נובמבר 2020

רופא/ה יקר/ה,
רוקח/ת יקר/ה,

הנדון: <u>INVANZ® - אינבנז</u>

Dosage form: Lyophillized Powder for Injection
Composition: Ertapenem (as sodium) 1 gr/vial

חברת מרק שארפ ודוהם (ישראל-1996) בע"מ, (MSD ישראל), מבקשת ליידע על עדכון העלון לרופא של התכשיר INVANZ.

להלן לשון ההתוויות המאושרות לתכשיר:
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.
- Complicated intra-abdominal infections.
- Complicated skin and skin structure infections including diabetic foot infections without osteomyelitis.
- Community acquired pneumonia.
- Complicated urinary tract infections including pyelonephritis.
- Acute pelvic infections including postpartum endomyometritis septic abortion and post surgical gynecologic infections.

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

<u>עדכונים מהותיים שבוצעו בעלון לרופא:</u>
טקסט שהוסף מודגש בקו תחתון, טקסט שנמחק מסומן בקו חוצה.

2.7 Preparation and Reconstitution for Administration
Vials
<u>Adults and pediatric patients 13 years of age and older</u>
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<u>, using a syringe equipped with a 21-gauge or smaller diameter needle. NOTE: Use with a needleless IV system is not recommended</u>.
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).
3. The reconstituted IM solution should be used within 1 hour after preparation. **NOTE: THE RECONSTITUTED SOLUTION SHOULD NOT BE ADMINISTERED INTRAVENOUSLY**.

<u>Pediatric patients 3 months to 12 years of age</u>
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.

[2] Refer to the prescribing information for lidocaine HCl.

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, using a syringe equipped with a 21-gauge or smaller diameter needle. NOTE: Use with a needleless IV system is not recommended.
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. Discard vial with unused portion of INVANZ reconstituted solution.
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). Discard vial with unused portion of INVANZ reconstituted solution.
3. The reconstituted IM solution should be used within 1 hour after preparation. **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.

6 ADVERSE REACTIONS

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6.2 Post-Marketing Experience

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

~~*Pregnancy Category B*~~

Risk Summary

Available data from a small number of postmarketing cases with INVANZ use in pregnancy are insufficient to inform any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In ~~mice and rats given~~ animal reproduction studies after intravenous administration of ertapenem during the period of organogenesis, there was no evidence of developmental malformations in rats at systemic exposures (AUC) up to approximately 1.2 times the human exposure at the maximum recommended human dose (MRHD) and in mice at doses ~~of~~ up to ~~700 mg/kg/day (for mice,~~ approximately 3 times the ~~recommended human dose of 1 g~~ MRHD based on body surface area ~~and for~~ comparison. In pregnant rats~~,~~ administered ertapenem during organogenesis through lactation, fetal toxicity, developmental delays, and impaired reproduction did not occur in first generation offspring at systemic exposures (AUC) approximately 1.2 times the human exposure at the ~~recommended dose of~~ MRHD *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In pregnant rats, intravenous administration of ertapenem dosages of up to 700 mg/kg/day (approximately 1~~ g~~.2 times the MRHD 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~~AUC) during the period of organogenesis (gestation days [GD] 6-20) revealed no maternal or embryofetal effects.

Pregnant mice intravenously administered ertapenem dosages of up to 700 mg/kg/day~~,~~ (approximately 3 times the MRHD based on body surface area comparison) during the period of organogenesis (GD 6-15) showed slight decreases in average fetal ~~weights~~weight and an associated decrease in the average number of ossified sacrocaudal vertebrae. There were no maternal effects at any dosage.

In a pre-postnatal study in rats, ertapenem administered to pregnant rats at dosages up to 700 mg/kg/day (approximately 1.2 times the MRHD based on AUC) during organogenesis through lactation, (GD 6 until Lactation Day (LD) 20) did not result in fetal toxicity, developmental delays, or impaired reproduction in first generation offspring, and fetal deaths and malformations were not increased in second generation offspring.

8.2 Lactation

Risk Summary

Ertapenem is present in human milk *(see Data)*. There are no data on the effects on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INVANZ and any potential adverse effects on the breastfed infant from INVANZ or from the underlying maternal condition.

Data

The concentration of ertapenem in breast milk from 5 lactating women with pelvic infections (5 to 14 days postpartum) measured at random time points daily for 5 consecutive days following the last 1 g dose of intravenous therapy (3 to 10 days of therapy) showed low levels. 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), although 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.~~were~~ The concentration of ertapenem in transitional milk observed~~. Ertapenem crosses the placental barrier in rats.~~ in this study may not reflect the concentration of ertapenem in mature milk.

~~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.~~

12.3 Pharmacokinetics

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Distribution

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~~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.~~

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

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

Ertapenem was ~~neither mutagenic nor~~not genotoxic in ~~the following~~ *in vitro* or *in vivo* assays~~:~~, including: an alkaline elution/rat hepatocyte assay, chromosomal aberration assay in Chinese hamster ovary cells, ~~and~~a TK6 human lymphoblastoid cell mutagenesis assay~~;~~ and ~~in the *in vivo*~~a mouse micronucleus assay.

Impairment of Fertility

In ~~mice and~~ rats, ~~IV doses of~~ intravenous dosages 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 human dose of 1 g based on plasma ~~AUCs) resulted in no effects on mating performance, fecundity,~~ AUC) did not impair fertility~~, or embryonic survival~~.

בעלון לרופא היו עדכונים נוספים שאינם מהותיים ואינם נכללים בהודעה זו. העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום, חברת MSD ישראל, בטלפון 09-9533333.
INVNAZ מופץ ע"י חברת נובולוג בע"מ.

בברכה,

אורית בילין
רוקחת ממונה
MSD ישראל

Refrences:
INVANZ SPC 11/2020