Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INVANZ safely and effectively. See full prescribing information for INVANZ.

INVANZ® (ertapenem for injection) for intravenous (IV) or intramuscular (IM) use
Initial U.S. Approval: 2001

To reduce the development of drug-resistant bacteria and maintain the effectiveness of INVANZ and other antibacterial drugs, INVANZ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

----------INDICATIONS AND USAGE----------
INVANZ is a penem antibacterial indicated in adult patients and pediatric patients (3 months of age and older) for the treatment of the following moderate to severe infections caused by susceptible bacteria:
- Complicated intra-abdominal infections. (1.1)
- Complicated skin and skin structure infections, including diabetic foot infections without osteomyelitis. (1.2)
- Community-acquired pneumonia. (1.3)
- Complicated urinary tract infections including pyelonephritis. (1.4)
- Acute pelvic infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections. (1.5)

INVANZ is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery. (1.6)

---------- DOSAGE AND ADMINISTRATION----------
Do not mix or co-infuse INVANZ with other medications. Do not use diluents containing dextrose (α–D–glucose). (2.1)
INVANZ should be infused over 30 minutes in both the Treatment and Prophylactic regimens. (2.1)
Dosing considerations should be made in adults with advanced or end-stage renal impairment and those on hemodialysis. (2.4, 2.5)
Treatment regimen:
- Adults and pediatric patients 13 years of age and older. The dosage should be 1 gram once a day intravenously or intramuscularly. (2.2)
- Patients 3 months to 12 years of age should be administered 15 mg/kg twice daily (not to exceed 1 g/day intravenously or intramuscularly.) (2.2)
- Intravenous infusion may be administered in adults and pediatrics for up to 14 days or intramuscular injection for up to 7 days. (2.1)

Prophylaxis regimen for adults:
- 1 gram single dose given 1 hour prior to elective colorectal surgery. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Vial 1 gram. (3)
- ADD-Vantage® vial: 1 gram. (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to product components or anaphylactic reactions to β-lactams. (4)
- Due to the use of lidocaine HCl as a diluent, INVANZ administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type. (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious hypersensitivity (anaphylactic) reactions have been reported in patients receiving β-lactams. (5.1)
- Seizures and other central nervous system adverse experiences have been reported during treatment. (5.2)
- Co-administration of INVANZ with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures. (5.3)
- *Clostridium difficile*-associated diarrhea (ranging from mild diarrhea to fatal colitis): Evaluate if diarrhea occurs. (5.4)
- Caution should be taken when administering INVANZ intramuscularly to avoid inadvertent injection into a blood vessel. (5.5)

---------- ADVERSE REACTIONS ----------
Adults:
The most common adverse reactions (≥5%) in patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, were diarrhea, nausea, headache and infused vein complication. (6.1)
In the prophylaxis indication the overall adverse experience profile was generally comparable to that observed for ertapenem in other clinical trials. (6.1)
Pediatrics:
Adverse reactions in this population were comparable to adults. The most common adverse reactions (≥5%) in pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, were diarrhea, vomiting and infusion site pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Co-administration with probenecid inhibits the renal excretion of ertapenem and is therefore not recommended. (7.1)
- 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. (5.2, 7.2)

---------- USE IN SPECIFIC POPULATIONS ----------
- Renal Impairment: Dose adjustment is necessary, if creatinine clearance is ≤30 mL/min/1.73 m^2. (2.4, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Complicated Intra-Abdominal Infections
1.2 Complicated Skin and Skin Structure Infections, Including Diabetic Foot Infections without Osteomyelitis
1.3 Community Acquired Pneumonia
1.4 Complicated Urinary Tract Infections Including Pyelonephritis
1.5 Acute Pelvic Infections Including Postpartum Endomyometritis, Septic Abortion and Post Surgical Gynecologic Infections
1.6 Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery
2 DOSAGE AND ADMINISTRATION
2.1 Instructions for Use in All Patients
2.2 Treatment Regimen
2.3 Prophylactic Regimen in Adults
2.4 Patients with Renal Impairment
2.5 Patients on Hemodialysis
2.6 Patients with Hepatic Impairment
2.7 Preparation and Reconstitution for Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
5.2 Seizure Potential
5.3 Interaction with Valproic Acid
5.4 *Clostridium difficile*-Associated Diarrhea (CDAD)
5.5 Caution with Intramuscular Administration
5.6 Development of Drug-Resistant Bacteria
5.7 Laboratory Tests
6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
6.2 Post-Marketing Experience
6.3 Adverse Laboratory Changes in Clinical Trials
7 DRUG INTERACTIONS
7.1 Probenecid
7.2 Valproic Acid
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Renal Impairment
8.7 Patients with Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Adults
14.2 Pediatric Patients
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION
17.1 Instructions for Patients

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of INVANZ® and other antibacterial drugs, INVANZ 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.

Treatment

INVANZ is indicated for the treatment of adult patients and pediatric patients (3 months of age and older) with the following moderate to severe infections caused by susceptible isolates of the designated microorganisms *[see Dosage and Administration (2)].*

1.1 Complicated Intra-Abdominal Infections

INVANZ is indicated for the treatment of complicated intra-abdominal infections due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, or *Bacteroides uniformis*.

1.2 Complicated Skin and Skin Structure Infections, Including Diabetic Foot Infections without Osteomyelitis

INVANZ is indicated for the treatment of complicated skin and skin structure infections, including diabetic foot infections without osteomyelitis due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus* species, *Porphyromonas asaccharolytica*, or *Prevotella bivia*. INVANZ has not been studied in diabetic foot infections with concomitant osteomyelitis *[see Clinical Studies (14)].*

1.3 Community Acquired Pneumonia

INVANZ is indicated for the treatment of community acquired pneumonia due to *Streptococcus pneumoniae* (penicillin susceptible isolates only) including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates only), or *Moraxella catarrhalis*.

1.4 Complicated Urinary Tract Infections Including Pyelonephritis

INVANZ is indicated for the treatment of complicated urinary tract infections including pyelonephritis due to *Escherichia coli*, including cases with concurrent bacteremia, or *Klebsiella pneumoniae*.

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

INVANZ is indicated for the treatment of acute pelvic infections including postpartum endomyometritis, septic abortion and post surgical gynecological infections due to *Streptococcus agalactiae, Escherichia coli*, *Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species, or *Prevotella bivia*.

Prevention

INVANZ is indicated in adults for:

Reference ID: 3346441

1.6 Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery

INVANZ is indicated for the prevention of surgical site infection following elective colorectal surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Use in All Patients

For Intravenous or Intramuscular Use

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

INVANZ may be administered by intravenous infusion for up to 14 days or intramuscular injection for up to 7 days. When administered intravenously, INVANZ should be infused over a period of 30 minutes. Intramuscular administration of INVANZ may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate.

2.2 Treatment Regimen

13 years of age and older

The dose of INVANZ in patients 13 years of age and older is 1 gram (g) given once a day *[see Clinical Pharmacology (12.3)].*

3 months to 12 years of age

The dose of INVANZ 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 INVANZ.

Table 1
Treatment Guidelines for Adults and Pediatric Patients With Normal Renal Function* and Body Weight

Infection†	Daily Dose (IV or IM) Adults and Pediatric Patients 13 years of age and older	Daily Dose (IV or IM) Pediatric Patients 3 months to 12 years of age	Recommended Duration of Total Antimicrobial Treatment
Complicated intra-abdominal infections	1 g	15 mg/kg twice daily‡	5 to 14 days
Complicated skin and skin structure infections, including diabetic foot infections§	1 g	15 mg/kg twice daily‡	7 to 14 days¶
Community acquired pneumonia	1 g	15 mg/kg twice daily‡	10 to 14 days#
Complicated urinary tract infections, including pyelonephritis	1 g	15 mg/kg twice daily‡	10 to 14 days#
Acute pelvic infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections	1 g	15 mg/kg twice daily‡	3 to 10 days

* defined as creatinine clearance >90 mL/min/1.73 m^2
† due to the designated pathogens *[see Indications and Usage (1)]*
‡ not to exceed 1 g/day
§ INVANZ has not been studied in diabetic foot infections with concomitant osteomyelitis *[see Clinical Studies (14.1)].*
¶ adult patients with diabetic foot infections received up to 28 days of treatment (parenteral or parenteral plus oral switch therapy)
\# duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

2.3 Prophylactic Regimen in Adults

Table 2 presents prophylaxis guidelines for INVANZ.

Reference ID: 3346441

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 surgical incision

2.4 Patients with Renal Impairment

INVANZ may be used for the treatment of infections in adult patients with renal impairment. In patients whose creatinine clearance is >30 mL/min/1.73 m^2, no dosage adjustment is necessary. Adult patients with severe renal impairment (creatinine clearance ≤30 mL/min/1.73 m^2) and end-stage renal disease (creatinine clearance ≤10 mL/min/1.73 m^2) should receive 500 mg daily. A supplementary dose of 150 mg is recommended if ertapenem is administered within 6 hours prior to hemodialysis. There are no data in pediatric patients with renal impairment.

2.5 Patients on Hemodialysis

When adult patients on hemodialysis are given the recommended daily dose of 500 mg of INVANZ within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session. If INVANZ is given at least 6 hours prior to hemodialysis, no supplementary dose is needed. 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[1] may be used to estimate creatinine clearance. 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)

2.6 Patients with Hepatic Impairment

No dose adjustment recommendations can be made in patients with hepatic impairment *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].*

2.7 Preparation and Reconstitution for Administration

Vials

Adults and pediatric patients 13 years of age and older

Preparation for intravenous administration:

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

INVANZ MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of one of the following: Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately transfer contents of the reconstituted vial to 50 mL of 0.9% Sodium Chloride Injection.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:

INVANZ MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 3.2 mL of 1.0% lidocaine HCl injection[2] (**without epinephrine**). Shake vial thoroughly to form solution.
2. 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).

[1] Cockcroft and Gault equation: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976
[2] Refer to the prescribing information for lidocaine HCl.

Reference ID: 3346441

3. 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 INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

INVANZ MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of one of the following: Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and dilute in 0.9% Sodium Chloride Injection to a final concentration of 20 mg/mL or less.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:

INVANZ MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of INVANZ with 3.2 mL of 1.0% lidocaine HCl injection (**without epinephrine**). Shake vial thoroughly to form solution.
2. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **NOTE: THE RECONSTITUTED SOLUTION SHOULD NOT BE ADMINISTERED INTRAVENOUSLY**.

ADD-Vantage®[3] Vials

INVANZ in ADD-Vantage® vials should be reconstituted with ADD-Vantage® diluent containers containing 50 mL or 100 mL of 0.9% Sodium Chloride Injection.

INSTRUCTIONS FOR USE OF
INVANZ®
(Ertapenem for Injection)
IN ADD-Vantage VIALS

For I.V. Use Only.

To Open Diluent Container:

Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container:
(Use Aseptic Technique)

Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:

To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening. (SEE FIGURE 1.) Pull the ring approximately half way around the cap and then pull straight up to remove the cap. (SEE FIGURE 2.) NOTE: DO NOT ACCESS VIAL WITH SYRINGE.

[3] Registered trademark of Hospira Laboratories, Inc.

Reference ID: 3346441

Fig. 1

Fig. 2

To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)

Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately ½ turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go. NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)

Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.

Label appropriately.

Fig. 3

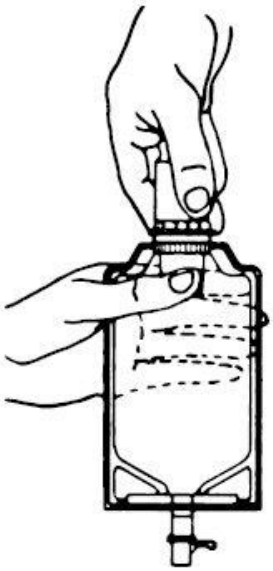


Fig. 4

To Prepare Admixture:

Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.

Reference ID: 3346441

With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)

Pull the inner cap from the drug vial. (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.

Mix container contents thoroughly and use within the specified time.

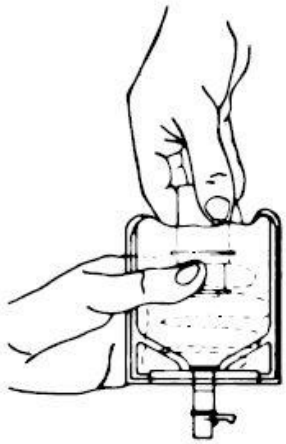


Fig. 5

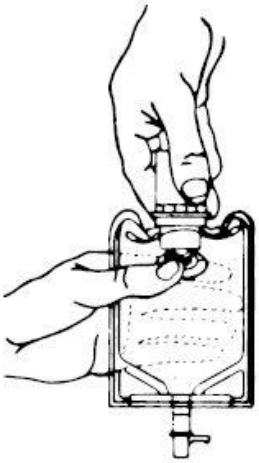


Fig. 6

Preparation for Administration:
(Use Aseptic Technique)

Confirm the activation and admixture of vial contents.

Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

Close flow control clamp of administration set.

Remove cover from outlet port at bottom of container.

Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.

Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.

Squeeze and release drip chamber to establish proper fluid level in chamber.

Open flow control clamp and clear air from set. Close clamp.

Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.

Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

Storage

INVANZ (Ertapenem for Injection) 1 g single dose ADD-Vantage® vials should be prepared with ADD-Vantage® diluent containers containing 50 mL or 100 mL of 0.9% Sodium Chloride Injection. When prepared with this diluent, INVANZ (Ertapenem for Injection) maintains satisfactory potency **for 6 hours at room temperature (25°C) or for 24 hours under refrigeration (5°C) and used within 4 hours after removal from refrigeration. Solutions of INVANZ should not be frozen**.

Before administering, see accompanying package circular for INVANZ (Ertapenem for Injection).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. Solutions of INVANZ range from colorless to pale yellow. Variations of color within this range do not affect the potency of the product.

Reference ID: 3346441

3 DOSAGE FORMS AND STRENGTHS

Vials

INVANZ is a sterile lyophilized powder in a vial containing 1.046 g ertapenem sodium equivalent to 1 g ertapenem for intravenous infusion or for intramuscular injection.

ADD-Vantage® Vials

INVANZ is a lyophilized powder in an ADD-Vantage® vial containing 1.046 g ertapenem sodium equivalent to 1 g ertapenem for intravenous infusion.

4 CONTRAINDICATIONS

- INVANZ is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.
- Due to the use of lidocaine HCl as a diluent, INVANZ administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These 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. Before initiating therapy with INVANZ, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to INVANZ occurs, discontinue the drug immediately. Serious anaphylactic reactions require immediate emergency treatment as clinically indicated.

5.2 Seizure Potential

Seizures and other central nervous system (CNS) adverse experiences have been reported during treatment with INVANZ *[see Adverse Reactions (6.1)]*. During clinical investigations in adult patients treated with INVANZ (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 Adverse Reactions (6.1)]*. 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 INVANZ re-examined to determine whether it should be decreased or discontinued.

5.3 Interaction with 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 in 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. Increasing the dose of valproic acid or 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 INVANZ is necessary, supplemental anti-convulsant therapy should be considered *[see Drug Interactions (7.2)].*

5.4 *Clostridium difficile*-Associated Diarrhea (CDAD)

CDAD has been reported with use of nearly all antibacterial agents, including ertapenem, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*.

Clostridium difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can

Reference ID: 3346441

be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated.

5.5 Caution with Intramuscular Administration

Caution should be taken when administering INVANZ intramuscularly to avoid inadvertent injection into a blood vessel *[see Dosage and Administration (2.7)]*.

5.6 Development of Drug-Resistant Bacteria

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

Prescribing INVANZ in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.7 Laboratory Tests

While INVANZ 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.

6 ADVERSE REACTIONS

The following are described in greater detail in the Warnings and Precautions section.

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Seizure Potential *[see Warnings and Precautions (5.2)]*
- Interaction with Valproic Acid *[see Warnings and Precautions (5.3)]*
- *Clostridium difficile*-Associated Diarrhea (CDAD) *[see Warnings and Precautions (5.4)]*
- Caution with Intramuscular Administration *[see Warnings and Precautions (5.5)]*
- Development of Drug-Resistant Bacteria *[see Warnings and Precautions (5.6)]*
- Laboratory Tests *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults Receiving INVANZ as a Treatment Regimen

Clinical trials enrolled 1954 patients treated with INVANZ; in some of the clinical trials, parenteral therapy was followed by a switch to an appropriate oral antimicrobial *[see Clinical Studies (14)].* Most adverse experiences reported in these clinical trials were described as mild to moderate in severity. INVANZ was discontinued due to adverse experiences in 4.7% of patients. Table 3 shows the incidence of adverse experiences reported in ≥2.0% of patients in these trials. The most common drug-related adverse experiences in patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, were diarrhea (5.5%), infused vein complication (3.7%), nausea (3.1%), headache (2.2%), and vaginitis in females (2.1%).

Table 3
Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥2.0% of Adult Patients Treated With INVANZ in Clinical Trials

Adverse Events	INVANZ* 1 g daily (N=802)	Piperacillin/ Tazobactam* 3.375 g q6h (N=774)	INVANZ† 1 g daily (N=1152)	Ceftriaxone† 1 or 2 g daily (N=942)
Local:				
Infused vein complication	7.1	7.9	5.4	6.7

Systemic:				
Death	2.5	1.6	1.3	1.6
Edema/swelling	3.4	2.5	2.9	3.3
Fever	5.0	6.6	2.3	3.4
Abdominal pain	3.6	4.8	4.3	3.9
Hypotension	2.0	1.4	1.0	1.2
Constipation	4.0	5.4	3.3	3.1
Diarrhea	10.3	12.1	9.2	9.8
Nausea	8.5	8.7	6.4	7.4
Vomiting	3.7	5.3	4.0	4.0
Altered mental status[‡]	5.1	3.4	3.3	2.5
Dizziness	2.1	3.0	1.5	2.1
Headache	5.6	5.4	6.8	6.9
Insomnia	3.2	5.2	3.0	4.1
Dyspnea	2.6	1.8	1.0	2.4
Pruritus	2.0	2.6	1.0	1.9
Rash	2.5	3.1	2.3	1.5
Vaginitis	1.4	1.0	3.3	3.7

* Includes Phase IIb/III Complicated intra-abdominal infections, Complicated skin and skin structure infections and Acute pelvic infections trials

† Includes Phase IIb/III Community acquired pneumonia and Complicated urinary tract infections, and Phase IIa trials

‡ Includes agitation, confusion, disorientation, decreased mental acuity, changed mental status, somnolence, stupor

In patients treated for complicated intra-abdominal infections, death occurred in 4.7% (15/316) of patients receiving INVANZ and 2.6% (8/307) of patients receiving comparator drug. These deaths occurred in patients with significant co-morbidity and/or severe baseline infections. Deaths were considered unrelated to study drugs by investigators.

In clinical trials, seizure was reported during study therapy plus 14-day follow-up period in 0.5% of patients treated with INVANZ, 0.3% of patients treated with piperacillin/tazobactam and 0% of patients treated with ceftriaxone *[see Warnings and Precautions (5.2)].*

Additional adverse experiences that were reported with INVANZ with an incidence >0.1% within each body system are listed below

Body as a Whole: abdominal distention, pain, chills, septicemia, septic shock, dehydration, gout, malaise, asthenia/fatigue, necrosis, candidiasis, weight loss, facial edema, injection site induration, injection site pain, extravasation, phlebitis/thrombophlebitis, flank pain, syncope

Cardiovascular System: heart failure, hematoma, chest pain, hypertension, tachycardia, cardiac arrest, bradycardia, arrhythmia, atrial fibrillation, heart murmur, ventricular tachycardia, asystole, subdural hemorrhage

Digestive System: acid regurgitation, oral candidiasis, dyspepsia, gastrointestinal hemorrhage, anorexia, flatulence, *C. difficile*-associated diarrhea, stomatitis, dysphagia, hemorrhoids, ileus, cholelithiasis, duodenitis, esophagitis, gastritis, jaundice, mouth ulcer, pancreatitis, pyloric stenosis

Musculoskeletal System: leg pain

Nervous System & Psychiatric: anxiety, nervousness, seizure *[see Warnings and Precautions (5.2)]*, tremor, depression, hypesthesia, spasm, paresthesia, aggressive behavior, vertigo

Respiratory System: cough, pharyngitis, rales/rhonchi, respiratory distress, pleural effusion, hypoxemia, bronchoconstriction, pharyngeal discomfort, epistaxis, pleuritic pain, asthma, hemoptysis, hiccups, voice disturbance

Skin & Skin Appendage: erythema, sweating, dermatitis, desquamation, flushing, urticaria

Special Senses: taste perversion

Urogenital System: renal impairment, oliguria/anuria, vaginal pruritus, hematuria, urinary retention, bladder dysfunction, vaginal candidiasis, vulvovaginitis.

In a clinical trial for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with INVANZ, the adverse experience profile was generally similar to that seen in previous clinical trials.

Prophylaxis of Surgical Site Infection following Elective Colorectal Surgery

In a clinical trial in adults for the prophylaxis of surgical site infection following elective colorectal surgery in which 476 patients received a 1 g dose of INVANZ 1 hour prior to surgery and were then followed for safety 14 days post surgery, the overall adverse experience profile was generally comparable to that observed for INVANZ in previous clinical trials. Table 4 shows the incidence of adverse

experiences other than those previously described above for INVANZ that were reported regardless of causality in ≥2.0% of patients in this trial.

Table 4
Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥2.0% of Adult Patients Treated With INVANZ for Prophylaxis of Surgical Site Infections Following Elective Colorectal Surgery

Adverse Events	INVANZ 1 g (N = 476)	Cefotetan 2 g (N = 476)
Anemia	5.7	6.9
Small intestinal obstruction	2.1	1.9
Pneumonia	2.1	4.0
Postoperative infection	2.3	4.0
Urinary tract infection	3.8	5.5
Wound infection	6.5	12.4
Wound complication	2.9	2.3
Atelectasis	3.4	1.9

Additional adverse experiences that were reported in this prophylaxis trial with INVANZ, regardless of causality, with an incidence >0.5% within each body system are listed below:

Gastrointestinal Disorders: *C. difficile* infection or colitis, dry mouth, hematochezia

General Disorders and Administration Site Condition: crepitations

Infections and Infestations: cellulitis, abdominal abscess, fungal rash, pelvic abscess

Injury, Poisoning and Procedural Complications: incision site complication, incision site hemorrhage, intestinal stoma complication, anastomotic leak, seroma, wound dehiscence, wound secretion

Musculoskeletal and Connective Tissue Disorders: muscle spasms

Nervous System Disorders: cerebrovascular accident

Renal and Urinary Disorders: dysuria, pollakiuria

Respiratory, Thoracic and Mediastinal Disorders: crackles lung, lung infiltration, pulmonary congestion, pulmonary embolism, wheezing.

Pediatric Patients Receiving INVANZ as a Treatment Regimen

Clinical trials enrolled 384 patients treated with INVANZ; in some of the clinical trials, parenteral therapy was followed by a switch to an appropriate oral antimicrobial *[see Clinical Studies (14)].* The overall adverse experience profile in pediatric patients is comparable to that in adult patients. Table 5 shows the incidence of adverse experiences reported in ≥2.0% of pediatric patients in clinical trials. The most common drug-related adverse experiences in pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, were diarrhea (6.5%), infusion site pain (5.5%), infusion site erythema (2.6%), vomiting (2.1%).

Table 5
Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥2.0% of Pediatric Patients Treated With INVANZ in Clinical Trials

Adverse Events	INVANZ*,† (N=384)	Ceftriaxone* (N=100)	Ticarcillin/ Clavulanate† (N=24)
Local:			
Infusion Site Erythema	3.9	3.0	8.3
Infusion Site Pain	7.0	4.0	20.8
Systemic:			
Abdominal Pain	4.7	3.0	4.2
Constipation	2.3	0.0	0.0
Diarrhea	11.7	17.0	4.2
Loose Stools	2.1	0.0	0.0
Vomiting	10.2	11.0	8.3
Pyrexia	4.9	6.0	8.3
Upper Respiratory Tract Infection	2.3	3.0	0.0
Headache	4.4	4.0	0.0

Reference ID: 3346441

Cough	4.4	3.0	0.0
Diaper Dermatitis	4.7	4.0	0.0
Rash	2.9	2.0	8.3

* Includes Phase IIb Complicated skin and skin structure infections, Community acquired pneumonia and Complicated urinary tract infections trials in which patients 3 months to 12 years of age received INVANZ 15 mg/kg IV twice daily up to a maximum of 1 g or ceftriaxone 50 mg/kg/day IV in two divided doses up to a maximum of 2 g, and patients 13 to 17 years of age received INVANZ 1 g IV daily or ceftriaxone 50 mg/kg/day IV in a single daily dose.

† Includes Phase IIb Acute pelvic infections and Complicated intra-abdominal infections trials in which patients 3 months to 12 years of age received INVANZ 15 mg/kg IV twice daily up to a maximum of 1 g and patients 13 to 17 years of age received INVANZ 1 g IV daily or ticarcillin/clavulanate 50 mg/kg for patients <60 kg or ticarcillin/clavulanate 3.0 g for patients >60 kg, 4 or 6 times a day.

Additional adverse experiences that were reported with INVANZ with an incidence >0.5% within each body system are listed below:

Gastrointestinal Disorders: nausea

General Disorders and Administration Site Condition: hypothermia, chest pain, upper abdominal pain; infusion site pruritus, induration, phlebitis, swelling, and warmth

Infections and Infestations: candidiasis, oral candidiasis, viral pharyngitis, herpes simplex, ear infection, abdominal abscess

Metabolism and Nutrition Disorders: decreased appetite

Musculoskeletal and Connective Tissue Disorders: arthralgia

Nervous System Disorders: dizziness, somnolence

Psychiatric Disorders: insomnia

Reproductive System and Breast Disorders: genital rash

Respiratory, Thoracic and Mediastinal Disorders: wheezing, nasopharyngitis, pleural effusion, rhinitis, rhinorrhea

Skin and Subcutaneous Tissue Disorders: dermatitis, pruritus, rash erythematous, skin lesion

Vascular Disorders: phlebitis.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during the post-approval use of INVANZ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: anaphylaxis including anaphylactoid reactions

Musculoskeletal and Connective Tissue Disorders: muscular weakness

Nervous System Disorders: coordination abnormal, depressed level of consciousness, dyskinesia, gait disturbance, myoclonus, tremor

Psychiatric Disorders: altered mental status (including aggression, delirium), hallucinations

Skin and Subcutaneous Tissue Disorders: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)

6.3 Adverse Laboratory Changes in Clinical Trials

Adults Receiving INVANZ as Treatment Regimen

Laboratory adverse experiences that were reported during therapy in ≥2.0% of adult patients treated with INVANZ in clinical trials are presented in Table 6. Drug-related laboratory adverse experiences that were reported during therapy in ≥2.0% of adult patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, in clinical trials were ALT increased (6.0%), AST increased (5.2%), serum alkaline phosphatase increased (3.4%), and platelet count increased (2.8%). INVANZ was discontinued due to laboratory adverse experiences in 0.3% of patients.

Table 6
Incidence* (%) of Laboratory Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥2.0% of Adult Patients Treated With INVANZ in Clinical Trials

Adverse laboratory experiences	INVANZ‡ 1 g daily (n†=766)	Piperacillin/ Tazobactam‡ 3.375 g q6h (n†=755)	INVANZ§ 1 g daily (n†=1122)	Ceftriaxone§ 1 or 2 g daily (n†=920)

ALT increased	8.8	7.3	8.3	6.9
AST increased	8.4	8.3	7.1	6.5
Serum alkaline phosphatase increased	6.6	7.2	4.3	2.8
Eosinophils increased	1.1	1.1	2.1	1.8
Hematocrit decreased	3.0	2.9	3.4	2.4
Hemoglobin decreased	4.9	4.7	4.5	3.5
Platelet count increased	6.5	6.3	4.3	3.5
Urine RBCs increased	2.5	2.9	1.1	1.0
Urine WBCs increased	2.5	3.2	1.6	1.1

* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test
† Number of patients with one or more laboratory tests
‡ Includes Phase IIb/III Complicated intra-abdominal infections, Complicated skin and skin structure infections and Acute pelvic infections trials
§ Includes Phase IIb/III Community acquired pneumonia and Complicated urinary tract infections, and Phase IIa trials

Additional laboratory adverse experiences that were reported during therapy in >0.1% of patients treated with INVANZ in clinical trials include: increases in serum creatinine, serum glucose, BUN, total, direct and indirect serum bilirubin, serum sodium and potassium, PT and PTT; decreases in serum potassium, serum albumin, WBC, platelet count, and segmented neutrophils.

In a clinical trial for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with INVANZ, the laboratory adverse experience profile was generally similar to that seen in previous clinical trials.

Prophylaxis of Surgical Site Infection following Elective Colorectal Surgery

In a clinical trial in adults for the prophylaxis of surgical site infection following elective colorectal surgery in which 476 patients received a 1 g dose of INVANZ 1 hour prior to surgery and were then followed for safety 14 days post surgery, the overall laboratory adverse experience profile was generally comparable to that observed for INVANZ in previous clinical trials.

Pediatric Patients Receiving INVANZ as a Treatment Regimen

Laboratory adverse experiences that were reported during therapy in ≥2.0% of pediatric patients treated with INVANZ in clinical trials are presented in Table 7. Drug-related laboratory adverse experiences that were reported during therapy in ≥2.0% of pediatric patients treated with INVANZ, including those who were switched to therapy with an oral antimicrobial, in clinical trials were neutrophil count decreased (3.0%), ALT increased (2.2%), and AST increased (2.1%).

Table 7
Incidence* (%) of Specific Laboratory Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥2.0% of Pediatric Patients Treated With INVANZ in Clinical Trials

Adverse laboratory experiences	INVANZ ($n^{\dagger}$=379)	Ceftriaxone ($n^{\dagger}$=97)	Ticarcillin/ Clavulanate ($n^{\dagger}$=24)
ALT Increased	3.8	1.1	4.3
AST Increased	3.8	1.1	4.3
Neutrophil Count Decreased	5.8	3.1	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 laboratory adverse experiences that were reported during therapy in >0.5% of patients treated with INVANZ in clinical trials include: alkaline phosphatase increased, eosinophil count increased, platelet count increased, white blood cell count decreased and urine protein present.

Reference ID: 3346441

7 DRUG INTERACTIONS

7.1 Probenecid

Probenecid interferes with the active tubular secretion of ertapenem, resulting in increased plasma concentrations of ertapenem *[see Clinical Pharmacology (12.3)]*. Co-administration of probenecid with ertapenem is not recommended.

7.2 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 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. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid *[see Warnings and Precautions (5.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

In mice and rats given intravenous doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs), there was no evidence of developmental toxicity as assessed by external, visceral, and skeletal examination of the fetuses. However, in mice given 700 mg/kg/day, slight decreases in average fetal weights and an associated decrease in the average number of ossified sacrocaudal vertebrae were observed. Ertapenem crosses the placental barrier in rats.

There are, however, no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

INVANZ has not been studied for use during labor and delivery.

8.3 Nursing Mothers

Ertapenem is excreted in human breast milk *[see Clinical Pharmacology (12.3)]*. Caution should be exercised when INVANZ is administered to a nursing woman. INVANZ should be administered to nursing mothers only when the expected benefit outweighs the risk.

8.4 Pediatric Use

Safety and effectiveness of INVANZ in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled trials in adults, pharmacokinetic data in pediatric patients, and additional data from comparator-controlled trials in pediatric patients 3 months to 17 years of age *[see Indications and Usage (1.1), (1.2), (1.3), (1.4) and (1.5) and Clinical Studies (14.2)]*.

INVANZ is not recommended in infants under 3 months of age as no data are available.

INVANZ is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration.

8.5 Geriatric Use

Of the 1,835 patients in Phase 2b/3 trials treated with INVANZ, approximately 26 percent were 65 and over, while approximately 12 percent were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 Dosage and Administration (2.2)].*

8.6 Patients with Renal Impairment

Dosage adjustment is necessary in patients with creatinine clearance 30 mL/min or less *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Reference ID: 3346441

8.7 Patients with Hepatic Impairment

The pharmacokinetics of ertapenem in patients with hepatic impairment have not been established. Of the total number of patients in clinical trials, 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.

10 OVERDOSAGE

No specific information is available on the treatment of overdosage with INVANZ. Intentional overdosing of INVANZ is unlikely. Intravenous administration of INVANZ at a dose of 2 g over 30 min or 3 g over 1-2h in healthy adult volunteers resulted in an increased incidence of nausea. In clinical trials in adults, inadvertent administration of three 1 g doses of INVANZ in a 24 hour period resulted in diarrhea and transient dizziness in one patient. In pediatric clinical trials, a single intravenous dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity.

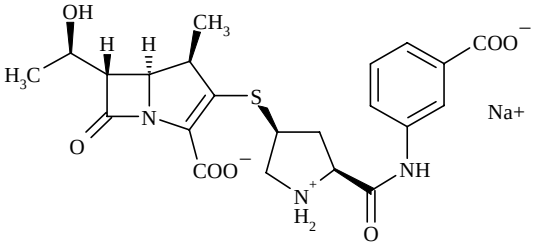
In the event of an overdose, INVANZ should be discontinued and general supportive treatment given until renal elimination takes place.

INVANZ can be removed by hemodialysis; the plasma clearance of the total fraction of ertapenem was increased 30% in subjects with end-stage renal disease when hemodialysis (4 hour session) was performed immediately following administration. However, no information is available on the use of hemodialysis to treat overdosage.

11 DESCRIPTION

INVANZ (Ertapenem for Injection) is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics.

Chemically, INVANZ is described as [4*R*-[3(3*S**,5*S**),4α,5β,6β(*R**)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt. Its molecular weight is 497.50. The empirical formula is $C_{22}H_{24}N_3O_7SNa$, and its structural formula is:



Ertapenem sodium is a white to off-white hygroscopic, weakly crystalline powder. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran.

INVANZ is supplied as sterile lyophilized powder for intravenous infusion after reconstitution with appropriate diluent *[see Dosage and Administration (2.7)]* and transfer to 50 mL 0.9% Sodium Chloride Injection or for intramuscular injection following reconstitution with 1% lidocaine hydrochloride. Each vial contains 1.046 grams ertapenem sodium, equivalent to 1 gram ertapenem. The sodium content is approximately 137 mg (approximately 6.0 mEq).

Each vial of INVANZ contains the following inactive ingredients: 175 mg sodium bicarbonate and sodium hydroxide to adjust pH to 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ertapenem sodium is a carbapenem antibiotic *[see Clinical Pharmacology (12.4)].*

Reference ID: 3346441

12.3 Pharmacokinetics

Average plasma concentrations (mcg/mL) of ertapenem following a single 30-minute infusion of a 1 g intravenous (IV) dose and administration of a single 1 g intramuscular (IM) dose in healthy young adults are presented in Table 8.

Table 8
Plasma Concentrations of Ertapenem in Adults After Single Dose Administration

	Average Plasma Concentrations (mcg/mL)								
Dose/Route	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr
1 g IV*	155	115	83	48	31	20	9	3	1
1 g IM	33	53	67	57	40	27	13	4	2

*Infused at a constant rate over 30 minutes

The area under the plasma concentration-time curve (AUC) of ertapenem in adults increased less-than dose-proportional based on total ertapenem concentrations over the 0.5 to 2 g dose range, whereas the AUC increased greater-than dose-proportional based on unbound ertapenem concentrations. Ertapenem exhibits non-linear pharmacokinetics due to concentration-dependent plasma protein binding at the proposed therapeutic dose *[see Clinical Pharmacology (12.3)]*. There is no accumulation of ertapenem following multiple IV or IM 1 g daily doses in healthy adults.

Average plasma concentrations (mcg/mL) of ertapenem in pediatric patients are presented in Table 9.

Table 9
Plasma Concentrations of Ertapenem in Pediatric Patients After Single IV* Dose Administration

Age Group	Dose	Average Plasma Concentrations (mcg/mL)							
		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

* Infused at a constant rate over 30 minutes
† up to a maximum dose of 1 g/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 trials

Absorption

Ertapenem, reconstituted with 1% lidocaine HCl injection, USP (in saline without epinephrine), is almost completely absorbed following intramuscular (IM) administration at the recommended dose of 1 g. The mean bioavailability is approximately 90%. Following 1 g daily IM administration, mean peak plasma concentrations (C_{max}) are achieved in approximately 2.3 hours (T_{max}).

Distribution

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

The apparent volume of distribution at steady state (V_{ss}) of ertapenem in adults is approximately 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.

The concentrations of ertapenem achieved in suction-induced skin blister fluid at each sampling point on the third day of 1 g once daily IV doses are presented in Table 10. The ratio of AUC_{0-24} in skin blister fluid/AUC_{0-24} in plasma is 0.61.

Table 10
Concentrations (mcg/mL) of 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 from 5 lactating women with pelvic infections (5 to 14 days postpartum) was measured at random time points daily for 5 consecutive days following the last 1 g dose of intravenous therapy (3-10 days of therapy). The concentration of ertapenem in breast milk within 24 hours of the last dose of therapy in all 5 women ranged from <0.13 (lower limit of quantitation) to 0.38 mcg/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 below the lower limit of quantitation (<0.13 mcg/mL) in 1 woman.

Metabolism

In healthy young adults, after infusion of 1 g IV radiolabeled ertapenem, the plasma radioactivity consists predominantly (94%) of ertapenem. The major metabolite of ertapenem is the inactive ring-opened derivative formed by hydrolysis of the beta-lactam ring.

Elimination

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults is approximately 4 hours and the plasma clearance is approximately 1.8 L/hour. The mean plasma half-life in pediatric 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 the administration of 1 g IV radiolabeled 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 ring-opened metabolite.

In healthy young adults given a 1 g IV dose, the mean percentage of the administered dose excreted in urine was 17.4% during 0-2 hours postdose, 5.4% during 4-6 hours postdose, and 2.4% during 12-24 hours postdose.

Special Populations

Renal Impairment

Total and unbound fractions of ertapenem pharmacokinetics were investigated in 26 adult subjects (31 to 80 years of age) with varying degrees of renal impairment. Following a single 1 g IV dose of ertapenem, the unbound AUC increased 1.5-fold and 2.3-fold in subjects with mild renal impairment (CL_{CR} 60-90 mL/min/1.73 m^2) and moderate renal impairment (CL_{CR} 31-59 mL/min/1.73 m^2), respectively, compared with healthy young subjects (25 to 45 years of age). No dosage adjustment is necessary in patients with $CL_{CR} \geq 31$ mL/min/1.73 m^2. The unbound AUC increased 4.4-fold and 7.6-fold in subjects with advanced renal impairment (CL_{CR} 5-30 mL/min/1.73 m^2) and end-stage renal disease (CL_{CR} <10 mL/min/1.73 m^2), respectively, compared with healthy young subjects. The effects of renal impairment on AUC of total drug were of smaller magnitude. The recommended dose of ertapenem in adult patients with $CL_{CR} \leq 30$ mL/min/1.73 m^2 is 0.5 grams every 24 hours. Following a single 1 g IV dose given immediately prior to a 4 hour hemodialysis session in 5 adult patients with end-stage renal disease, approximately 30% of the dose was recovered in the dialysate. Dose adjustments are recommended for patients with severe renal impairment and end-stage renal disease *[see Dosage and Administration (2.4)]*. There are no data in pediatric patients with renal impairment.

Hepatic Impairment

The pharmacokinetics of ertapenem in patients with hepatic impairment have not been established. However, ertapenem does not appear to undergo hepatic metabolism based on *in vitro* studies and approximately 10% of an administered dose is recovered in the feces *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.6)]*.

Reference ID: 3346441

Gender

The effect of gender on the pharmacokinetics of ertapenem was evaluated in healthy male (n=8) and healthy female (n=8) subjects. The differences observed could be attributed to body size when body weight was taken into consideration. No dose adjustment is recommended based on gender.

Geriatric Patients

The impact of age on the pharmacokinetics of ertapenem was evaluated in healthy male (n=7) and healthy female (n=7) subjects ≥65 years of age. The total and unbound AUC increased 37% and 67%, respectively, in elderly adults relative to young adults. These changes were attributed to age-related changes in creatinine clearance. No dosage adjustment is necessary for elderly patients with normal (for their age) renal function.

Pediatric Patients

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 (N=6) were generally comparable to those in healthy young adults.

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 Clinical Pharmacology (12.3)]*. 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 1 g IV dose of ertapenem.

Drug Interactions

When ertapenem is co-administered with probenecid (500 mg p.o. every 6 hours), probenecid competes for active tubular secretion and reduces the renal clearance of ertapenem. Based on total ertapenem concentrations, probenecid increased the AUC of ertapenem by 25%, and reduced the plasma and renal clearance of ertapenem by 20% and 35%, respectively. The half-life of ertapenem was increased from 4.0 to 4.8 hours.

In vitro studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the following cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

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.

12.4 Microbiology

Mechanism of Action

Ertapenem has *in vitro* activity against 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.

Mechanism of Resistance

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.

Ertapenem has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section*:*

Gram-positive bacteria:

Staphylococcus aureus (methicillin susceptible isolates only)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin susceptible isolates only)
Streptococcus pyogenes

Gram-negative bacteria:

Escherichia coli
Haemophilus influenzae (beta-lactamase negative isolates only)
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis

Reference ID: 3346441

Anaerobic bacteria:

Bacteroides fragilis
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Clostridium clostridioforme
Eubacterium lentum
Peptostreptococcus species
Porphyromonas asaccharolytica
Prevotella bivia

The following *in vitro* data are available, **but their clinical significance is unknown**. At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ertapenem. However, the efficacy of ertapenem in treating clinical infections due to these bacteria **has not been** established in adequate and well-controlled clinical trials:

Gram-positive bacteria:

Staphylococcus epidermidis (methicillin susceptible isolates only)
Streptococcus pneumoniae (penicillin-intermediate isolates)

Gram-negative bacteria:

Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus influenzae (beta-lactamase positive isolates only)
Haemophilus parainfluenzae
Klebsiella oxytoca (excluding ESBL producing isolates)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Anaerobic bacteria:

Bacteroides vulgatus
Clostridium perfringens
Fusobacterium spp.

Susceptibility Test Methods:

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility tests for antimicrobial drug products used in resident hospitals to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

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 broth dilution method {1} or equivalent with standardized inoculum concentrations and standardized concentrations of ertapenem powder. The MIC values should be interpreted according to criteria provided in Table 11 and {4}.

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 {2} 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 should be interpreted according to criteria provided in Table 11 and {4}.

Reference ID: 3346441

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to ertapenem as MICs can be determined by standardized test methods {3}. The MIC values obtained should be interpreted according to criteria provided in Table 11 and {4}.

Table 11
Susceptibility Interpretive Criteria for Ertapenem

Pathogen	Minimum Inhibitory Concentrations* MIC (μg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤0.5	1	≥2	≥22	19-21	≤18
Staphylococcus aureus†	≤2.0	4.0	≥8.0	≥19	16-18	≤15
Haemophilus spp.*	≤0.5	-	-	≥19	-	-
Streptococcus pneumoniae‡	≤1.0	2	≥4	-	-	-
Streptococcus spp. Beta Hemolytic Group*,‡,§	≤1.0	-	-	-	-	-
Streptococcus spp. Viridans Group*	≤1.0	-	-	-	-	-
Anaerobes	≤4.0	8.0	≥16.0	-	-	-

* For some organism/antimicrobial combinations, the absence or rare occurrence of resistant strains precludes defining any results categories other than "susceptible". For strains yielding results suggestive of a "non-susceptible" category, organism identification and antimicrobial susceptibility test results should be confirmed.

† For oxacillin-susceptible *S. aureus* results for carbapenems, including ertapenem, if tested, should be reported according to the results generated using routine interpretive criteria. For oxacillin-resistant *S. aureus* and coagulase negative staphylococci, other beta lactam agents, including carbapenems, may appear active *in vitro* but are not effective clinically. Results for beta lactam agents other than cephalosporins with anti-MRSA activity should be reported as resistant or should not be reported.

‡ *S. pneumoniae* penicillin MICs ≤2 mcg/mL indicate susceptibility to ertapenem.

§ A beta hemolytic *Streptococcus* spp. (Groups A, B, C, G) isolate susceptible to penicillin (MIC ≤0.12 μg/mL) can be considered susceptible to ertapenem and need not be tested against ertapenem.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound at the infection site 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 at the infection site reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. 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. Standard ertapenem powder should provide the following range of values noted in Table 12 and {4,5}.

Table 12
Acceptable Quality Control Ranges for Ertapenem

Microorganism	Minimum Inhibitory Concentrations MIC Range (μg/mL)	Disk Diffusion Zone Diameter (mm)
Escherichia coli ATCC 25922	0.004-0.016	29-36
Haemophilus influenzae ATCC 49766	0.015-0.06	27-33
Staphylococcus aureus ATCC 29213	0.06-0.25	-
Staphylococcus aureus ATCC 25923	-	24-31
Streptococcus pneumoniae ATCC 49619	0.03-0.25	28-35
Bacteroides fragilis ATCC 25285	0.06-0.5*	-

Reference ID: 3346441

	0.06-0.25†	
Bacteroides thetaiotaomicron ATCC 29741	0.5-2.0* 0.25-1.0†	-
Eubacterium lentum ATCC 43055	0.5-4.0* 0.5-2.0†	-

* Quality control ranges for broth microdilution testing
† Quality control ranges for agar dilution testing

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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.

In mice and rats, IV doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs) resulted in no effects on mating performance, fecundity, fertility, or embryonic survival.

13.2 Animal Toxicology and/or Pharmacology

In repeat-dose studies in rats, treatment-related neutropenia occurred at every dose-level tested, including the lowest dose of 2 mg/kg (approximately 2% of the human dose on a body surface area basis).

Studies in rabbits and Rhesus monkeys were inconclusive with regard to the effect on neutrophil counts.

14 CLINICAL STUDIES

14.1 Adults

Complicated Intra-Abdominal Infections

Ertapenem was evaluated in adults for the treatment of complicated intra-abdominal infections in a randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 5 to 14 days and enrolled 665 patients with localized complicated appendicitis, and any other complicated intra-abdominal infection including colonic, small intestinal, and biliary infections and generalized peritonitis. The combined clinical and microbiologic success rates in the microbiologically evaluable population at 4 to 6 weeks posttherapy (test-of-cure) were 83.6% (163/195) for ertapenem and 80.4% (152/189) for piperacillin/tazobactam.

Complicated Skin and Skin Structure Infections

Ertapenem was evaluated in adults for the treatment of complicated skin and skin structure infections in a randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 7 to 14 days and enrolled 540 patients including patients with deep soft tissue abscess, posttraumatic wound infection and cellulitis with purulent drainage. The clinical success rates at 10 to 21 days posttherapy (test-of-cure) were 83.9% (141/168) for ertapenem and 85.3% (145/170) for piperacillin/tazobactam.

Diabetic Foot Infections

Ertapenem was evaluated in adults for the treatment of diabetic foot infections without concomitant osteomyelitis in a multicenter, randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours). Test-of-cure was defined as clinical response between treatment groups in the clinically evaluable population at the 10-day posttherapy follow-up visit. The trial included 295 patients randomized to ertapenem and 291 patients to piperacillin/tazobactam. Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 5 to 28 days of treatment (parenteral and oral). All patients were eligible to receive appropriate adjunctive treatment methods, such as debridement, as is typically required in the treatment of diabetic foot infections, and most patients received these treatments. Patients with suspected osteomyelitis could be enrolled if all the infected bone was removed within 2 days of initiation of

Reference ID: 3346441

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 or if patients had a history of MRSA infection and additional therapy was indicated in the opinion of the investigator. Two hundred and four (204) patients randomized to ertapenem and 202 patients randomized to piperacillin/tazobactam were clinically evaluable. The clinical success rates at 10 days posttherapy were 75.0% (153/204) for ertapenem and 70.8% (143/202) for piperacillin/tazobactam.

Community Acquired Pneumonia

Ertapenem was evaluated in adults for the treatment of community acquired pneumonia in two randomized, double-blind, non-inferiority clinical trials. Both trials compared ertapenem (1 g parenterally once a day) with ceftriaxone (1 g parenterally once a day) and enrolled a total of 866 patients. Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 10 to 14 days of treatment (parenteral and oral). In the first trial the primary efficacy parameter was the clinical success rate in the clinically evaluable population and success rates were 92.3% (168/182) for ertapenem and 91.0% (183/201) for ceftriaxone at 7 to 14 days posttherapy (test-of-cure). In the second trial the primary efficacy parameter was the clinical success rate in the microbiologically evaluable population and success rates were 91% (91/100) for ertapenem and 91.8% (45/49) for ceftriaxone at 7 to 14 days posttherapy (test-of-cure).

Complicated Urinary Tract Infections Including Pyelonephritis

Ertapenem was evaluated in adults for the treatment of complicated urinary tract infections including pyelonephritis in two randomized, double-blind, non-inferiority clinical trials. Both trials compared ertapenem (1 g parenterally once a day) with ceftriaxone (1 g parenterally once a day) and enrolled a total of 850 patients. 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). The microbiological success rates (combined trials) at 5 to 9 days posttherapy (test-of-cure) were 89.5% (229/256) for ertapenem and 91.1% (204/224) for ceftriaxone.

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

Ertapenem was evaluated in adults for the treatment of acute pelvic infections in a randomized, double-blind, non-inferiority clinical trial. This trial compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 3 to 10 days and enrolled 412 patients including 350 patients with obstetric/postpartum infections and 45 patients with septic abortion. The clinical success rates in the clinically evaluable population at 2 to 4 weeks posttherapy (test-of-cure) were 93.9% (153/163) for ertapenem and 91.5% (140/153) for piperacillin/tazobactam.

Prophylaxis of Surgical Site Infections Following Elective Colorectal Surgery

Ertapenem was evaluated in adults for prophylaxis of surgical site infection following elective colorectal surgery in a multicenter, randomized, double-blind, non-inferiority clinical trial. This trial compared a single intravenous dose of ertapenem (1 g) versus cefotetan (2 g) administered over 30 minutes, 1 hour before elective colorectal surgery. Test-of-prophylaxis was defined as no evidence of surgical site infection, post-operative anastomotic leak, or unexplained antibiotic use in the clinically evaluable population up to and including at the 4-week posttreatment follow-up visit. The trial included 500 patients randomized to ertapenem and 502 patients randomized to cefotetan. The modified intent-to-treat (MITT) population consisted of 451 ertapenem patients and 450 cefotetan patients and included all patients who were randomized, treated, and underwent elective colorectal surgery with adequate bowel preparation. The clinically evaluable population was a subset of the MITT population and consisted of patients who received a complete dose of study therapy no more than two hours prior to surgical incision and no more than six hours before surgical closure. Clinically evaluable patients had sufficient information to determine outcome at the 4-week follow-up assessment and had no confounding factors that interfered with the assessment of that outcome. Examples of confounding factors included prior or concomitant antibiotic violations, the need for a second surgical procedure during the study period, and identification of a distant site infection with concomitant antibiotic administration and no evidence of subsequent wound infection. Three-hundred forty-six (346) patients randomized to ertapenem and 339 patients randomized to cefotetan were clinically evaluable. The prophylactic success rates at 4 weeks posttreatment in the clinically evaluable population were 70.5% (244/346) for ertapenem and 57.2% (194/339) for cefotetan (difference 13.3%, [95% C.I.: 6.1, 20.4], $p<0.001$). Prophylaxis failure due to surgical site infections occurred in 18.2% (63/346) ertapenem patients and 31.0% (105/339) cefotetan patients. Post-operative

Reference ID: 3346441

anastomotic leak occurred in 2.9% (10/346) ertapenem patients and 4.1% (14/339) cefotetan patients. Unexplained antibiotic use occurred in 8.4% (29/346) ertapenem patients and 7.7% (26/339) cefotetan patients. Though patient numbers were small in some subgroups, in general, clinical response rates by age, gender, and race were consistent with the results found in the clinically evaluable population. In the MITT analysis, the prophylactic success rates at 4 weeks posttreatment were 58.3% (263/451) for ertapenem and 48.9% (220/450) for cefotetan (difference 9.4%, [95% C.I.: 2.9, 15.9], p=0.002). A statistically significant difference favoring ertapenem over cefotetan with respect to the primary endpoint has been observed at a significance level of 5% in this trial. A second adequate and well-controlled trial to confirm these findings has not been conducted; therefore, the clinical superiority of ertapenem over cefotetan has not been demonstrated.

14.2 Pediatric Patients

Ertapenem was evaluated in pediatric patients 3 months to 17 years of age in two randomized, multicenter clinical trials.

The first trial enrolled 404 patients and compared ertapenem (15 mg/kg intravenous (IV) every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ceftriaxone (50 mg/kg/day IV in two divided doses in patients 3 months to 12 years of age and 50 mg/kg/day IV as a single daily dose in patients 13 to 17 years of age) for the treatment of complicated urinary tract infection (UTI), skin and soft tissue infection (SSTI), or community-acquired pneumonia (CAP). Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of up to 14 days of treatment (parenteral and oral). The microbiological success rates in the evaluable per protocol (EPP) analysis in patients treated for UTI were 87.0% (40/46) for ertapenem and 90.0% (18/20) for ceftriaxone. The clinical success rates in the EPP analysis in patients treated for SSTI were 95.5% (64/67) for ertapenem and 100% (26/26) for ceftriaxone, and in patients treated for CAP were 96.1% (74/77) for ertapenem and 96.4% (27/28) for ceftriaxone.

The second trial enrolled 112 patients and compared ertapenem (15 mg/kg IV every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ticarcillin/clavulanate (50 mg/kg for patients <60 kg or 3.0 g for patients >60 kg, 4 or 6 times a day) up to 14 days for the treatment of complicated intra-abdominal infections (IAI) and acute pelvic infections (API). In patients treated for IAI (primarily patients with perforated or complicated appendicitis), the clinical success rates were 83.7% (36/43) for ertapenem and 63.6% (7/11) for ticarcillin/clavulanate in the EPP analysis. In patients treated for API (post-operative or spontaneous obstetrical endomyometritis, or septic abortion), the clinical success rates were 100% (23/23) for ertapenem and 100% (4/4) for ticarcillin/clavulanate in the EPP analysis.

15 REFERENCES

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Reference ID: 3346441

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

INVANZ is supplied as a sterile lyophilized powder in single dose vials containing ertapenem for intravenous infusion or for intramuscular injection as follows:

No. 3843—1 g ertapenem equivalent

NDC 0006-3843-71 in trays of 10 vials.

INVANZ is supplied as a sterile lyophilized powder in single dose ADD-Vantage® vials containing ertapenem for intravenous infusion as follows:

No. 3845—1 g ertapenem equivalent

NDC 0006-3845-71 in trays of 10 ADD-Vantage® vials.

16.2 Storage and Handling

Before reconstitution

Do not store lyophilized powder above 25°C (77°F).

Reconstituted and infusion solutions

The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection *[see Dosage and Administration (2.7)],* 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 INVANZ should not be frozen.

17 PATIENT COUNSELING INFORMATION

17.1 Instructions for Patients

Patients should be advised that allergic reactions, including serious allergic reactions could occur and that serious reactions may require immediate treatment. Advise patients to report any previous hypersensitivity reactions to INVANZ, other beta-lactams or other allergens.

Patients should be counseled to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with INVANZ. If treatment with INVANZ is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed.

Patients should be counseled that antibacterial drugs including INVANZ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When INVANZ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by INVANZ or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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