recovery of total radioactivity in urine and feces indicates that the majority (approximately 80%) of the dose is excreted in urine and only a small percent (approximately 10%) is eliminated by biliary/fecal excretion. Mass balance is achieved after a single IV dose. Ertapenem and its ring- opened metabolite, L-774183, together account for about 95% of the radioactivity excreted in urine, each in turn accounting for about half of this. Several other minor radioactive components are detected in urine, each of which accounts for approximately 1% or less of the administered dose.

An open-label, 2-period study to evaluate the pharmacokinetics, safety, and tolerability of ertapenem in patients with defined degrees of renal function. In Period 1, ertapenem was administered as a single 30-minute IV dose of 1 g in 4 groups of patients. The 4 groups of renal insufficiency (RI) were: mild, moderate, advanced, and end stage. For end- stage RI patients, Period 1 was defined as a non-dialysis day. In Period 2, patients with end-stage RI received a single 1 g dose of ertapenem immediately prior to the initiation of hemodialysis.	1 g (n=6 mild; n=7 moderate; n=6 advanced; n=7 end-stage RI) RI based on creatinine clearances in the following ranges: 60 to 90 mL/min/1.73 m^2 (mild RI), 31 to 59 mL/min/1.73 m^2 (moderate RI), 5 to 30 mL/min/1.73 m^2 (advanced RI), and < 10 mL/min/1.73 m^2 (for patients with end- stage RI who were on hemodialysis).	26/24 P[§] (13F, 11M/11B, 11C, 1H, 1NA)	Plasma concentrations of ertapenem are increased in patients with end-stage RI following a single 1 g IV dose as reflected by an AUC increase of approximately 2.9-fold relative to the pooled control group of healthy young adult and elderly subjects. A dosage adjustment to 0.5 g once daily is recommended for the standard dose (instead of 1 g). Plasma concentrations of ertapenem are increased in patients with advanced RI following a single 1 g IV dose as reflected by an AUC increase of approximately 2.6-fold relative to the pooled control group. A dosage adjustment to 0.5 g daily is recommended for the standard dose (1 g). Plasma concentrations of ertapenem are similar (approximately 1.5- fold increase for $AUC_{0-\infty}$) in patients with moderate RI relative to the pooled control group following a single 1 g IV dose. No dosage adjustment is recommended for the standard dose. Plasma concentrations of ertapenem following a single 1 g IV dose are similar in patients with mild RI relative to the pooled control group. No dosage adjustment is recommended for the standard dose. Plasma concentrations of total ertapenem are decreased in patients with end-stage RI following a single 1 g IV dose given immediately prior to a hemodialysis session relative to the dose given on a non-dialysis day and approximately 30% of the dose is recovered in the dialysate. If the ertapenem dose is given at least 6 hours prior to hemodialysis, a supplementary

			dose of ertapenem is not needed. If the dose is given within 6 hours prior to hemodialysis, a supplementary dose of 30% of the daily dose is recommended following the hemodialysis session.
A 2-part, randomized, placebo- controlled, single- dose, 3-period, crossover (Part A) and multiple-dose (Part B) study to investigate the pharmacokinetics, safety, and tolerability of the IM formulation of ertapenem in healthy subjects. Part A was a 3-period, crossover, single- dose investigation. Fasted subjects received 3 single 1 g doses of ertapenem (or placebo) administered intramuscularly, infused intravenously over 30 minutes, and infused intravenously over 2 hours in a randomized, balanced order in Periods 1 through 3. In Part B, fasted subjects received a 1 g IM dose of ertapenem (or placebo) administered once daily for 7 days.	Part A (n=18) 1 g -administered IM -infused IV over 30 minutes -infused IV over 2 hours Part B (n=17) 1 g administered IM	Part A 22/18 S (6F, 12M/1A, 9B, 6C, 2H) Part B 22/17 S (6F, 11M/1A, 7B, 7C, 2H)	The $AUC_{0-\infty}$ is similar following a 1 g IM and IV dose of ertapenem. The bioavailability of the IM dose is 92%; thus, the IM route of administration may be used interchangeably with IV administration because both IV and IM routes of administration are anticipated to give comparable results. Ertapenem administered as 1 g IM daily for 7 days does not accumulate. Following a 1 g IM dose, the time over which plasma concentrations of total ertapenem exceeds 4 µg/mL is slightly longer than with IV administration (18.1 versus 16.9 hours, respectively). Urine concentrations of ertapenem are high (above 16 µg/mL in all post dose collections) following administration of a 1 g dose by either the IM or IV route.

An open-label, multiple- dose study investigating the penetration of ertapenem into suction- induced skin blisters on the third day of 1 g once-daily IV dosing. Subjects had 1 blister formed on Day 1 as a predose blank and 10 uniform blisters formed 12 hours prior to drug administration on Day 3. On Day 3, the IV dose of ertapenem was administered 12 hours following blister formation. Following IV administration, blister fluid and plasma were sampled for ertapenem concentrations.	1 g (n=12)	13/12 S (2F, 10M/12C)	On the third day of 1 g once- daily IV dosing, the concentration of total ertapenem in suction-induced skin blister fluid exceeds 4 µg/mL (MIC90 of generally susceptible organisms) over virtually the entire 24-hour interval. Peak blister fluid concentrations are much higher than this MIC90 value (approximately 6-fold). The mean ratio of AUC in blister fluid to AUC in plasma (0.61) indicates that ertapenem penetrates well into suction- induced skin blisters. On the third day of 1 g once-daily IV dosing, ertapenem concentrations in skin blister fluid appear adequate to treat generally susceptible organisms in complicated skin infections.
A randomized, open-label, 2-period, crossover study. Treatment A was probenecid 500 mg every 6 hours for 5 doses (one 500 mg tablet) prior to a single 1 g IV dose of ertapenem and 4 additional 500 mg doses of probenecid every 6 hours starting 6 hours after the fifth dose of probenecid. Treatment B was a single dose of 1 g IV ertapenem.	Treatment A 1 g MK-0826 500 mg probenecid (n=14) Treatment B 1 g MK-0826 (n=14)	14/14 S (7F, 7M/4B, 10C)	Renal clearance of unbound ertapenem decreases by approximately 54% with probenecid an inhibitor or renal tubular secretion, consistent with inhibition of tubular secretion of ertapenem by probenecid. Probenecid slightly increases total plasma concentrations of ertapenem ($AUC_{0-\infty}$ increases 25%), and slightly increases half-life of total ertapenem (from 4.03 to 4.80 hours). Coadministration of ertapenem and probenecid to extend the half-life of ertapenem is not recommended.

† Active treatment only (subjects on placebo not included in number entered).

‡ Gender and race provided for analyzed subjects/patients: S = healthy subjects, P = patients, M = male, F = female, A = Asian,
B = Black, C = Caucasian, CB = Cuban, H = Hispanic, I = South Pacific Islander, MZ = Mestizo, NA= Native American, O = Other.

§ Counted as patients due to organ dysfunction, not due to bacterial infection.

Renal Elimination/Hemodialysis

Renal clearance of unbound ertapenem was reduced by approximately 54% in the presence of probenecid (mean renal clearance = 203.7 mL/min without probenecid and 94.5 mL/min with

probenecid), an inhibitor of renal tubular secretion. The results suggest that tubular secretion and passive glomerular filtration are significant pathways of the renal clearance of ertapenem.

In a clinical study, following a single 1 g IV dose of ertapenem given immediately prior to a hemodialysis session, approximately 30% of the dose was recovered in the dialysate.

***In Vitro* Pharmacokinetics**

Ertapenem penetrated poorly into erythrocytes. This may be due to the extensive plasma protein binding and polarity of the compound (log10 p<-2) that limit the ability of the drug to cross the erythrocyte cell membrane.

11 STORAGE, STABILITY AND DISPOSAL

Before Reconstitution

Store lyophilized powder between 15°C and 25°C.

Reconstituted and Infusion Solutions

The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection (see 4.4 DOSAGE AND ADMINISTRATION, Administration), may be stored at room temperature (25°C) and used within 6 hours or stored for 24 hours under refrigeration (5°C) and used within 4 hours after removal from refrigeration. Solutions of ERTAPENEM FOR INJECTION (ertapenem monosodium) should not be frozen (see 4.3 DOSAGE AND ADMINISTRATION, Reconstitution).

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

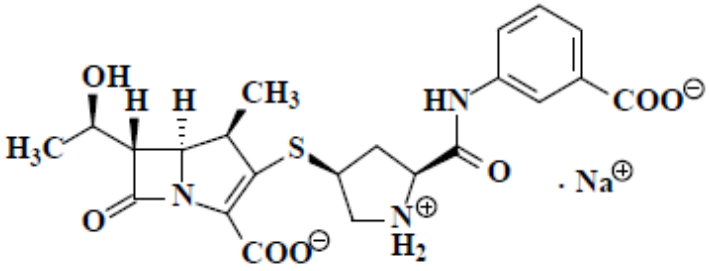
Drug Substance

Proper name: Ertapenem Monosodium

Chemical name: (4R,5S,6S)-3-[[(3S,5S)-5-[[(3- CARBOXYPHENYL)-AMINO]CARBONYL]-3-PYRROLIDINYL]THIO]-6-[(1R)-1- HYDROXYETHYL]-4-METHYL-7-OXO-1-AZABICYCLO[3.2.0]HEPT-2-ENE-2- CARBOXYLIC ACID SODIUM SALT

Molecular formula and molecular mass: $C_{22}H_{24}N_3O_7SNa$ and 497.50 g/mol

Structural formula:



Physicochemical properties: Ertapenem monosodium is a white to off-white hygroscopic powder. Freely soluble in water and 0.9% sodium chloride solution and practically insoluble in ethanol. Ertapenem monosodium exhibits polymorphism. pH is in between 5.0 and 6.8.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Adult Patients

Complicated Intra-Abdominal Infections

Table 15: Summary of Patient Demographics for the Pivotal Trial in Complicated Intra-Abdominal Infections

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
017	randomized, multicenter, double-blind, controlled clinical trial. Patients were stratified at baseline into two groups: localized complicated appendicitis (stratum 1) and any other complicated intra-abdominal infection including colonic, small intestinal, and biliary infections and generalized peritonitis (stratum 2)	ertapenem (1 g IV once a day) for 5 to 14 days versus	665 patients	17–92	140/255
		piperacillin/tazobactam (3.375 g IV every 6 hours)			

Results

Table 16: Clinical and Microbiological Success Rates in Complicated Intra-Abdominal Infections for Study 017

	Ertapenem n/N (%)	Comparator n/N (%)	95% CI for the difference
At 1 to 2 weeks post therapy	190/212 (89.6%)	162/196 (82.7%)	--
4 to 6 weeks post therapy (Test of Cure)†	176/203 (86.7%)	157/193 (81.2%)	(-2.2, 13.1)
Test of Cure (Stratum 1)	85/94 (90.4%)	82/91 (90.1%)	--
Test of Cure (Stratum 2)	91/109 (83.5%)	75/102 (73.5%)	--

† Percentages and the 95% CI for study 017 (Test of Cure) were computed from a statistical model adjusting for strata

Table 17: Clinical Success Rates at the Test of Cure by Pathogen for Microbiologically Evaluable Adult Patients with Complicated Intra-Abdominal Infections for Study 017

Pathogen	Ertapenem % (n/N)*	Comparator % (n/N)*
Escherichia coli	86.7 (137/158)	80.0 (108/135)
Clostridium clostridioforme	89.5 (17/19)	90.5 (19/21)
Eubacterium lentum	90.5 (19/21)	83.3 (10/12)
Peptostreptococcus species	80.6 (29/36)	88.5 (23/26)
Bacteroides fragilis	82.9 (63/76)	82.4 (56/68)
Bacteroides distasonis	78.9 (15/19)	96.0 (24/25)
Bacteroides ovatus	95.2 (20/21)	90.9 (20/22)
Bacteroides uniformis	95.5 (21/22)	90.5 (19/21)
Bacteroides thetaiotaomicron	87.2 (41/47)	85.3 (29/34)

* Number of isolates with favorable response assessment/Total number of isolates

Complicated Skin and Skin Structure Infections

Table 18: Summary of Patient Demographics for the Pivotal Trial in Complicated Skin and Skin Structure Infections

Study #	Trial design	Treatments: Dosage, route of administration and duration	Number of patients	Age range	Gender (males/ females)
016	randomized, multicenter, double-blind, controlled clinical trial.	ertapenem (1 g IV once a day) for 7 to 14 days versus piperacillin/tazobactam (3.375 g IV every 6 hours) for 7 to 14 days	540 patients*	18–99	351/189

* Including patients with deep soft tissue abscess, posttraumatic wound infection and cellulitis with purulent drainage.

Results

Table 19: Clinical Success Rates at the Test of Cure in Complicated Skin and Skin Structure Infections for Study 016

	Ertapenem n/N (%)	Comparator n/N (%)	95% CI for the difference
10 to 21 days post therapy (Test of Cure)†	152/185 (82.4%)	147/174 (84.4%)	(-10.2, 6.2)
Deep soft tissue abscess	29/30 (96.7%)	34/36 (94.4%)	--
Posttraumatic wound infection	25/30 (83.3%)	22/26 (84.6%)	--
Cellulitis with purulent drainage	27/29 (93.1%)	21/24 (87.5%)	--

† Percentages and the 95% CI for study 016 (Test of Cure) were computed from a statistical model adjusting for strata.

Table 20: Clinical Success Rates at the Test of Cure by Pathogen for Clinically Evaluable Adult Patients with Complicated Skin and Skin Structure Infections for Study 016

Pathogen	Ertapenem % (n/N)*	Comparator % (n/N)*
Staphylococcus aureus	76.1 (54/71)	78.9 (56/71)
Streptococcus pyogenes	81.3 (13/16)	93.8 (15/16)
Escherichia coli	94.1 (16/17)	80.0 (12/15)
Peptostreptococcus species	87.1 (27/31)	90.9 (20/22)

* Number of isolates with favorable response assessment/Total number of isolates.

Diabetic Foot Infections

Table 21: Summary of Patient Demographics for the Clinical Trial in Diabetic Foot Infections

Study #	Trial design	Treatments: Dosage, route of administration and duration*	Number of patients	Mean age (Range)	Gender (males/ females
034	multicenter, randomized, double- blind, clinical trial conducted in the US.	ertapenem (1 g intravenously once a day) versus	586 patients**	Mean: 59.2 (22–94)	370/206

Ertapenem was evaluated in adults treated for 28 days or less for diabetic foot infections without concomitant osteomyelitis. The large majority of patients had non-ischemic grade 1 and 2 diabetic foot infections graded according to the Texas Health Sciences Centre classification system.	piperacillin/ tazobactam (3.375 g intravenously every 6 hours).	

* Both regimens allowed the option to switch to oral amoxicillin/clavulanate beyond day 5 of the maximal 28 day treatment (parenteral and oral). Most patients received appropriate adjunctive treatments such as debridement, wound off-loading and saline compresses as is typically required in the treatment of diabetic foot infections. Patients with suspected osteomyelitis could be enrolled if all the infected bone was removed within 2 days of initiation of study therapy, and preferably within the prestudy period. Investigators had the option to add open-label vancomycin if enterococci or methicillin-resistant Staphylococcus aureus (MRSA) were among the pathogens isolated in polymicrobial infections or if patients had a history of MRSA infection and, such additional therapy was indicated in the opinion of the investigator.
** Five hundred and eighty-six (586) patients were randomized into 1 of 2 treatment groups: 289 patients received ertapenem and 287 patients received piperacillin/tazobactam. Ten (10) patients were randomized to 1 of the 2 treatment arms (6 to ertapenem and 4 to piperacillin/tazobactam) but received no parenteral study therapy.

Results

Table 22: Clinical Success Rates at the Test of Cure* in Diabetic Foot Infections for Study 034

	Ertapenem n/N (%)	Comparator n/N (%)	95 % CI
10 days post therapy (Test of Cure)	153/204 (75.0%)	143/202 (70.8%)	(-4.5, 12.8)

* Test-of-cure was defined as a favorable clinical response (resolution of all or most of the signs and symptoms of the index infection) in the clinically evaluable population at a follow-up visit 10-days post therapy.

Table 23: Clinical Success Rates at the Post therapy Visit by Pathogen for Clinically Evaluable

Adult Patients with Diabetic Foot Infections for Study 034

Pathogen	Ertapenem % (n/N)*	Comparator % (n/N)*
Staphylococcus aureus (MSSA)**	70.8 (51/72)	71.0 (49/69)
Peptostreptococcus species	78.7 (48/61)	68.5 (37/54)

* n/N = Number of pathogens with associated favorable assessment/number of pathogens with an assessment.
** MSSA = Methicillin sensitive Staphylococcus aureus.

Community Acquired Pneumonia

Table 24: Summary of Patient Demographics for the Clinical Trials in Community Acquired Pneumonia

Study #	Trial design	Treatments: Dosage, route of administration and duration*	Number of patients	Age range	Gender (males/ females)
018	pivotal randomized, multicenter, double-blind, controlled clinical study	ertapenem (1 g parenterally once a day) versus ceftriaxone (1 g parenterally once a day)	502 patients	17–96	287/215
020	supportive randomized, multicenter, double-blind, controlled clinical study	ertapenem (1 g parenterally once a day) versus ceftriaxone (1 g parenterally once a day)	364 patients	18–97	223/141

* Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 10 to 14 days of treatment (parenteral and oral).

Results

Table 25: Clinical Success Rates at the Test of Cure in Community Acquired Pneumonia for Combined Studies 018 and 020

	Ertapenem n/N (%)	Comparator n/N (%)	95% CI for the difference
7 to 14 days post therapy (Test of Cure)†	335/364 (91.9%)	270/294 (92.0%)	(-4.5, 4.4)

† Percentages and the 95% confidence interval for the combined studies 018 and 020 (Test of Cure) were calculated from a statistical model adjusting for strata.

Table 26: Clinical Success Rates at the Test of Cure by Pathogen for Microbiologically Evaluable Adult Patients with Community Acquired Pneumonia for Combined Studies 018 and 020

Pathogen	Ertapenem % (n/N)*	Comparator % (n/N)*
Streptococcus pneumoniae	89.6 (86/96)	93.7 (74/79)
Haemophilus influenzae	87.9 (29/33)	93.5 (29/31)
Moraxella catarrhalis	90.0 (27/30)	88.9 (24/27)

* Number of isolates with favorable response assessment/Total number of isolates.

Complicated Urinary Tract Infections Including Pyelonephritis

Table 27: Summary of Patient Demographics for the Clinical Trials in Complicated Urinary Tract Infections Including Pyelonephritis

Study #	Trial design	Treatments: Dosage, route of administration and duration*	Number of patients	Age range	Gender (males/ females)
014	pivotal randomized, multicenter, double-blind, controlled clinical study; Patients were stratified at baseline into two groups: pyelonephritis and any other complicated urinary tract infections.	ertapenem (1 g parenterally once a day) versus ceftriaxone (1 g parenterally once a day)	592 patients	17–98	189/403

021	supportive randomized, multicenter, double-blind, controlled clinical study; Patients were stratified at baseline into two groups: pyelonephritis and any other complicated urinary tract infections.	ertapenem (1 g parenterally once a day) versus	258 patients	18–90	109/149
		ceftriaxone (1 g parenterally once a day)			

*Both regimens allowed the option to switch to oral ciprofloxacin (500 mg twice daily) for a total of 10 to 14 days of treatment (parenteral and oral).

Results

Table 28: Microbiological Success Rates in Complicated Urinary Tract Infections Including Pyelonephritis for Combined Studies 014 and 021

	Ertapenem n/N (%)	Comparator n/N (%)	95 % CI for the difference
5 to 9 days post therapy (Test of Cure)†	229/256 (89.4%)	204/224 (91.1%)	(-7.4, 4.0)
Pyelonephritis stratum	116/127 (91.3%)	99/106 (93.4%)	--

† Percentages and the 95% confidence interval for the combined studies 014 and 021 (Test of Cure) were calculated from a statistical model adjusting for strata.

Table 29: Eradication Rates at the Test of Cure by Pathogen for Microbiologically Evaluable Adult Patients with Complicated Urinary Tract Infections for Combined Studies 014 and 021

Pathogen	Ertapenem % (n/N)*	Comparator % (n/N)*
Escherichia coli	92.1 (176/191)	92.3 (143/155)
Klebsiella pneumoniae	85.7 (24/28)	96.0 (24/25)
Proteus mirabilis	75.0 (9/12)	87.5 (7/8)

* Number of isolates with favorable response assessment/Total number of isolates.

Acute Pelvic Infections Including Postpartum Endomyometritis, Septic Abortion and Post-Surgical Gynecologic Infections

Table 30: Summary of Patient Demographics for the Pivotal Clinical Trial in Acute Pelvic

Infections Including Postpartum Endomyometritis, Septic Abortion and Post-Surgical Gynecologic Infections

Study #	Trial design	Treatments: Dosage, route of administration and duration	Number of patients	Age range
023	randomized, multicenter, double-blind, controlled clinical trial	ertapenem (1 g IV once a day) for 3 to 10 days versus	412 patients including 350 patients with obstetric/post-partum infections and 45 patients with septic abortion.	15–68
		piperacillin/tazobactam (3.375 g IV every 6 hours) for 3 to 10 days		

Results

Table 31: Clinical Success Rate at the Test of Cure in Acute Pelvic Infections Including Postpartum Endomyometritis, Septic Abortion and Post-Surgical Gynecologic Infections for Study 023

	Ertapenem n/N (%)	Comparator n/N (%)	95 % CI for the difference
2 to 4 weeks post therapy (Test of Cure)†	153/163 (93.9%)	140/153 (91.5%)	(-4.0, 8.8)

† Percentages and the 95% confidence interval for Study 023 (Test of Cure) were calculated from a statistical model adjusting for strata.

Table 32: Clinical Success Rates at the Test of Cure by Pathogen for Microbiologically Evaluable Adult Patients with Acute Pelvic Infections for Study 023

Pathogen	Ertapenem % (n/N)*	Comparator % (n/N)*
Streptococcus agalactiae	90.9 (10/11)	93.8 (15/16)
Escherichia coli	87.8 (36/41)	92.3 (36/39)
Peptostreptococcus species	96.4 (80/83)	92.7 (76/82)
Bacteroides fragilis	100 (15/15)	95.0 (19/20)
Porphyromonas asaccharolytica	92.9 (13/14)	92.3 (12/13)
Prevotella species	96.3 (52/54)	92.0 (46/50)

* Number of isolates with favorable response assessment/Total number of isolates.

Prophylaxis of Surgical Site Infections Following Elective Colorectal Surgery

Table 33: Summary of Patient Demographics for the Clinical Trial in Colorectal Surgical Prophylaxis (Evaluable Population)

Study #	Trial Design†	Treatment Groups/Doses/Duration	Age Range (Mean Age)	Number of Patients	Gender (males/females)
039	Double-blind, multicenter (with in-house blind), prospective, randomized, comparative study to evaluate the safety, efficacy and tolerability of ertapenem sodium versus cefotetanfor the prophylaxis of surgical site infection following elective colorectal surgery	One time administration of Intravenous (IV) study therapy given 60 minutes prior to the planned initial surgical incision as a single IV dose infused over 30 min Ertapenem treatment group: 1 g	23–92 Avg: 63	338	190/148
		Cefotetan treatment group: 2 g	21–94 Avg: 62	334	176/158

† This study included 500 patients randomized to ertapenem and 502 patients randomized to cefotetan. To be in the evaluable cohort, a patient must have received a complete dose of study therapy infused over 30 minutes within 2 hours prior to incision and within 6 hours of surgical closure with adequate time for completion of bowel preparation prior to surgery. Adequate bowel preparations included: osmotic oral bowel preparations containing polyethylene glycol solutions or oral sodium phosphate preparations. For the primary analysis, patients with documented surgical site infections, in addition to those with post- operative anastomotic leak or unexplained antibiotic use, were considered to have failed prophylaxis.

Results

Table 34: Proportion of Patients with Favorable Clinical Response Assessment at 4-Weeks Post- Treatment (Evaluable Population)(Estimated†) for Study 039

Treatment Group						Estimated† Difference (A-B)	
Ertapenem (A) (N=338)			Comparator (B) (N=334)				
	Estimated† Response			Estimated† Response			
n	%	(95% CI)	n	%	(95% CI)	%	(95% CI) p-value
243	72.0	(67.2, 76.8)	191	57.2	(51.9, 62.6)	14.8	(7.5, 21.9) p<0.001

†Percents, confidence intervals and p-values were calculated from a methodology proposed by Miettinen and Nurminen, accounting for the surgical procedure performed (intraperitoneal procedure or abdominoperineal resection) using Cochran-Mantel-Haenszel weights. The treatment by surgical procedure interaction was not significant (p>0.10).
N = Number of evaluable patients in each treatment group.

n = Number of evaluable patients with a favorable clinical response assessment in each treatment group. CI = Confidence interval.

Table 35: Proportion of Patients with Favorable Clinical Response Assessment at 4-Weeks Post- Treatment Displayed by Surgical Procedure (Evaluable Population) for Study 039

	Treatment Group						Observed Differences (A-B)	
	Ertapenem (A) (N=338)			Comparator (B) (N=334)				
	Observed Response			Observed Response				
Surgical Procedure	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Intraperitoneal	185/253	73.1	(67.2, 78.5)	150/265	56.6	(50.4, 62.7)	16.5	(8.3, 24.5)
Abdominoperineal	58/85	68.2	(57.2, 77.9)	41/69	59.4	(46.9, 71.1)	8.8	(-6.4, 23.9)

N = Number of evaluable patients in each treatment group.
n/m = Number of evaluable patients with favorable assessment / number of evaluable patients with assessment.
CI = Confidence Interval.

Table 36: Proportion of Patients with Favorable Clinical Response Assessment at 4-Weeks Post Treatment (MITT Population)(Estimated†) for Study 039

Treatment Group						Estimated† Difference (A-B)		
Ertapenem (A) (N=451)			Comparator (B) (N=450)					
	Estimated† Response			Estimated† Response				
n	%	(95% CI)		%	(95% CI)	%	(95% CI)	p-value
269	59.8	(55.2, 64.3)	221	49.1	(44.4, 53.7)	10.7	(4.2, 17.1)	p<0.001

† Percents, confidence intervals and p-values were calculated from a methodology proposed by Miettinen and Nurminen, accounting for the surgical procedure performed (intraperitoneal procedure or abdominoperineal resection) using Cochran-Mantel-Haenszel weights. The treatment by surgical procedure interaction was not significant (p>0.10).

MITT = Modified Intent To Treat.

N = Number of MITT qualified patients in each treatment group.

n = Number of MITT qualified patients with a favorable clinical response assessment in each treatment group.

CI = Confidence interval.

Table 37: Proportion of Patients who Failed Prophylaxis at 4-Weeks Post-Treatment Displayed by Reason for Failure (Evaluable Population) for Study 039

Reason for Failure	Treatment Group						Estimated† Difference (A-B)	
	Ertapenem (A) (N=338)			Comparator (B) (N=334)				
	Estimated† Response			Estimated† Response				
	n	%	(95% CI)	n	%	(95% CI)	%	(95% CI)
Any Failure	95	28.0	(23.2, 32.8)	143	42.8	(37.4, 48.1)	-14.8	(-21.9, -7.5)‡
Surgical Site Infection	62	18.1	(14.0, 22.2)	104	31.1	(26.1, 36.1)	-13.0	(-19.5, -6.5)‡
Organ/Space	4	1.2	(0.0, 2.3)	12	3.7	(1.7, 5.7)	-2.5	(-5.2, -0.2)
Deep Incisional	13	3.7	(1.7, 5.8)	17	5.1	(2.7, 7.4)	-1.3	(-4.7, 1.9)
Superficial Incisional	45	13.1	(9.5, 16.8)	75	22.4	(17.9, 26.8)	-9.2	(-15.0, -3.5)
Unexplained Antibiotic Use	23	6.9	(4.2, 9.6)	25	7.5	(4.7, 10.3)	-0.6	(-4.6, 3.4)
Anastomotic Leak	10	3.0	(1.2, 4.8)	14	4.2	(2.0, 6.3)	-1.1	(-4.2, 1.8)

† Percents, confidence intervals and p-values were calculated from a methodology proposed by Miettinen and Nurminen, accounting for the surgical procedure performed (intraperitoneal procedure or abdominoperineal resection) using Cochran-Mantel-Haenszel weights. The treatment by surgical procedure interaction was not significant (p>0.10).
‡ Statistical test for treatment difference was significant (p<0.001).
N = Number of evaluable patients in each treatment group. n = Number of evaluable patients within failure category.
CI = Confidence interval.

Pediatric Patients

Ertapenem was evaluated primarily for pediatric safety and secondarily for efficacy in randomized comparative, multicenter studies in patients 3 months to 17 years of age with community acquired pneumonia (CAP), urinary tract infections (UTI), skin and soft tissue infections (SSTI), intra-abdominal infections (IAI) and acute pelvic infections (API).

Table 38: Summary of Patient Demographics for Clinical Trials in Pediatric Patients

Study #	Trial Design	Treatment Groups/Doses†	Age Range‡ (Mean Age)	Number of Patients‡	Gender‡ (boys/girls)
036	Double-blind, multicenter (United States and internationally) study in pediatric patients with UTI, SSTI, and CAP	Ertapenem treatment group: 3 months to 12 years(15 mg/kg IV every 12 hours; maximum of 1 g daily) 13 to 17 years(1 g IV once a day)	3 to 23 months (12.3 months) 2 to 12 years (5.1 years) 13 to 17 years (14.5 years)	152 225	(161/241)
		Ceftriaxone treatment group: 3 months to 12 years(50 mg/kg/day IV in two divided doses; maximum of 2 g daily) 13 years to 17 years(50 mg/kg/day IV as a single daily dose; maximum of 2 g		25	

		daily)			
038	Open-label, multicenter (United States and internationally) study in pediatric patients with IAI and API	Ertapenem treatment group: 3 months to 12 years(15 mg/kg IV every 12 hours; maximum of 1 g daily) 13 to 17 years(1 g IV once a day) Ticarcillin/clavulanate treatment group: < 60 kg (50 mg/kg); 4 or 6 times a day > 60 kg (3.0 g); 4 or 6 times a day	3 to 23 months 2 to 12 years (7.8 years) 13 to 17 years (15.2 years)	0 47 58	(40/65)

† Study 036 allowed the option to switch to oral amoxicillin/clavulanate after at least 3 days of parenteral therapy if clinical response criteria were met, for a total of up to 14 days of treatment (parenteral and oral). Study 038 did not allow for an oral switch; suggested parenteral treatment duration was 3–14 days for API and 5–14 days for IAI.

‡ Number of patients that received at least 1 dose of parenteral study therapy.

Results:

Table 39: The Proportion of Pediatric Patients in the Evaluable Per Protocol (EPP) Analysis with a Favorable Assessment† at the Test-of-cure Visit for Studies 036 (CAP, UTI, SSTI) and 038 (IAI, API)

Disease Stratum	Ertapenem % (n/N)	Comparator % (n/N)
CAP	96.1 (74/77)	96.4 (27/28)
UTI	87.0 (40/46)	90.0 (18/20)
SSTI	95.5 (64/67)	100 (26/26)
IAI‡	83.7 (36/43)	63.6 (7/11)
API§	100 (23/23)	100 (4/4)

† A favorable clinical response rate is displayed for SSTI, CAP, IAI, and API. A favorable microbiological response rate is displayed for UTI.

‡ Included patients with perforated or complicated appendicitis.

§ Included patients with post-operative or spontaneous obstetrical endomyometritis, or septic abortion.

14.2 Comparative Bioavailability Studies

Not applicable.

15 MICROBIOLOGY

The antibacterial spectrum of ertapenem was evaluated using standard *in vitro* microbiological procedures. Table 40 displays the *in vitro* antibacterial activity of ertapenem against 9911 isolates from surveillance studies and from the clinical studies. The ratios of MBC to MIC in broth (inoculum 105 CFU/mL) are shown in Table 41. Ertapenem was found to have limited activity against *Corynebacterium jeikeium*, *Pseudomonas* spp., *Burkholderia cepacia*, *Stenotrophomonas maltophilia, Acinetobacter* spp., *Bacteroides distasonis,* and *Clostridium difficile*. Enterococci and methicillin-resistant staphylococci are resistant to ertapenem.

Table 40: Summation of *in Vitro* Activity of Ertapenem Including Aerobic and Anaerobic Isolates Obtained in the Phase II to Phase III Clinical Efficacy Trials (North American Isolates Only)

Organism	N	Range	Ertapenem MIC, µg/mL MIC50	MIC90
Aerobic Gram-positive				
Corynebacterium spp.	34	0.008 to 32	0.5	32
Enterococcus faecalis	595	0.06 to > 64	8	16
Enterococcus faecium	211	0.125 to 64	32	32
Enterococcus gallinarum	16	8 to > 64	16	32
Enterococcus spp.	32	0.125 to 32	16	16
Staphylococcus aureus (Methicillin-Susceptible*)	618	≤ 0.008 to 4	0.125	0.25
Staphylococcus aureus (Methicillin-Resistant*)	210	0.125 to > 32	16	32
Staphylococcus spp.	75	≤ 0.016 to 4	0.5	2
Staphylococcus, coagulase-negative (Methicillin-Susceptible*)	373	0.03 to > 32	0.25	2
Staphylococcus, coagulase-negative (Methicillin-Resistant*)	404	0.06 to > 32	8	32
Streptococcus agalactiae	269	0.008 to > 16	0.06	0.06
Streptococcus beta-hemolytic	82	0.008 to 0.5	0.03	0.25
Streptococcus milleri group	36	0.008 to 4	0.125	0.25
*Streptococcus pneumoniae (*Penicillin-Sensitive†)	475	0.004 to 0.125	0.016	0.03
*Streptococcus pneumoniae (*Penicillin-Intermediate†)	132	0.008 to 1	0.25	0.5
Streptococcus pneumoniae (Penicillin-Resistant†)	149	0.12 to 4	1	2
Streptococcus pyogenes	317	0.004 to 2	0.008	0.016
Streptococcus viridans	42	≤ 0.016 to 8	0.125	1
Streptococcus viridans group	66	≤ 0.016 to 4	0.25	2
Streptococcus spp.	37	≤ 0.008 to 4	0.06	2
Aerobic Gram-negative				
Achromobacter xylosoxidans	15	0.06 to 0.5	0.125	0.5
Acinetobacter anitratus	12	2 to 8	4	8
Acinetobacter baumannii	104	0.5 to > 32	8	16
Acinetobacter spp.	26	≤ 0.016 to > 16	4	8
Aeromonas hydrophila	11	0.03 to 0.5	0.06	0.25
Burkholderia cepacia	18	4 to 32	16	32
Citrobacter diversus	33	0.008 to 0.125	0.008	0.016
Citrobacter freundii	190	0.008 to > 8	0.016	0.25
Citrobacter koserii	72	≤ 0.008 to 2	0.008	0.016
Enterobacter aerogenes	168	≤ 0.008 to > 32	0.06	0.25
Enterobacter cloacae	245	≤ 0.008 to 32	0.06	1

Escherichia coli	741	0.008 to 0.5	0.016	0.016
Haemophilus influenzae	493	≤ 0.008 to 0.5	0.03	0.06
Haemophilus parainfluenzae	76	≤ 0.008 to 1	0.03	0.125
Haemophilus species (not influenzae)	40	0.008 to 0.5	0.016	0.25
Klebsiella oxytoca	169	≤ 0.008 to 4	0.008	0.03
Klebsiella pneumoniae	460	0.008 to 32	0.016	0.03
Morganella morganii	142	≤ 0.008 to 2	0.03	0.06
Moraxella catarrhalis	221	0.004 to 0.25	0.008	0.016
Neisseria gonorrhoeae	20	0.004 to 0.03	0.008	0.03
Neisseria meningitidis	42	0.008 to 0.03	0.008	0.03
Pasteurella multocida	24	0.008 to 0.03	0.016	0.03
Proteus mirabilis	192	0.008 to 0.25	0.016	0.03
Proteus vulgaris	52	0.008 to 0.06	0.016	0.03
Providencia rettgeri	36	0.008 to 0.125	0.03	0.06
Providencia stuartii	50	0.016 to 8	0.06	0.125
Pseudomonas aeruginosa (IPM-Sensitive)	233	0.125 to > 32	4	16
Pseudomonas aeruginosa (IPM-Resistant)	131	0.5 to > 32	16	32
Pseudomonas spp.	41	0.008 to 32	8	32
Salmonella group A	48	0.008 to 0.06	0.008	0.008
Salmonella typhimurium (B)	23	0.008 to 0.03	0.008	0.008
Salmonella spp.	71	0.008 to 0.120	0.008	0.03
Serratia marcescens	132	0.008 to 32	0.03	0.125
Serratia spp.	43	0.016 to 0.25	0.03	0.125
Shigella sonnei	27	0.008	0.008	0.008
Shigella spp.	35	0.008 to 0.5	0.008	0.016
Stenotrophomonas maltophilia	66	1 to 32	32	32
Anaerobes				
Actinomyces israelii	11	0.06 to 2	0.125	1
Actinomyces odontolyticus	36	0.06 to 4	0.5	0.5
Actinomyces viscosus	15	0.06 to 1	0.125	0.5
Actinomyces spp.	15	0.008 to 2	0.25	1
Anaerobiospirillum thomasii	15	0.016 to 0.03	0.016	0.016
Bacteroides caccae	13	0.125 to 2	1	1
Bacteroides capillosus	12	0.03 to 0.25	0.06	0.25
Bacteroides distasonis	39	0.125 to 8	1	8
Bacteroides fragilis	206	0.016 to > 16	0.25	2
Bacteroides ovatus	55	0.25 to 8	1	2
Bacteroides tectum	17	0.016 to 0.25	0.03	0.125
Bacteroides thetaiotaomicron	92	0.06 to 4	1	2
Bacteroides uniformis	23	0.12 to 2	1	2
Bacteroides vulgatus	35	0.03 to 8	0.25	1
Bacteroides spp.	69	0.016 to > 16	0.125	1
Bilophila wadsworthia	22	0.016 to > 32	0.125	16
Campylobacter gracilis	11	0.016 to 0.25	0.06	0.125

Clostridium bifermentans	12	0.016 to 0.125	0.06	0.06
Clostridium butyricum	12	0.125 to 1	0.25	0.25
Clostridium cadaveris	11	0.008 to 0.016	0.016	0.0158
Clostridium clostridioforme	13	0.125 to 4	1	2
Clostridium difficile	39	0.004 to 8	1	4
Clostridium innocuum	20	0.008 to 8	2	4
Clostridium perfringens	57	0.004 to 0.125	0.03	0.125
Clostridium ramosum	18	0.25 to 2	1	2
Clostridium spp.	27	0.016 to 1	0.125	0.5
Eubacterium lentum	28	0.25 to 2	1	1
Fusobacterium mortiferum	11	0.06 to 0.125	0.06	0.125
Fusobacterium naviforme	10	0.016	0.016	0.016
Fusobacterium russii	12	0.016 to 0.03	0.016	0.0158
Fusobacterium varium	15	0.016 to 0.06	0.06	0.06
Fusobacterium spp.	14	0.008 to 2	0.25	0.5
Gardnerella vaginalis	11	0.06 to 2	0.125	2
Lactobacillus spp.	29	0.03 to > 32	1	16
Peptostreptococcus micros	12	0.016 to 0.06	0.03	0.06
Peptostreptococcus tetradius	30	≤ 0.004 to 4	0.04	1
Porphyromonas canoris	10	0.016	0.016	0.016
Porphyromonas gingivalis	14	0.016	0.016	0.016
Porphyromonas macacae	15	0.016 to 0.03	0.016	0.03
Prevotella bivia (Bacteroides bivus)	14	0.016 to 0.5	0.125	0.25
Prevotella heparinolytica	14	0.06 to 0.25	0.125	0.125
Prevotella melaninogenica	12	0.03 to 0.5	0.125	0.5
Prevotella oralis	12	0.06 to 1	0.125	1
Prevotella oris	13	0.03 to 0.5	0.125	0.25
Prevotella spp.	19	0.016 to 1	0.06	0.25
Propionobacterium acnes	25	0.03 to 4	0.125	0.25
Veillonella spp.	21	0.016 to 4	0.125	1
Total	9911			
Aerobic Gram-positive	4173			
Aerobic Gram-negative	4502			
Anaerobes	1236			

* As per the NCCLS the term "methicillin-resistant" when applied to the staphylococci has referred to resistance to the antistaphylococcal β-lactamase stable penicillins while "methicillin-sensitive" meant susceptibility to these agents. Oxacillin, and not methicillin, is currently the agent of choice for screening for these organisms but the term "methicillin-resistant" is still commonly used to describe them. Staphylococcus aureus strains with oxacillin MICs ≤ 2 µg/mL and coagulase-negative staphylococci with oxacillin MICs ≤ 0.25 µg/mL can be considered methicillin-susceptible staphylococci (MSS) while S. aureus strains with oxacillin MICs ≥ 4 µg/mL and coagulase-negative staphylococci ≥ 5 µg/mL can be considered methicillin-resistant staphylococci (MRS).
† As per the NCCLS Streptococcus pneumoniae strains are considered penicillin-susceptible if their MICs to penicillin are ≤ 0.06 µg/mL; they are considered penicillin-intermediate if the penicillin MICs are between 0.12 and 1 µg/mL and penicillin-resistant if their penicillin MICs are ≥ 2 µg/mL.

Table 41: Ratios of MBC to MIC in Broth (Inoculum 10^5 CFU/mL)

Ertapenem				
	Strain Number	**MIC µg/mL**	**MBC µg/mL**	**MBC:MIC**
Streptococcus pneumoniae	ATCC 49619	0.125	0.125	1
Staphylococcus aureus	ATCC 29213	2	2	1
Staphylococcus aureus	MB 210	0.06	0.06	1
Escherichia coli	ATCC 25922	0.016	0.016	1
Pseudomonas aeruginosa	ATCC 27853	8	8	1
Pseudomonas aeruginosa	MB 3286	16	32	2
Haemophilus influenzae	ATCC 49247	0.06	0.06	1
Morganella morganii	MB 2834	≤ 0.03	≤ 0.03	~1
Serratia marcescens	MB 2855	≤ 0.03	≤ 0.03	~1
Susceptibility Distribution with Multiple Isolates	**No.**	**MIC_{90} µg/mL**	**MBC_{90} µg/mL**	**MBC_{90}:MIC_{90}**
Acinetobacter baumannii	32	16	16	1
Pseudomonas aeruginosa	25	32	32	1
Citrobacter freundii	16	0.5	0.5	1
Enterobacter cloacae	16	4	4	1
Escherichia coli	18	0.125	0.06	0.5
Klebsiella oxytoca Klebsiella	15	≤ 0.03	≤ 0.03	~1
pneumoniae Morganella	15	0.25	0.25	1
morganii Proteus mirabilis	15	0.06	0.06	1
Proteus vulgaris	15	≤ 0.03	≤ 0.03	~1
Serratiamarcescens	15	≤ 0.03	0.06	~2
Neisseria meningitidis	14	8	8	1
Enterococcus faecalis	14	≤ 0.03	≤ 0.03	~1
	20	32	32	1

Resistance to Ertapenem

In vitro studies, which have focused on gram-negative pathogens, have partially elucidated the mechanisms of resistance to ertapenem. These studies suggest that the main forms of resistance to ertapenem in gram-negative bacilli, involve combinations of reduced accumulation (due to decreased influx and/or increased efflux) and β-lactamase hydrolysis.

In vitro development of resistance to ertapenem has been studied in Pseudomonas aeruginosa and in Escherichia coli strains. In a P. aeruginosa strain, resistance rates ranged from $2x10^{-7}$ at 2 times MIC to 2.2x10-9 at 8 times the MIC. In E. coli strains expressing either low levels of AmpC β-lactamase or significant amounts of β-lactamases TEM-1 or SHV-1, frequencies at 4 to 8 times MIC were in the range of 4x10-8 to 3x10-9. Frequencies obtained with E. coli clinical strains containing ESβLs ranged from 3.3x10-7 to 8x10-8 (Table 42).

Although cross-resistance between ertapenem and other carbapenems is possible, in vitro studies and surveillance studies indicate that cross-resistance between ertapenem and other

carbapenems is not complete. Target-based cross-resistance with non-β-lactam antimicrobials is not anticipated as β- lactams do not share common mechanisms of actions with these agents.

Stability of Ertapenem to Beta-Lactamases

Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, cephalosporinases, and extended spectrum beta-lactamases. Ertapenem is hydrolyzed by metallo-beta- lactamases. Table 42 shows *in vitro* activity of ertapenem against strains producing extended spectrum β-lactamase (ESβLs) and AmpC β-lactamase.

Table 42: *In Vitro* Activity of Ertapenem Against Strains Producing Extended Spectrum Beta-Lactamases (ESβLs) and AmpCbeta-Lactamases

Strains (n)	Wild-type			Resistant/Mutant Organisms		
	MIC Range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL
Escherichia coli wild-type† (47) and ESβL-resistant (32)	≤ 0.015 to 0.06	≤ 0.015	≤ 0.015	≤ 0.015 to 1	0.06	0.5
Klebsiella pneumoniae wild-type† (38) and ESβL-resistant (61)	≤ 0.015 to 0.5	≤ 0.015	≤ 0.015	≤ 0.015 to 16	0.06	0.5
Enterobacteriaceae‡ wild-type† (20) and SD AmpC§-resistant (93)	≤ 0.015 to 8	≤ 0.015	0.12	≤ 0.015 to 32	0.25	1
Enterobacteriaceae (76)%	NA			≤ 0.015 to 16	0.06	0.5
Klebsiella pneumoniae wild-type (25)	0.007 to 0.06	0.007	0.007			
Klebsiella oxytoca wild-type (25)	0.007 to 0.015	0.007	0.007			
Klebsiella spp. ESβL¶ (181)				0.007 to 8	0.03	0.06
Klebsiella spp. AmpC (7)				0.015 to 0.06	0.03	
Klebsiella oxytoca HP K1 (19)				0.007 to 0.125	0.015	0.015
Enterobacteriaceae						
Isogenic strains wild-type AmpC (18)						
Constitutive AmpC (14)	0.007 to 0.25	0.015	0.06	0.007 to 0.5	0.015	0.25
Defective AmpC (18)				0.004 to 0.015	0.007	0.015

Escherichia coli ESβL (47)	NA			0.004 to 0.5	0.015	0.03
Klebsiella pneumoniae ESβL (101)				0.004 to 0.25	0.015	0.06
*Enterobacter aerogenes ES*βL (24)				0.015 to 8	0.03	0.5
Enterobacter aerogenes AmpC wild-type (6)	0.007 to 0.25	0.06	#			
Enterobacter aerogenes AmpC mutant (13)				0.12 to 8	0.12	1.0
Enterobacter cloacae AmpC wild-type (9)	0.06 to 0.5	0.06	#			
Enterobacter cloacae AmpC mutant derepressed				0.12 to 2	0.25	1.0
(12)*Morganella morganii* AmpC wild-type (11)	0.007 to 0.015	0.007	0.015			
Morganella morganii AmpC mutant (9)				0.007 to 0.12	0.015	#
Serratia marcescens AmpC wild-type (15)	0.007 to 0.5	0.03	0.12			
Serratia marcescens AmpC mutant (5)				0.06 to 0.25	0.12	#
Serratia marcescens AmpC +porin mutant (1)				8	#	#

† Wild-type = susceptible to ceftazidime and many other 3rd generation cephems.
‡ Includes C. freundii (30) and Enterobacter spp. (83).
§ SD AmpC = stably derepressed, expression of AmpC cephalosporinase.
% Data includes: ESβL TEM (19) SHV (33) Chromosomal constitutive AmpC (12), Plasmid-borne AmpC (12).
¶ EsβL = ceftazidime: ceftazidime + clavulanate MIC ratio ≥ 16 by agar dilution.
# Not determined sample size < 10.
MIC = Minimal inhibitory concentration.
NA = Not applicable

.

Parameters of *in Vitro* Susceptibility Testing

MIC values of ertapenem against Staphylococcus aureus increased 4- to 8-fold in the presence of 50% human serum while they increased 2- to 4-fold against Klebsiella pneumoniae. Heat inactivation of human serum did not alter the serum effects on MIC values, suggesting that increases were most likely attributable to the effects of plasma protein binding. The low serum effect on the susceptibility of K. pneumoniae against ertapenem is consistent with the concept of reversible serum protein binding of ertapenem. Although the presence of serum increased the MIC of ertapenem by 2- to 8-fold, the bactericidal effect as demonstrated by the MBC/MIC ratio was unaffected by serum (equal to 2-fold).

The activity of ertapenem was not affected by the addition of the standard 5% sheep blood or 3% horse blood. A significant decrease in the activity of ertapenem was observed in thioglycollate broth and in brain heart infusion broth containing L-cysteine.

Sets of trays containing serial dilutions of ertapenem in cation-adjusted Mueller-Hinton broth (MHB) (pH 7.3) were stored in sealed plastic bags at various temperatures and for various periods of time and thereafter assayed for activity by the broth microdilution method. The activity of ertapenem was unchanged following storage for at least 3 months at -70 °C, for at least 4 weeks at -20 °C, for at least 7 days at 4 °C and at 23° to 25 °C and for at least 2 to 3 days at 37 °C. The effects of incubation in MHB at 37 °C on the stability of ertapenem were determined. Over 80% of intact ertapenem remained after 7 hours of incubation, which decreased to about 67.3% by 24 hours.

The effect of inoculum on in vitro susceptibility was studied against a variety of organisms including Staphylococcus aureus, members of the Enterobacteriaceae (including those producing ESβLs and/or AmpC β-lactamases), Pseudomonas aeruginosa, and Acinetobacter species. The inocula evaluated varied in different studies with the highest inoculum tested being 1000-fold greater than the control inoculum. No inoculum effect was demonstrated for S. aureus. For Enterobacteriaceae, an inoculum effect was demonstrated against some, but not all, organisms studied, but in all cases the ertapenem MIC90 values remained ≤ 2 µg/mL at the higher inocula. The greatest increase in MIC values was observed in Enterobacteriaceae expressing one or more extended-spectrum and/or broad-spectrum β- lactamase. For example, in one study the inocula tested ranged from 6x105 to 6x106 cfu/mL to 1.8x106 to 1.8x107 cfu/mL. In each case, the higher inoculum was 10-fold higher than the lower inoculum. In a study of a panel including E. coli clinical isolates containing broad- spectrum β-lactamases (BDSβLs) TEM-1 and SHV-1, and the ESßLs TEM-7, TEM-12, and TAZ-25 and K. pneumoniae isolates containing the ESßLs TEM-5, TEM-10, TAZ-3 and TAZ-10, as well as 1 unidentified β-lactamase, ertapenem MICs at the lower inoculum ranged from ≤ 0.03 µg/mL to 0.12 µg/mL. At 10-fold higher inocula, increased MICs for ertapenem were noted against many of the strains containing BDSβLs and ESßLs; however, in all cases the ertapenem MIC values remained ≤ 2 µg/mL. In another study, the activity of ertapenem was evaluated in routine MIC tests and at 100 times the standard inocula against 100 well characterized clinical and laboratory strains of Enterobacteriaceae expressing the following enzymes: TEM-1, 3-10, 12, 16, 24, 26, 50, SHV-1, 2-

5, 7, Toho-1 and 2, OXA-2, K1, inducible AmpC, MIR-1, LAT-2, ACT-1, FOX-3 and several unidentified plasmid-borne AmpC enzymes and TEM-derived ESßLs. The MIC90 of ertapenem against these strains was 0.5 µg/mL at the lower inoculum; at the higher inocula, the MIC90 of ertapenem increased to 1 µg/mL.

A broth microdilution checkerboard study of synergy was carried out for combinations of ertapenem and ciprofloxacin, and of ertapenem and gentamicin against methicillin-sensitive S. aureus, methicillin-sensitive coagulase-negative staphylococci, E. coli, and K. pneumoniae. No antagonism was demonstrated. Synergy, complete or partial, was seen with < 50% of the strains for either combination.

Dilution Techniques
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method(a) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ertapenem powder. The MIC values should be interpreted according to criteria provided in Table 43.

Diffusion Techniques
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[(b)] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 µg ertapenem to test the susceptibility of microorganisms to ertapenem. The disk diffusion interpretive criteria are provided in Table 43.

Anaerobic Techniques
For anaerobic bacteria, susceptibility to ertapenem as MICs can be determined by standardized test methods[(c)(d).] The MIC values obtained should be interpreted according to the criteria provided in Table 43.

Table 43: NCCLS Interpretive Susceptibility Criteria for Ertapenem

	Dilution Test (MICs in µg/mL)			Disk Diffusion Test (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤ 2	4	≥ 8	≥ 19	16–18	≤ 15
Staphylococcus spp.	≤ 2	4	≥ 8	≥ 19	16–18	≤ 15
Streptococcuspneumoniae (penicillin- susceptible non-meningitis strains only)[b]	≤ 1[c]	2	≥ 4	–	–	–
Streptococcus spp. (beta-hemolytic only)[a,d]	≤ 1[c]	–	–	–	–	–
Haemophilus spp.[a]	≤0.5[e]	–	–	≥ 19[f]	–	–

Anaerobes	≤ 4[g]	8	≥ 16	–	–	–

S = Susceptible; I = Intermediate; R = Resistant.

a The current absence of data on resistant strains precludes defining any category other than "susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

b Isolates of *Streptococcus pneumoniae* should be tested against a 1 µg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to penicillin and can be considered susceptible to ertapenem.

c *Streptococcus pneumoniae* that are susceptible to penicillin (MIC ≤ 0.06 µg/mL) and *Streptococcus* spp. other than *S. pneumoniae* that are susceptible to penicillin (MIC ≤ 0.12 µg/mL), can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

d *Streptococcus* spp. should be tested with a 10-unit penicillin disk. Isolates with penicillin zone sizes of ≥ 24 mm are susceptible to penicillin and can be considered susceptible to ertapenem.

e These interpretive standards are applicable to the broth microdilution procedure using *Haemophilus* Test Medium (HTM) inoculated with a direct colony suspension and incubated in ambient air at 35 °C for 20–24 hrs.

f These zone diameters are applicable to tests performed by disk diffusion using *Haemophilus* Test Medium (HTM) agar inoculated with a direct colony suspension and incubated in 5% CO_2 at 35 °C for 16–18 hrs.

g These interpretative standards are applicable only to agar dilution using *Brucella* agar supplemented with hemin, vitamin K1 and 5% defibrinated or laked sheep blood inoculated with a direct colony suspension or a 6- to 24-hour fresh culture in enriched thioglycollate medium and incubated in an anaerobic jar or chamber at 35–37 °C for 42–48 hrs.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control (QC)

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard ertapenem powder should provide the following range of values noted in Table 44. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 44: Acceptable Quality Control (QC) Ranges for Ertapenem

QC Strain	ATCC®	Dilution Test (MICs in µg/mL)	Disk Diffusion Test (zone diameters in mm)
Enterococcus faecalis	29212	4–16	Not Applicable
Staphylococcus aureus	29213	0.06–0.25	Not Applicable
Staphylococcus aureus	25923	Not Applicable	24–31
*Streptococcus pneumoniae*h	49619	0.03–0.25i	28–35j
Escherichia coli	25922	0.004–0.016	29–36
Haemophilus influenzae	49766	0.016–0.06k	27–33l
Pseudomonas aeruginosa	27853	2–8	13–21
Bacteroides fragilis	25285	0.06–0.25m (0.06–0.5)n	Not Applicable
Bacteroidesthetaiotaomicron	29741	0.25–1.0m (0.5–2.0)n	Not Applicable
Eubacterium lentum	43055	0.5–2.0m (0.5–4.0)n	Not Applicable

h This organism is used for quality control of susceptibility testing of Streptococcus pneumoniae and Streptococcus spp.
i These quality control ranges are applicable to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35 °C for 20–24 hrs.
j These quality control ranges are applicable to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% sheep blood inoculated with a direct colony suspension and incubated in 5% CO 2 at 35 °C for 20–24 hrs.
k These quality control ranges are applicable to the broth microdilution procedure using Haemophilus Test Medium (HTM) inoculated with a direct colony suspension and incubated in ambient air at 35 °C for 20–24 hrs.
l These quality control ranges are applicable to tests performed by disk diffusion using Haemophilus Test Medium (HTM) agar inoculated with a direct colony suspension and incubated in 5% CO 2 at 35 °C for 16–18 hrs.
m These quality control ranges are applicable only to agar dilution using Brucella agar supplemented with hemin, vitamin K1 and 5% defibrinated or laked sheep blood inoculated with a direct colony suspension or a 6- to 24-hour fresh culture in enriched thioglycollate medium and incubated in an anaerobic jar or chamber at 35–37 °C for 42–48 hrs.
n Quality control ranges applicable for broth microdilution method.
ATCC® is a registered trademark of the American Type Culture Collection.

16 NON-CLINICAL TOXICOLOGY

Animal Pharmacology

The pharmacologic assays were part of a screening effort to assess potential liabilities of the compound.

In Vivo

Pharmacokinetics

Ertapenem showed no interaction with the cardiovascular system, respiratory system, or gastrointestinal function.

Tissue distribution was assessed in rats by measuring the concentration of total radioactivity in various tissues after single dose administration of radiolabeled ertapenem. Following

administration of a single 15 mg/kg IV dose of [14C] ertapenem, concentrations declined with time in all tissues (Table 45). At 0.5 hr post dose, the concentrations (radio equivalents) were highest in the liver, kidneys, small intestine, and plasma. The kidneys consistently contained the highest concentrations, which occurred most likely because ertapenem radio equivalents are eliminated primarily by renal excretion. With the exception of the kidney (~6 µg/g), ertapenem radio equivalent concentrations at 72 hr post dose had declined to less than 0.7 µg/g in all tissues.

Table 45: Tissue Concentrations of Radioactivity in Rats After IV Administration of 15 mg/kg [^{14}C] Ertapenem

Tissue	Ertapenem Radioequivalents(µg/g)							
	0.5 hr		3 hr		24 hr		72 hr	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Heart	4.99	1.66	0.525	0.299	0.176	0.015	0.07	0.01
Lungs	5.80	2.31	1.19	0.09	0.211	0.048	0.15	0.01
Liver	18.2	3.67	55.4	12.7	11.9	1.8	0.36	0.05
Kidneys	71.7	25.0	81.9	25.6	7.82	0.39	5.55	0.74
Spleen	3.31	1.04	2.10	2.47	0.163	0.054	0.65	0.15
Testes	4.54	0.60	1.04	0.41	0.102	0.008	0.08	0.01
Stomach	4.72	1.10	0.68	0.18	1.59	0.92	0.08	0.01
Small Intestine	31.5	7.3	22.1	13.3	1.99	0.92	0.08	0.01
Large Intestine	4.16	3.60	0.801	0.377	7.58	2.15	0.12	0.04
Cecum	6.31	0.73	2.61	1.60	15.4	6.5	0.13	0.03
Fat	3.94	2.00	1.53	1.19	0.063	0.028	0.08	0.02
Pancreas	6.04	1.64	0.444	0.19	0.289	0.146	0.11	0.03
Muscle	5.95	1.47	0.280	0.14	0.131	0.011	0.04	0.00
Skin	18.4	6.7	0.787	0.13	0.585	0.093	0.37	0.04
Mesenteric Lymph Nodes	7.03	0.93	0.780	0.24	0.154	0.012	0.11	0.03
Adrenals	12.6	2.8	1.24	0.74	0.393	0.057	0.16	0.04
Brain	0.622	0.123	0.062	0.02	0.005	0.007	0.00	0.00
Plasma	54.1	9.8	4.06	0.20	0.571	0.049	0.16	0.01

Shown as the mean and S.D. of three animals per time point.

Ertapenem was transferred from the maternal to the fetal circulation (3% and 174% of maternal plasma concentrations at 5 and 240 minutes after dosing, respectively), when administered at 700 mg/kg/day to pregnant rats.

Cardiovascular and Respiratory System

Ertapenem was evaluated for cardiovascular response in the conscious, remote monitored dog. Measurements of blood pressure (BP) and heart rate (HR) were conducted to determine indicators of potential cardiovascular effects outside the normal sphere of the test compound's actions. Ertapenem administered at 10 mg/kg IV had no effect on BP and/or HR when compared to the placebo controls. Arterial BP and HR responses to ertapenem (100 mg/kg IV) were also determined in the hypertensive rat. No significant effects on either systolic or diastolic BP or HR were detected when compared to vehicle controls.

Furthermore, BP, HR, electrocardiogram (ECG), air flow, and respiratory rate were also measured in the anesthetized cat as indicators of potential cardiovascular and respiratory effects in response to ertapenem. A 100 mg/kg IV dose showed no effect on either systolic or diastolic BP. At 1 minute post dose, a transitory increase in HR was detected but was not considered significant. No effects on respiratory parameters were observed in the cat. Respiratory parameters measured in anesthetized guinea pigs also were not statistically different in baseline values between groups following a
100 mg/kg IV dose of ertapenem.

Central Nervous System

To assess any behavioral changes brought on by ertapenem (100 mg/kg IV dose), parameters including locomotor activity, muscle tone, stereotypy, straub tail, salivation, ptosis, tremors, righting reflex, mydriasis, convulsions, lethality, body temperature circulation, respiration, and other measurements were evaluated and showed no significant changes over vehicle-treated mice. Central nervous system (CNS) stimulation or depression due to ertapenem was assessed by measuring decrease or increase in barbiturate-induced sleep time in mice. Ertapenem was reported inactive in all instances.

Gastrointestinal System

A direct measure of intestinal motility and gastrointestinal function was explored in mice with the use of the charcoal meal test. This analysis determines the possible side effects of ertapenem on intestinal transit. No changes at a dose of 100 mg/kg IV of ertapenem were observed when compared to the (water) control animals.

The influence of ertapenem on gastric acid secretion was evaluated in anesthetized rats. No significant activity over normal was detected based on acid secretion over time in response to the 100 mg/kg IV dose of ertapenem.

Urinary Tract

The diuretic evaluation of ertapenem administered IV at 100 mg/kg body weight was conducted in conscious Wistar rats. Compared to the control group, ertapenem demonstrated no change in water, sodium, potassium, and chloride excretion and osmolality over a period of up to 6 hours after IV administration.

Other Systems

To determine the sedative liability or muscle relaxant properties of ertapenem, 8 trained male Wistar rats were administered 100 mg/kg IV and then placed on a rotating rod for a 1-minute period at 15, 30, 60, 90, and 120 minutes after dosing to assess motor coordination. All rats were able to perform this coordinated locomotor task and, thus, ertapenem was inactive in this study.
To evaluate its effect on acute inflammatory edema, ertapenem was administered at 100 mg/kg IV 1 hour prior to injection of edema-producing carrageen in into the right hind paw of male Wistar rats. Edema was inhibited 14% by ertapenem; this level of inhibition was not significant compared to vehicle-treated animals (student's t-test, $p<0.05$).

The dose rate of 100 mg/kg ertapenem was evaluated in 10 Swiss Webster male mice for local anesthetic activity following intramuscular injection in the area of the sciatic nerve. All animals were able to use the injected limb to walk normally both upright and inverted on a wire mesh screen.
Therefore, ertapenem was devoid of effects in this assay.

No significant activities were observed in a variety of in vitro tissue preparations to assess potential antagonist and agonist effects. Biochemical assays further demonstrate the specificity of ertapenem as an antibacterial agent. Specifically, ertapenem (100 µM) did not demonstrate lipoxygenase or cyclooxygenase activity as evidenced by a lack of effect on LTB4 and TXB2 generation in human whole blood. Ertapenem (100 µM) also did not alter ADP-induced aggregation of human citrated platelet rich plasma.

Growth rates of tumor cells (KB nasopharyngeal carcinoma cell line and HeLa cells) were not influenced by 10 and 100 µM ertapenem, and no significant inhibition of microsomal squalene synthetase was observed at 25 µM ertapenem. Ertapenem exhibited no cytotoxicity in COLO 205 cells at concentrations from 10-8 to 10-3 M.

The effect of ertapenem on the intrinsic and extrinsic coagulation pathways was determined using the plasma from male Sprague Dawley(SD) or Alderly Park(AP) rats administered 100 mg/kg IV and measured by the activated partial thromboplastin time (APTT) and prothrombin time (PT) assays, respectively. In these tests, the ertapenem-treated group was not significantly different from vehicle control.

The effect of ertapenem on the fibrinolytic system was determined using the plasma from male SD or AP rats dosed with 100 mg/kg IV and measured by the Euglobulin Clot Lysis (ECLT) assay. The ertapenem-treated group was not significantly different from vehicle control and, therefore, no profibrinolytic or antifibrinolytic activity was detected.

Animal Toxicology

General Toxicology:

Acute Toxicity

In rats and mice, the approximate LD50 was greater than 700 mg/kg IV of ertapenem for both species since all animals survived until the end of the 14-day observation period. In an additional study in mice conducted as a range-finding study, the approximate 3-day LD_{50} was> 2000 mg/kg. In mice that received a single oral dose of 500 mg/kg ertapenem, all mice survived through the 7-day observation period, and therefore the approximate LD50 was> 500 mg/kg. An acute nephrotoxicity study in rabbits indicated that the drug was not nephrotoxic at a dose of 225 mg/kg.

A treatment-related decrease in absolute neutrophil count was first observed in a 5-week intravenous toxicity study in rats at doses of 30, 60, and 180 mg/kg/day. The lowest dose in repeat-dose studies in rats in which a treatment-related decrease in neutrophils occurred was 2 mg/kg/day. The decrease in neutrophil count did not progress with continued dosing, and for most groups, the magnitude of the change diminished over the course of the study. Similar changes occurred in the 14-week and 27-week studies in rats. In each study, there was no evidence of a compensatory left shift, and there were no histopathologic changes in any organ, including the bone marrow. Furthermore, this change occurred in the absence of any treatment-related physical signs (except for slight injection site irritation at 675 mg/kg/day) or changes in body weight gain.

This change in neutrophil count was shown to require at least 2 doses of ertapenem and to be reversible after discontinuation of treatment. It was not accompanied by changes in the bones, bone marrows, or bone marrow smears.

Rats that had an ertapenem-induced decrease in neutrophils had this change reversed by subcutaneous injections of granulocyte colony stimulating factor (G-CSF; ®NEUPOGEN*). Following a 6- day treatment with G-CSF, the neutrophil counts returned to the levels of controls, and remained in that range following cessation of the G-CSF treatment.

Studies in rhesus monkeys were inconclusive with regard to the effect on neutrophil counts. Table 46 reports long term (repeat-dose) studies in several species.

®NEUPOGEN* (filgrastim), Registered Trademark of Amgen Canada Inc.

Table 46: Long-Term Toxicity

Species/ Sex/ No. per Group	Duration/Route	Dosage Levels mg/kg/day	Parameters Evaluated	Findings
General Toxicology				
Rabbit New Zealand White 2 females 1 male	15 days/IV	100	Physical examination, body weight, hematology, urinalysis (occult blood, erythrocytes), clinical chemistry (urea nitrogen and creatinine), gross and histomorphologic examination of kidneys.	No treatment-related changes; no-effect level ≥ 100 mg/kg/day.
Rabbit New Zealand White 8 females/group 8 males/group	15 days/IV	60	Physical examination, body weight, clinical chemistry, gross and histomorphologic examination of liver.	Mortality, diarrhea, body weight loss, decreased food consumption, reddish urine, increased ALT, triglycerides, and/or AST in 1 rabbit/sex, increased serum cholesterol. No treatment-related gross or histomorphologic changes in the livers. Changes similar to meropenem effects in rabbits.
Monkey *Macaca mulatta* 2 males 2 females	15 days/IV	200	Physical examination, body weight, food consumption, hematology, clinical chemistry, urinalysis, necropsy, histopathology.	Unformed stools, increased serum ALT. No treatment-related gross or histomorphologic changes.
Rat Crl:CD® (SD) BR 15 males/group 15 females/group	5 weeks/IV	30, 60, 180	Physical examination, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, plasma drug levels, necropsy, organ weights, histopathology.	Decreased neutrophil counts at all doses, increased urinary urobilinogen in high dose. No treatment-related gross, organ weight, or histomorphology changes. Toxicokinetic parameters similar in female and males. Systemic exposure (AUC) (µg·hr/mL) for females/males was 142/130, 148/168, and 264/240 for the low, mid, and high doses, respectively. Terminal half-life was approximately 42 minutes.

Subacute Toxicity Studies				
Rat Crl:CD® (SD)BR 15 males/group 15 females/group	11 weeks/IV	2, 10, 60	Physical examination, body weight, food consumption, hematology (differential leukocyte count).	Treatment-related decrease in neutrophil counts that increased during the recovery period to levels similar to the concurrent controls and generally within the normal range.
Rat Crl:CD® (SD)BR 15 females	15 days/IV	60	Physical examination, body weight, food consumption, hematology (differential leukocyte count), necropsy, histopathology.	Decreases in absolute neutrophil counts that were not accompanied by any histomorphologic changes in the bone or bone marrow.
Rat Crl:CD® (SD)BR 10 or 20 females/group	21 days/IV	MK-0826: 60 G-CSF: 25µg/kg/day	Physical examination, body Weight,hematology(differential leukocyte count).	Decreases in absolute neutrophil counts that were ameliorated by G-CSF treatment.
Rat Crl:CD® (SD)BR 15 females/group 15 males/group	14 weeks/IV	75, 225, 675	Physical examination, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, plasma drug levels, necropsy, organ weights, histopathology.	Decreases in absolute neutrophil counts at all doses. Injection site irritation at the high dose. One mid-dose and 2 high-dose rats had a thrombocytopenia associated with decreases in erythroid parameters, decreases in erythrocytes, hemoglobin, hematocrit, decreases in serum protein, and ALT, increases in A/G ratio, urinary bilirubin and ketones at all doses. Mean AUC (µg·min/mL) for female/males was 11,134/9333, 16,401/13,592, and 34,897/36,022 at 75, 225, and 675 mg/kg/day, respectively. Terminal half- life was approximately 50 to 55 minutes.

Monkey *Macaca mulatta* 4 males/group 4 females/group	5 weeks/IV	30, 60, 180	Physical examination, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, plasma drug levels, necropsy, organ weights, histopathology.	Unformed stools, increases in ALT at all doses. Systemic exposure (AUC) (µg·min/mL) for females/males was 78,870/83,438; 76,520/73,423; and 124,954/136,588 for the low, mid, and high doses, respectively. Terminal half-life was approximately 300 minutes.
Monkey *Macaca mulatta* 4males/group 4 females/group	14 weeks/IV	40, 120, 360	Physical examination, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, plasma drug levels, necropsy, organ weights, histopathology.	Unformed stools, increases in ALT at all doses. Salivation at the high dose. No organ weight, gross, or histomorphologic changes at any dose. Systemic exposure (AUC) (µg·min/mL) for females/males was 66,087/66,446; 91,939/101,172; and 186,341/193,475 for the low, mid, and high doses, respectively. Terminal half-life was approximately 280 minutes.

Monkey *Macaca mulatta* 4 males/group 4 females/group	5 weeks/IV	500, 750, 1250	Physical examination, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, plasma drug levels, necropsy, organweights, histopathology.	Salivation, liquid/unformed stools, and emesis at all doses; decreased activity, crouching at mid and high doses, increases in serum ALT, phosphorus, triglycerides, urinary bilirubin at all doses; decreases in serum chloride in high dose only; kidney pallor at all doses; increases in kidney and liver weights at all doses; cytoplasmic rarefaction and vacuolation in cortical tubular epithelial cells of kidneys at all doses; in liver, hepatocellular swelling at all doses and single cell necrosis of hepatocytes at the mid and high doses. Plasma AUC0-24hr (µg•min/mL) for females/males: 210,000/236,190; 294,375/246,900; 378,480/382,590 at 500, 750, and 1250 mg/kg/day, respectively, in Drug Week 1. Terminal half-life of 4.55 to 5.32 hours. Similar values in Drug Week 4/5.
Chronic Toxicology Studies				
Rat Crl:CD® (SD)BR 15 females/group 15 males/group	27 weeks/IV	60, 180, 540	Physical examination, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, plasma drug levels, necropsy, organ weights, histopathology.	Decreases in neutrophils at all doses, decreases in serum protein in females at all doses, increases in A/G ratio at all doses in males and mid and high doses in females, increases in urinary bilirubin at all doses in males. Plasma AUC0-5 hr (µg·min/mL) for females/males: 10,298/7705; 14,001/11,007; 24,692/20,311, respectively, for the low, mid, and high doses. Mean terminal half-life of approximately 50 minutes.

Monkey *Macaca mulatta* 4 males/group 4 females/group	27 weeks/IV	40, 120, 360	Physical examination, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, necropsy, organ weights, histopathology.	Loose/unformed stools, low incidence of rectal prolapse at all doses, low incidence of emesis at mid and high doses, transient salivation at high dose, increases in ALT at all doses, increases in kidney weights at all doses, tubular cytoplasmic rarefaction and luminal eosinophilic granularity at all doses.
Reproductive Toxicology Studies				
Rat Crl:CD® (SD)BR 24 females/group	2 weeks prior to cohabitation – GD 7/IV	70, 350, 700	Physical examination, food consumption, necropsy, reproductive parameters, C- section, counting of implants (live fetus, dead fetus, or resorption).	No treatment-related changes.
Rat Crl:CD® (SD)BR 25 males/group	29 days prior to cohabitation through GD 15/IV	175, 350, 700	Physical examination, food consumption, mating performance including fertility indices, embryonic/fetal survival, sperm count and motility, and testicular/epididymal organ weights and histology.	No treatment-related changes.
Embryo-Fetal & Perinatal Toxicology Studies				
Rat, pregnant Crl:CD® (SD)BR 10 females/group	GD 6 through LD 20/IV	75, 150, 350, 700	Physical examination, body weight, hematology, clinical chemistry, necropsy, reproductive parameters, fetal weight, fetal sex, fetal external examination, pup survival, pup weights.	Transient, soft feces at 700 mg/kg/day, increase in body weight gain at 700 mg/kg/day during lactation. No treatment-related effects on reproductive performance. In F1 generation, no effects on physical signs, pup weights, or external morphology.

Rat Crl:CD® (SD)BR 22 females/group	GD 6 through 20/IV	70, 350, 700	Physical examination, body weight, food consumption, necropsy, reproductive parameters, C-section, counting of implants (live fetus, dead fetus, or resorption), fetal weight, fetal sex, fetal external, visceral, and skeletal examination.	No treatment-related effects. No-effect level ≥ 700 mg/kg/day.
Rat Crl:CD® (SD)BR 22 females/group	GD 6 through LD 20/IV	70, 350, 700	Physical examination, body weight, food consumption, necropsy, reproductive parameters, pup evaluation including development and behavior.	During lactation, increases in maternal body weight gain at all doses. No treatment-related effects in either F1 or F2 generations. No-effect level for developmental toxicity ≥ 700 mg/kg/day.
Rabbit New Zealand White 6 females/group	14-days/IV	30, 150, 300, 700	Physical examination, body weight, food consumption, hematology, clinical chemistry.	Mortality≥ 150 mg/kg/day, diarrhea, decreased food consumption, soft feces, no feces, and/or no urine, reddish brown urine. Increases in serum AST, ALT, cholesterol, and triglycerides in 30 and 150 mg/kg/day groups. No-effect level was < 30 mg/kg/day.
Rabbit, pregnant 10 females/group	GD 7 through 20/IV	20, 60, 120	Physical examination, body weight, food consumption.	Mortality≥ 60 mg/kg/day. Increases in ALT. Rabbits considered unacceptable species for developmental toxicity evaluation.
Mouse, pregnant Crl:CD-1® (ICR) BR 10 females/group	GD 6 through 15/IV	75, 150, 350, 700	Physical examination, body weight, food consumption, C-section, fetal survival, fetal weight, fetal external examination.	No treatment-related changes.
Mouse Crl:CD-1® (ICR) BR 25 females/group	GD 6 through 15/IV	70, 350, 700	Physical examination, body weight, food consumption, necropsy, fetal external, visceral, and skeletal examination.	Decrease in fetal weight at high dose only with an associated decrease in average number of ossified sacrocaudal vertebrae. No-effect level: 350 mg/kg/day.

Rat Crl:CD® (SD) IGS BR 26 females	GD 6 through 20 GD 6 through LD 14/IV	700	Maternal plasma and milk concentrations of MK-0826, maternal and fetal plasma concentrations of MK-0826.	Mean maternal plasma concentrations were 1468 µg/mL and 2.85 µg/mL at 5 and 240 minutes post dosing, respectively. Fetal plasma concentrations at these times were 3% and 174% of the maternal concentrations. Maternal plasma concentration of MK-0826 in lactating rats was 138 µg/mL at 30 minutes post dosing, and MK-0826 milk concentration was 9.69 µg/mL.

GD = Gestation Day
LD = Lactation Day
IV = Intravenous

In a 14-week rat study, 2 of 15 males that received 675 mg/kg/day and 1 of 15 females that received 225 mg/kg/day had a thrombocytopenia, usually associated with decreases in the erythron in Drug Weeks 4, 8, and/or 12. The no-effect level for this change was 75 mg/kg/day. Similar changes were not observed in rats that received 30, 60, and 180 mg/kg/day for 5 weeks, or in rats that received doses as high as 540 mg/kg/day for 27 weeks. There were no microscopic changes in any tissues, including the bone marrow, of the rats on study, including the ones that had the thrombocytopenias (except for slight injection site irritation in some rats at 675 mg/kg/day).

Slight increases in serum ALT were observed both in monkeys and in female rabbits. There was a slight, non-dose-related increase in mean serum ALT in monkeys that received 30, 60, or 180 mg / kg / day in a 5-week study, and 40, 120, or 360 mg / kg/ day in 14- and 27-week studies. These increases were not progressive and not accompanied by any histopathologic change in the livers. In a 27- week study in monkeys at doses of 40, 120, and 360 mg / kg / day, and in a 5-week study in monkeys at doses of 500, 750, and 1250 mg/ kg / day, similar increases in serum ALT also occurred, as well as increases in serum triglycerides and phosphorus. There were treatment-related liver weight increases at doses of 500, 750 and 1250 mg / kg / day in monkeys in a 5-week study. The 5-week study also showed decreases in chloride in the high-dose group. There were increases in kidney weights and renal tubular cytoplasmic rarefaction in both the 27-week and higher dose 5-week study. The 27-week study also had luminal eosinophilic granularity observed, whereas the higher dose 5-week study had renal cortical tubular vacuolation. This slight difference may be due to a more severe change in the 5-week study resulting from the same process. Furthermore, in the higher dose 5-week study the kidneys were removed from the body cavity first because of the expectation that there were treatment-related renal changes. The higher dose 5-week study also had hepatocellular swelling at all doses and hepatocellular single cell necrosis at doses ≥ 750 mg/kg/day.

Carcinogenesis:
No long-term studies in animals have been performed to evaluate the carcinogenic potential of

ertapenem.

Genotoxicity:
Ertapenem was neither mutagenic nor genotoxic in the following in vitro assays: alkaline elution/rat hepatocyte assay, chromosomal aberration assay in Chinese hamster ovary cells, and TK6 human lymphoblastoid cell mutagenesis assay; and in the in vivo mouse micronucleus assay.

Reproductive and Developmental Toxicology:
Reproduction
In the female fertility study in rats, ertapenem was administered at dosages of 70, 350, 700 mg / kg / day. There were no deaths or treatment-related physical signs. There were no treatment-related effects on mating, fertility, or fecundity indices, or embryonic/fetal survival. The no-effect level of ertapenem for effects on female fertility was≥ 700 mg / kg / day.

In the male fertility study in rats, ertapenem was administered at dosages of 175, 350, and 700 mg/kg/day. There were no treatment-related effects on mating index, fertility index, fecundity index, embryonic/fetal survival, sperm count and motility, and testicular/epididymal organ weights or histology. The no-effect level of ertapenem for effects on male fertility was≥ 700 mg/kg/day.

Development
A developmental toxicity study was conducted in rats at doses of 70, 350, and 700 mg/kg/day to assess the effects of ertapenem on fetal survival, growth, and development. There were no treatment-related changes at any dose. An additional developmental toxicity study was conducted at the same doses in rats to assess ertapenem on reproductive performance of F0 females and to evaluate the effects on development, growth, behavior, reproductive performance and fertility of the F1 generation. During lactation there were significant treatment-related increases in mean maternal bodyweight gain at all doses (63 to 111% above controls). There were no treatment-related changes, including on reproductive performance, and effects on the F1 or F2 generations. A toxicokinetic study was conducted in rats to determine concentrations of ertapenem in maternal and fetal plasma and in maternal milk following intravenous administration of 700 mg/kg/day of ertapenem to pregnant rats from Gestation Day 6 through 20 or through Lactation Day 14. Ertapenem was transferred from the maternal to the fetal circulation (3% and 174% of maternal plasma concentrations at 5 and 240 minutes after dosing, respectively).

Doses of 70, 350, and 700 mg/kg/day of ertapenem were used in the mouse developmental toxicity study. There was no maternal toxicity up to the highest dose. Developmental toxicity was observed only in the 700-mg/kg/day group in the form of slight decreases in average fetal weight and an associated decrease in the number of ossified sacrocaudal vertebrae. There were no effects on embryo survival or fetal morphology. Based on these results, the no-effect level in mice for maternal toxicity was ≥ 700 mg/kg/day and for developmental toxicity was 350 mg/kg/day (approximately 1.5-fold the typical human dose

based on body surface area).

17 SUPPORTING PRODUCT MONOGRAPHS

INVANZ® powder for solution, 1 g/vial, submission control 260091, Product Monograph, Merck Canada Inc. JUNE 3, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] ERTAPENEM FOR INJECTION

Ertapenem for injection

Read this carefully before you start taking **ERTAPENEM FOR INJECTION** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ERTAPENEM FOR INJECTION.**

Serious Warnings and Precautions

- Some people taking beta-lactam antibiotics like ERTAPENEM FOR INJECTION have reported serious allergic reactions (serious skin rashes), that can occasionally lead to death.

- Some people have had seizures and other nervous system problems such as dizziness while taking ERTAPENEM FOR INJECTION .This occurs mostly in people who:
  - have had seizures in the past
  - currently take certain medicines (valproic acid, sodium valproate, and divalproex sodium) for seizures
  - have brain injuries or other brain diseases
  - have problems with their kidneys
- For further information and symptoms see:
  - the "To help avoid side effects and ensure proper use…" section
  - the "Serious side effects and what to do about them" table

What is ERTAPENEM FOR INJECTION used for?

ERTAPENEM FOR INJECTION is used in children and adolescents (3 months to 17 years of age) and adults to treat one of the following bacterial infections:

- Infection in the abdomen.
- Infection of the skin, including diabetic foot infections in adults.
- Lung infections caught outside of hospitals or other health care facilities (Community Acquired Pneumonia).
- Urinary Tract Infection(UTIs). UTIs happen when bacteria (germs) get into the bladder or kidneys.
- Pelvic infection.

- prevent infections at the surgical site following surgery of the colon or rectum in adults. The colon and rectum are parts of the digestive system.

Antibacterial drugs like ERTAPENEM FOR INJECTION treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, ERTAPENEM FOR INJECTION should be used exactly as directed. Misuse or overuse of ERTAPENEM FOR INJECTION could lead to the growth of bacteria that will not be killed by ERTAPENEM FOR INJECTION (resistance). This means that ERTAPENEM FOR INJECTION may not work for you in the future.

How does ERTAPENEM FOR INJECTION work?
ERTAPENEM FOR INJECTION is an antibiotic. It contains a medicine called ertapenem. Ertapenem belongs to the carbapenem class of antibiotics. ERTAPENEM FOR INJECTION has the ability to kill a wide range of bacteria that cause infections.

What are the ingredients in ERTAPENEM FOR INJECTION?
Medicinal ingredients: Ertapenem monosodium
Non-medicinal ingredients: Sodium hydrogen carbonate and sodium hydroxide.

ERTAPENEM FOR INJECTION comes in the following dosage forms:
ERTAPENEM FOR INJECTION comes as a powder to mix with a specific liquid and give as a shot into a muscle or a vein. ERTAPENEM FOR INJECTION is supplied in a single dose glass vial.

Each vial of ERTAPENEM FOR INJECTION contains: 1 g of ertapenem (as ertapenem monosodium).

Do not use ERTAPENEM FOR INJECTION if you are allergic to:
- ertapenem or any of the ingredients in ERTAPENEM FOR INJECTION **(see What are the ingredients in ERTAPENEM FOR INJECTION).**
- other beta-lactams antibiotics such as medications from the:
    - penicillins class.
    - cephalosporins class.

Do not inject ERTAPENEM FOR INJECTION into a muscle if you:
- are allergic to medications such as local anesthetics of the amide type especially lidocaine hydrochloride. Lidocaine is used to relieve pain when injecting ERTAPENEM FOR INJECTION into the muscle.
- are in severe shock.
- have a problem with your heart rhythm called heart block.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ERTAPENEM FOR INJECTION. Talk about any health conditions or problems you may have, including if you or your child has now or has had:
- Any medical conditions, especially:
    - kidney disease.

- history of seizures or other brain diseases.

- Allergies to:
  - other antibiotics, in particular penicillins and cephalosporines. If you are allergic to any of these antibiotics you may be allergic to ERTAPENEM FOR INJECTION.
    - any other drugs or any other substances such as foods, preservatives or dyes.
  - Are pregnant or plan on getting pregnant. ERTAPENEM FOR INJECTION has not been studied in pregnant women. You will need to talk with your healthcare professional about the potential benefit and risk of using ERTAPENEM FOR INJECTION while you are pregnant.
  - Are breast-feeding or planning to breastfeed. ERTAPENEM FOR INJECTION is excreted in human milk. If you intend to breast-feed, you will need to talk with your healthcare professional about any risks to your baby.

Children: Do not give ERTAPENEM FOR INJECTION to a child younger than 3 months of age.

Other warnings you should know about: While taking ERTAPENEM FOR INJECTION:

- If you develop severe diarrhea (very loose or watery stool), tell your healthcare professional right away. Do this even if it occurs several weeks after you stopped taking ERTAPENEM FOR INJECTION. Diarrhea may mean that you have a serious condition affecting your bowel (colitis). You may need urgent medical care. Do not try to treat loose stools without first checking with your healthcare professional (see the "Serious side effects and what to do about them" table below).

- Stop taking ERTAPENEM FOR INJECTION at the first sign of a skin rash and call your healthcare professional. Skin rash may be a sign of a more serious reaction to ERTAPENEM FOR INJECTION (see the "Serious side effects and what to do about them" table below).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ERTAPENEM FOR INJECTION:

- medicines called valproic acid or sodium valproate or divalproex sodium (used to treat seizures). ERTAPENEM FOR INJECTION may affect how well these medicines work to prevent seizures. You may need different amounts of this medicine, or you may need to take another medicine. Your healthcare professional will decide whether you should use ERTAPENEM FOR INJECTION with these medicines.
- a medication called probenecid (usually used to treat or prevent gout).

How to take ERTAPENEM FOR INJECTION:

Your healthcare professional may give ERTAPENEM FOR INJECTION by:

- intravenous infusion (injected slowly into a vein) over a period of 30 minutes.
- intramuscular injection (as a shot into a muscle).

Usual dose:

- The dose of ERTAPENEM FOR INJECTION will depend on the type of infection you or your child may have and how well your kidneys are working.
- Your healthcare professional will work out the right dose of ERTAPENEM FOR INJECTION for you or your child.
- Your healthcare professional will also tell you how long to use ERTAPENEM FOR INJECTION.
- Ask your healthcare professional if you have any questions about how many doses of ERTAPENEM FOR INJECTION you or your child will need or when you or your child will receive them.

Overdose:

If you think you, or a person you are caring for, have taken too much ERTAPENEM FOR INJECTION, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

The injection schedule will be set by your healthcare professional, who will monitor your response and condition to determine what treatment is needed. However, if you are concerned that you or your child may have missed a dose, contact your healthcare professional immediately.

What are possible side effects from using ERTAPENEM FOR INJECTION?

These are not all the possible side effects you may have when taking ERTAPENEM FOR INJECTION. If you experience any side effects not listed here, tell your healthcare professional.

Adults 18 years of age and older:

The most common side effects are:

- loose stool (diarrhea), nausea, vomiting
- problems with the vein where you had the ERTAPENEM FOR INJECTION shot. For example pain, tenderness, redness, swelling
- inflammation of blood vessels which may lead to blood clots
- headache

Other side effects in adults include:

- sore, creamy-yellow, raised patches in the mouth (oral thrush)
- teeth staining
- loss of appetite
- confusion, dizziness, sleepiness, sleeplessness
- low blood pressure, slow heart rate, shortness of breath
- abdominal pain
- acid regurgitation, constipation, indigestion
- dry mouth
- skin redness, itching, swelling at the injection site

- swelling, redness, burning, itching, or irritation of the vagina
- unusual tiredness or weakness, swelling, feeling unwell, fever, pain, chest pain, fungal infection, change in taste
- swelling of the lower limbs
- changes in some laboratory blood tests

Children and adolescents (3 months to 17 years of age):
Side effects in children are generally similar to those in adults. The most common side effects in children are:

- loose stools (diarrhea), vomiting
- rash
- pain, redness, swelling in the area where the child received the ERTAPENEM FOR INJECTION shot.

Other side effects in children include:

- oral thrush
- loss of appetite
- hot flush, high blood pressure
- wheezing
- pain in the abdomen, toothache, loose stools, gas, nausea
- diaper rash, skin redness, skin itching, skin rash (red or purple), flat pinhead spots under the skin
- burning, itching, redness and warmth at infusion site, redness or formation of lump at the injection site
- changes in some laboratory blood tests

Serious side effects and what to do about them			
Symptom/ effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Seizures		√	
Serious and sometimes deadly allergic reactions: • severe rash with or without high fever, itching, hives on the skin • swelling of the face, lips, tongue or other parts of the body • shortness of breath, wheezing or trouble breathing			√
Bowel infection (Clostridium difficile colitis): • diarrhea (very loose stool) that does not go away(bloody or			

watery) with or without : ○ fever ○ stomach cramps		√	
UNKNOWN			
Nervous system problems • decreased consciousness e.g. symptoms such as ○ persistent drowsiness ○ reduced response or awareness, slow to respond ○ shallow or irregular breathing, or stupor •abnormal movements tremors (shaking)		√	
Problems that affect behavioral health: •aggression •feeling restless •feeling lost or confused •seeing or hearing things that are not there (hallucinations) •mental status changes •change in thinking clearly		√	
Severe Cutaneous Adverse Reactions (SCAR): severe skin reactions that may also affect other organs: • Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish) • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough • Shortness of breath, chest pain or discomfort			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store lyophilized powder between 15^0C and 25^0C. Most of the time, ERTAPENEM FOR INJECTION will be given in a hospital or physician's office.

Keep ERTAPENEM FOR INJECTION and all medicines safely out of reach and sight of children.

If you want more information about ERTAPENEM FOR INJECTION:

- Talk to your healthcare professional
  Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) the manufacturer's www.auropharma.ca , or by calling 1-855-648-6681.

This leaflet was prepared by Auro Pharma Inc

Last Revised: January 17, 2023