INVANZ

(Ertapenem for Injection)

THERAPEUTIC CLASS

INVANZ (Ertapenem for Injection) is a sterile, synthetic, long-acting, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins, with activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria.

MICROBIOLOGY

Ertapenem has *in vitro* activity against a wide 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 has significant stability to hydrolysis by most classes of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

INVANZ has been shown to be active against most strains of the following microorganisms *in vitro* and in clinical infections (see INDICATIONS):

AEROBIC AND FACULTATIVE ANAEROBIC GRAM-POSITIVE MICROORGANISMS: *Staphylococcus aureus* (including penicillinase-producing strains)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Note: Methicillin-resistant staphylococci are resistant to INVANZ. Many strains of *Enterococcus faecalis* and most strains of *Enterococcus faecium* are resistant.

AEROBIC AND FACULTATIVE ANAEROBIC GRAM-NEGATIVE MICROORGANISMS:
Escherichia coli

Haemophilus influenzae (including beta-lactamase producing strains)
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis

ANAEROBIC MICROORGANISMS:
Bacteroides fragilis and other species in the *B. fragilis* Group
Clostridium species (excluding *C. difficile*)
Eubacterium species
Peptostreptococcus species
Porphyromonas asaccharolytica
Prevotella species.

The following *in vitro* data are available, but their clinical significance is unknown.
INVANZ exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤1 mcg/mL against most (≥90%) strains of *Streptococcus* species including *Streptococcus pneumoniae*, ≤0.5 mcg/mL against most (≥90%) strains of *Haemophilus* species, ≤2 mcg/mL against most (≥90%) strains of the other aerobic and facultative anaerobic microorganisms and ≤4 mcg/mL against most (≥90%) strains of the strict anaerobic microorganisms in the following list; however, the safety and effectiveness of INVANZ in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical studies:

AEROBIC AND FACULTATIVE ANAEROBIC GRAM-POSITIVE MICROORGANISMS: *Staphylococcus* species, coagulase negative, methicillin susceptible
Streptococcus pneumoniae, penicillin resistant
Viridans streptococci
Note: Methicillin-resistant staphylococci are resistant to INVANZ. Many strains of *Enterococcus faecalis* and most strains of *Enterococcus faecium* are resistant.

AEROBIC AND FACULTATIVE ANAEROBIC GRAM-NEGATIVE MICROORGANISMS:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli producing ESBLs
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae producing ESBLs

Morganella morganii
Proteus vulgaris
Serratia marcescens
Note: Many strains of the above organisms that are multiply resistant to other antibiotics, e.g., penicillins, cephalosporins (including third-generation) and aminoglycosides are susceptible to INVANZ.

ANAEROBIC MICROORGANISM*:*
Fusobacterium species.

INDICATIONS

Treatment of adult patients moderate to severe infections caused by susceptible strains of microorganisms which are suspected or proven to be resistant to all other anitbiotics, or patient unable to tolerate other antibiotics:

- *Complicated Intra-Abdominal Infections*
- *Complicated Skin and Skin Structure*
- *Community Acquired Pneumonia*
- *Complicated Urinary Tract Infections including pyelonephritis*
- *Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections*

DOSAGE AND ADMINISTRATION

The usual dose of INVANZ in adults is 1 gram (g) given once a day.

INVANZ may be administered by intravenous (IV) infusion or intramuscular (IM) injection. 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.

The usual duration of therapy with INVANZ is 3 to 14 days but varies by the type of infection and causative pathogen(s). (See INDICATIONS.) When clinically indicated, a switch to an appropriate oral antimicrobial may be implemented if clinical improvement has been observed.

In controlled clinical studies, patients were treated from 3 to 14 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response. In some studies, treatment was converted to oral therapy at the discretion of the treating physician after clinical improvement had been demonstrated.

Patients with renal insufficiency: INVANZ 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, no dosage adjustment is necessary. In patients with advanced renal insufficiency (creatinine clearance ≤30 mL/min/1.73 m^2), including those on hemodialysis, should receive 500 mg daily.

Patients on Hemodialysis: 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. 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.

When only the serum creatinine is available, the following formula** 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)

No dosage adjustment is recommended in patients with impaired hepatic function.
The recommended dose of INVANZ can be administered without regard to or gender.

INSTRUCTIONS FOR USE

Preparation for intravenous administration:
Should be infused over period of 30 minutes
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% or 2.0% lidocaine HCl injection*** (**without epinephrine**). Shake vial thoroughly to form solution. This solution is chemically and physically stable for only 1 hour at 2-8ºC.
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).

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

3. To ensure adequate potency and to avoid microbiological hazard, the reconstituted solution should be used immediately or stored at 2-8ºC for not more that 1 hour. **Note: The reconstituted solution should not be administered intravenously**.

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. Product is for single use in one patient only. Discard any residue.

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 betalactams.

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 and in patients with severe shock or heart block. (Refer to the prescribing information for lidocaine HCl.)

PRECAUTIONS

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 betalactam. 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.

Seizures and other central nervous system (CNS) adverse experiences have been reported during treatment with INVANZ (see ADVERSE REACTIONS). 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. 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 and the dosage of INVANZ re-examined to determine whether it should be decreased or discontinued.

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.)

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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

Mild cases usually respond to drug discontinuation alone. In moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluid, electrolytes and protein replacement should be provided when indicated.

Caution should be taken when administering INVANZ intramuscularly, to avoid inadvertent injection into a blood vessel.

Lidocaine HCl is the diluent for intramuscular administration of INVANZ. Refer to the prescribing information for lidocaine HCl for additional precautions.

During clinical investigation in adult patients treated with INVANZ (1g once a day), seizures, irrespective of drug relationship, occurred in 0.2% of patients during study therapy. Seizures 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 especially in patients with known factors that predispose to convulsive activity.

PREGNANCY

There are no adequate and well-controlled studies in pregnant women.
However, in mice given 700 mg/kg/day, slight decreases in average fetal weights and associated decrease in the average number of ossified sacrocandal vertebrae were observed. Ertapenem crosses in placental barrier in rats. INVANZ should not be used in pregnant women unless the expected therapeutic benefit to the mother clearly outweighs the potential risks to the mother and fetus.

NURSING MOTHERS

Ertapenem is excreted in human milk. INVANZ should not be used in a breastfeeding woman, unless

the expected therapeutic benefit to the mother clearly outweighs the potential risk to the infant.

PEDIATRIC USE

Safety and effectiveness in children have not been established. Therefore, use in patients under 18 years of age is not recommended.

USE IN THE ELDERLY

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

DRUG INTERACTIONS

When ertapenem is administered with probenecid, probenecid competes for active tubular secretion and thus inhibits the renal excretion of ertapenem. Based on total ertapenem concentration, probenecid increased the AUC by 25% and reduced the plasma and renal clearances by 20% and 35%, respectively. The half-life increased from 4.0 to 4.8 hours. Because of the small effect on half-life, the co-administration with probenecid to extend the half-life of ertapenem is not recommended.

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 ertapenem does not inhibit metabolism mediated by any of the six major 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 are unlikely. (See CLINICAL PHARMACOLOGY, *Distribution* and *Metabolism*.)

Other than with probenecid, no specific clinical drug interaction studies have been conducted.

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 PRECAUTIONS)

SIDE EFFECTS

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

In clinical studies, seizures was reported during parenteral therapy in 0.2% of patients treated with ertapenem, 0.3% of patients treated with piperacilline/tazobactam and 0% patients treated with ceftriaxone. Ertapenem was discontinued due to adverse experiences thought to be related in 1.3% of patients.

The most common drug-related adverse experiences reported during parenteral therapy in patients treated with ertapenem were diarrhea (4.3%), infused vein complication (3.9%), nausea (2.9%) and headache (2.1%).

The following drug-related adverse experiences were reported during parenteral therapy in adult patients treated with ertapenem:

Common (≥1/100, <1/10)	Nervous system disorders	Headache
	Vascular disorders	Infused vein complication, phlebitis/thrombophlebitis
	Gastrointestinal disorders	Diarrhea, nausea, vomiting
Uncommon (>1/1000, <1/100)	Nervous system disorders	Dizziness, somnolence, insomnia, seizure, confusion.
	Cardiac and vascular disorders	Extravasation, hypotension
	Respiratory, thoracic and	Dyspnea

mediastinal disorders	
Gastrointestinal disorders	Oral candidiasis, constipation, acid regurgitation, *C. difficile*-associated diarrhea, dry mouth, dyspepsia, anorexia
Skin and subcutaneous tissue disorders	Erythema, pruritus
General disorders and administration site conditions	Abdominal pain, taste perversion, asthenia/fatigue, candidiasis, edema/swelling, fever, pain,chest pain
Reproductive system and breast disorder	Vaginal pruritus

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial (see CLINICAL PHARMACOLOGY, Clinical Studies). During the entire treatment period and a 14 day post treatment follow-up period, drug-related adverse experiences in patients treated with INVANZ included those listed in the table above as well as rash and vaginitis at an incidence of ≥1.0% (common) and allergic reactions, malaise and fungal infections at an incidence of >0.1% but <1.0% (uncommon).

Post-Marketing Experience

The following post-marketing adverse experiences have been reported:

Immune System: anaphylaxis including anaphylactoid reactions

Psychiatric Disorders: altered mental status (including agitation, aggression, delirium, disorientation, mental status changes)

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

Gastrointestinal Disorders: teeth staining

Skin and Subcutaneous Tissue Disorders: Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), urticaria, hypersensitivity vasculitis

Musculoskeletal and Connective Tissue Disorders: muscular weakness

Laboratory Test Findings

The most frequently observed drug-related laboratory abnormalities during parenteral therapy in patients receiving INVANZ were elevations in ALT, AST, alkaline phosphatase and platelet count.

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

Other drug-related laboratory abnormalities included the following: increases in direct serum bilirubin, total serum bilirubin, eosinophils, indirect serum bilirubin, PTT, urine bacteria, BUN, serum creatinine, serum glucose, monocytes, urine epithelial cells, urine red blood cells; decreases in segmented neutrophils, white blood cells, hematocrit, hemoglobin and platelet count.

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 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 three 1-g doses of INVANZ in a 24-hours period resulted in diarrhea and transient dizziness in one patient.

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 insufficiency when hemodialysis (4 hour session) was performed immediately following administration. However, no information is available on the use of hemodialysis to treat overdosage.

Storage condition

Store below 25ºC

Presentation

INVANZ 1 g injection, available in box of 1 vial

Reg. No.: DKI1337700244A1

HARUS DENGAN RESEP DOKTER

Manufactured by:

FAREVA Mirabel

Clermont-Ferrand, France

Registered, Secondary packaged, and Released by:

PT. Merck Sharp Dohme Pharma Tbk,

Pasuruan, Jawa Timur

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