

# PHINPEN MEROPENEM

For IV Injection

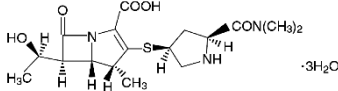
فن پین انجکشن  
(میدروپینم)

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## 500mg & 1gm IV Injection

### 1 DESCRIPTION

PHINPEN IV (meropenem for injection) is a sterile, pyrogen-free, synthetic, carbapenem (antibacterial for intravenous administration. It is (4R,5S,6S)-3-[[[3S,5S]-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6- [[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is  $C_{17}H_{25}N_3O_5S \cdot 3H_2O$  with a molecular weight of 437.52. Its structural formula is:



### COMPOSITION:

Each vial contains:  
Meropenem (as trihydrate) .... 500mg  
(Blended with Sodium Carbonate)  
(USP Specifications)

Each vial contains:  
Meropenem (as trihydrate) ... 1gm  
(Blended with Sodium Carbonate)  
(USP Specifications)

### 2 INDICATIONS AND USAGE

#### 2.1 Complicated Skin and Skin Structure Infections (Adult Patients and Pediatric Patients 3 Months of Age and Older Only)

PHINPEN IV is indicated for the treatment of complicated skin and skin structure infections (cSSSI) due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *viridans* group streptococci, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species.

#### 2.2 Complicated Intra-abdominal Infections (Adult and Pediatric Patients)

PHINPEN IV is indicated for the treatment of complicated appendicitis and peritonitis caused by *viridans* group streptococci, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *B. thetaiotaomicron*, and *Peptostreptococcus* species.

#### 2.3 Bacterial Meningitis (Pediatric Patients 3 Months of Age and Older Only)

PHINPEN IV is indicated for the treatment of bacterial meningitis caused by *Haemophilus influenzae*, *Neisseria meningitidis* and penicillin-susceptible isolates of *Streptococcus pneumoniae*.

PHINPEN IV has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis.

#### 2.4 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PHINPEN IV and other antibacterial drugs, PHINPEN IV should only be used 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.

### 3 DOSAGE AND ADMINISTRATION

#### 3.1 Adult Patients

The recommended dose of PHINPEN IV is 500 mg given every 8 hours for skin and skin structure infections and 1 gram given every 8 hours for intra-abdominal infections. When treating complicated skin and skin structure infections caused by *P. aeruginosa*, a dose of 1 gram every 8 hours is recommended. PHINPEN IV should be administered by intravenous infusion over approximately 15 minutes to 30 minutes. Doses of 1 gram may also be administered as an intravenous bolus injection (5 mL to 20 mL) over approximately 3 minutes to 5 minutes.

Product	Volume of Diluent added (ml)
Meropenem I.V. 500mg	10mL
Meropenem I.V. 1gm	20mL

#### 3.2 Use in Adult Patients with Renal Impairment

Dosage should be reduced in patients with creatinine clearance of 50 mL/min or less. (See dosing table below.)

When only serum creatinine is available, the following formula (Cockcroft and Gault equation) 5 may be used to estimate creatinine clearance.

Males: Creatinine Clearance (mL/min) =

Weight (kg) x (140 - age)  
72 x serum creatinine (mg/dL)

Females: 0.85 x above value

**Table 1: Recommended PHINPEN IV Dosage Schedule for Adult Patients with Renal Impairment**

Creatinine Clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
Greater than 50	Recommended dose (500 mg cSSSI and 1 gram Intra-abdominal)	Every 8 hours
26-50	One-half recommended dose	Every 12 hours
10-25	One-half recommended dose	Every 12 hours

There is inadequate information regarding the use of PHINPEN IV in patients on hemodialysis or peritoneal dialysis.

#### 3.3 Use in Pediatric Patients

##### Pediatric Patients 3 Months of Age and Older

- For pediatric patients 3 months of age and older, the PHINPEN IV dose is 10 mg/kg, 20 mg/kg or 40 mg/kg every 8 hours (maximum dose is 2 grams every 8 hours), depending on the type of infection (cSSSI, cIAI, intra-abdominal infection or meningitis). See dosing table 2 below.
- For pediatric patients weighing over 50 kg administer PHINPEN IV at a dose of 500 mg every 8 hours for cSSSI,
- 1 gram every 8 hours for cIAI and 2 grams every 8 hours for meningitis.
- Administer PHINPEN IV as an intravenous infusion over approximately 15 minutes to 30 minutes or as an intravenous bolus injection (5 mL to 20 mL) over approximately 3 minutes to 5 minutes.

- There is limited safety data available to support the administration of a 40 mg/kg (up to a maximum of 2 grams)
- bolus dose.

**Table 2: Recommended PHINPEN IV Dosage Schedule for Pediatric Patients 3 Months of Age and Older with Normal Renal Function**

Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dosing Interval
Complicated skin and skin structure Infections	10	500 mg	Every 8 hours
Complicated intra-abdominal Infections	20	1 gram	Every 8 hours
Meningitis	40	2 grams	Every 8 hours

There is no experience in pediatric patients with renal impairment. When treating cSSSI caused by *P. aeruginosa*, a dose of 20 mg/kg (or 1 gram for pediatric patients weighing over 50 kg) every 8 hours is recommended.

#### Pediatric Patients Less Than 3 Months of Age

For pediatric patients (with normal renal function) less than 3 months of age, with complicated intra-abdominal infections, the PHINPEN IV dose is based on gestational age (GA) and postnatal age (PNA). See dosing table 3 below. PHINPEN IV should be given as intravenous infusion over 30 minutes.

**Table 3: Recommended PHINPEN IV Dosage Schedule for Pediatric Patients Less than 3 Months of Age with Complicated Intra-abdominal Infections and Normal Renal Function**

Age Group	Dose (mg/kg)	Dose Interval
Infants less than 32 weeks GA and PNA less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks GA and PNA 2 weeks and older	20	Every 8 hours
Infants 32 weeks and older GA and PNA less than 2 weeks	20	Every 8 hours
Infants 32 weeks and older GA and PNA 2 weeks and older	30	Every 8 hours

There is no experience in pediatric patients with renal impairment.

#### 3.4 Preparation and Administration of PHINPEN IV

##### Important Administration Instructions:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### 3.5 Compatibility

Compatibility of PHINPEN IV with other drugs has not been established. PHINPEN IV should not be mixed with or physically added to solutions containing other drugs.

### 3.6 Stability and Storage

Freshly prepared solutions of PHINPEN IV should be used. However, re-constituted solutions of PHINPEN IV maintain satisfactory potency under the conditions described below. Solutions of intravenous PHINPEN IV should not be frozen.

Solutions prepared for infusion (PHINPEN IV concentrations ranging from 1 mg/mL to 20 mg/mL) re-constituted with Sodium Chloride Injection 0.9% may be stored for 1 hour at up to 25°C (77°F) or 15 hours at up to 5°C (41°F).

Solutions prepared for infusion (PHINPEN IV concentrations ranging from 1 mg/mL to 20 mg/mL) re-constituted with Dextrose Injection 5% should be used immediately.

## 4 DOSAGE FORMS AND STRENGTHS

Single dose clear glass vials of PHINPEN IV containing 500 mg or 1 gram (as the trihydrate blended with anhydrous sodium carbonate for re-constitution) of sterile meropenem powder.

## 5 CONTRAINDICATIONS

PHINPEN IV is contra indicated 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 ( $\beta$ )-lactams.

## 6 WARNINGS AND PRECAUTIONS

### 6.1 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 PHINPEN IV, it is important to inquire about previous hypersensitivity reactions to penicillins, cephalosporins, other  $\beta$ -lactams, and other allergens. If an allergic reaction to PHINPEN IV occurs, discontinue the drug immediately.

### 6.2 Seizure Potential

Seizures and other adverse CNS experiences have been reported during treatment with PHINPEN IV. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function [see Adverse Reactions) and Drug Interactions].

During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with the overall seizure rate being 0.7% (based on 20 patients with this adverse event). All meropenem-treated patients with seizures had pre-existing contributing factors. Among these are included prior history of seizures or CNS abnormality and concomitant medications with seizure potential. Dosage adjustment is recommended in patients with advanced age and/or adult patients with creatinine clearance of 50 mL/min or less [see Dosage and Administration].

Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Continue anti-convulsant therapy in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, evaluate neurologically, placed on anti-convulsant therapy if not already instituted, and re-examine the dosage of PHINPEN IV to determine whether it should be decreased or discontinued.

**6.3 Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid**  
The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended. Case reports in the literature have shown that co-administration of carbapenems, including meropenem, 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. Consider administration of antibacterial drugs other than carbapenems to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of PHINPEN IV is necessary, consider supplemental anti-convulsant therapy [see Drug Interactions].

### 6.4 Clostridium difficile-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including PHINPEN IV, 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 *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug 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 antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### 6.5 Development of Drug-Resistant Bacteria

Prescribing PHINPEN IV 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.

### 6.6 Overgrowth of Nonsusceptible Organisms

As with other broad-spectrum antibacterial drugs, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

### 6.7 Thrombocytopenia

In patients with renal impairment, thrombocytopenia has been observed but no clinical bleeding reported [see Dosage and Administration (2.2), Adverse Reactions (6.1), Use in Specific Populations (8.5) and (8.6), and Clinical Pharmacology].

### 6.8 Potential for Neuromotor Impairment

Alert patients receiving PHINPEN IV on an outpatient basis regarding adverse events such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that PHINPEN IV is well tolerated, advise patients not to operate machinery or motorized vehicles [see Adverse Reactions (6.1)].

## 7 ADVERSE REACTIONS

The following are discussed in greater detail in other sections of labeling:

- Hypersensitivity Reactions [see Warnings and Precautions]
- Seizure Potential [see Warnings and Precautions]
- Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid [see Warnings and Precautions]
- Clostridium difficile – associated Diarrhea [see Warnings and Precautions]
- Development of Drug-Resistant Bacteria [see Warnings and Precautions]
- Overgrowth of Nonsusceptible Organisms [see Warnings and Precautions]
- Thrombocytopenia [see Warnings and Precautions]
- Potential for Neuromotor Impairment [see Warnings and Precautions]

### 7.1 Adverse Reactions from Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reactions 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.

#### Adult Patients:

During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with PHINPEN IV (500 mg or 1 gram every 8 hours). Deaths in 5 patients were assessed as possibly related to meropenem; 36 (1.2%) patients had meropenem discontinued because of adverse events. Many patients in these trials were severely ill and had multiple background diseases, physiological impairments and were receiving multiple other drug therapies. In the seriously ill patient population, it was not possible to determine the relationship between observed adverse events and therapy with PHINPEN IV.

The following adverse reaction frequencies were derived from the clinical trials in the 2904 patients treated with PHINPEN IV.

#### Local Adverse Reactions

Local adverse events that were reported with PHINPEN IV were as follows:

Inflammation at the injection site	2.4%
Injection site reaction	0.9%
Phlebitis/thrombophlebitis	0.8%
Pain at the injection site	0.4%
Edema at the injection site	0.2%

#### Systemic Adverse Reactions

Systemic adverse events that were reported with PHINPEN IV occurring in greater than 1.0% of the patients were diarrhea (4.8%), nausea/vomiting (3.6%), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnea (1.3%), shock (1.2%), and pruritus (1.2%).

Additional systemic adverse events that were reported with PHINPEN IV and occurring in less than or equal to 1.0% but greater than 0.1% of the patients are listed below within each body system in order of decreasing frequency:

Bleeding events were seen as follows: gastrointestinal hemorrhage (0.5%), melena (0.3%), epistaxis (0.2%), hemoperitoneum (0.2%).

**Body as a Whole:** pain, abdominal pain, chest pain, fever, back pain, abdominal enlargement, chills, pelvic pain

**Cardiovascular:** heart failure, heart arrest, tachycardia, hypertension, myocardial infarction, pulmonary embolus, bradycardia, hypotension, syncope

**Digestive System:** oral moniliasis, anorexia, cholestatic jaundice/jaundice, flatulence, ileus, hepatic failure, dyspepsia, intestinal obstruction

**Hemic/Lymphatic:** anemia, hypochromic anemia, hypervolemia

**Metabolic/Nutritional:** peripheral edema, hypoxia

**Nervous System:** insomnia, agitation, delirium, confusion, dizziness, seizure, nervousness, paresthesia, hallucinations, somnolence, anxiety, depression, asthenia [see Warnings and Precautions (5.2) and (5.8)]

**Respiratory:** respiratory disorder, dyspnea, pleural effusion, asthma, cough increased, lung edema

**Skin and Appendages:** urticaria, sweating, skin ulcer

**Urogenital System:** dysuria, kidney failure, vaginal moniliasis, urinary incontinence

#### Adverse Laboratory Changes

Adverse laboratory changes that were reported and occurring in greater than 0.2% of the patients were as follows:

**Hepatic:** increased alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and bilirubin

**Hematologic:** increased platelets, increased eosinophils, decreased platelets, decreased hemoglobin, decreased hematocrit, decreased white blood cell (WBC), shortened prothrombin time and shortened partial thromboplastin time, leukocytosis, hypokalemia

**Renal:** increased creatinine and increased blood urea nitrogen (BUN)

**Urinalysis:** presence of red blood cells

#### Complicated Skin and Skin Structure Infections

In a study of complicated skin and skin structure infections, the adverse reactions were similar to those listed above. The most common adverse events occurring in greater than 5% of the patients were: headache (7.8%), nausea (7.8%), constipation (7.0%), diarrhea (7.0%), anemia (5.5%), and pain (5.1%). Adverse events with an incidence of greater than 1%, and not listed above, include: pharyngitis, accidental injury, gastrointestinal disorder, hypoglycemia, peripheral vascular disorder, and pneumonia.

#### Patients with Renal Impairment:

For patients with varying degrees of renal impairment, the incidence of heart failure, kidney failure, seizure and shock reported with PHINPEN IV, increased in patients with moderately severe renal impairment (creatinine clearance 10 to 26 mL/min) [see Dosage and Administration, Warnings and Precautions, Use in Specific Populations and Clinical Pharmacology].

#### Pediatric Patients:

##### Systemic and Local Adverse Reactions

Pediatric Patients with Serious Bacterial Infections (excluding Bacterial Meningitis):

PHINPEN IV was studied in 515 pediatric patients (3 months to less than 13 years of age) with serious bacterial infections (excluding meningitis, see next section) at dosages of 10 mg/kg to 20 mg/kg every 8 hours. The types of systemic and local adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably, or definitely related to PHINPEN IV and their rates of occurrence as follows:

Diarrhea	3.5%
Rash	1.6%
Nausea and Vomiting	0.8%

##### Pediatric Patients with Bacterial Meningitis:

PHINPEN IV was studied in 321 pediatric patients (3 months to less than 17 years of age) with meningitis at a dosage of 40 mg/kg every 8 hours. The types of

systemic and local adverse events seen in these patients are similar to the adults, with the most common adverse reactions reported as possibly, probably, or definitely related to PHINPEN IV and their rates of occurrence as follows:

Diarrhea	4.7%
Rash (mostly diaper area moniliasis)	3.1%
Oral Moniliasis	1.9%
Glossitis	1.0%

In the meningitis studies, the rates of seizure activity during therapy were comparable between patients with no CNS abnormalities who received meropenem and those who received comparator agents (either cefotaxime or ceftriaxone). In the PHINPEN IV treated group, 12/15 patients with seizures had late onset seizures (defined as occurring on day 3 or later) versus 7/20 in the comparator arm. The meropenem group had a statistically higher number of patients with transient elevation of liver enzymes.

##### Pediatric Patients (Neonates and Infants less than 3 months of Age):

PHINPEN IV was studied in 200 neonates and infants less than 3 months of age. The study was open-label, uncontrolled, 98% of the infants received concomitant medications, and the majority of adverse events were reported in neonates less than 32 weeks gestational age and critically ill at baseline, making it difficult to assess the relationship of the adverse events to PHINPEN IV.

The adverse reactions seen in these patients that were reported and their rates of occurrence are as follows:

Convulsion	5.0%
Hyperbilirubinemia (conjugated)	4.5%
Vomiting	2.5%

##### Adverse Laboratory Changes in Pediatric Patients:

Laboratory changes seen in the pediatric studies, including the meningitis studies, were similar to those reported in the adult studies.

#### 7.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of PHINPEN IV. 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.

Worldwide post-marketing adverse reactions not otherwise listed in the Adverse Reactions from Clinical Trials section of this prescribing information and reported as possibly, probably, or definitely drug related are listed within each body system in order of decreasing severity.

**Blood and Lymphatic System Disorders:** agranulocytosis, neutropenia, and leukopenia; a positive direct or indirect Coombs test, and hemolytic anemia.

**Immune System Disorders:** angioedema and drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

**Skin and Subcutaneous Disorders:** toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme.

## 8 DRUG INTERACTIONS

### 8.1 Probenecid

Probenecid competes with meropenem for active tubular secretion, resulting in increased plasma concentrations of meropenem. Co-administration of probenecid with meropenem is not recommended.

### 8.2 Valproic Acid

Case reports in the literature have shown that co-administration of carbapenems, including meropenem, 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. 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. If administration of PHINPEN IV is necessary, then supplemental anti-convulsant therapy should be considered [see Warnings and Precautions.

## 9 USE IN SPECIFIC POPULATIONS

### 9.1 Pregnancy

#### Pregnancy Category B.

There are no adequate and well-controlled studies with meropenem 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.

Reproductive studies have been performed with meropenem in rats at doses of up to 1000 mg/kg/day, and cynomolgus monkeys at doses of up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times higher, respectively, than human exposure at the usual dose of 1 gram every 8 hours). These studies revealed no evidence of impaired fertility or harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (on the basis of AUC comparisons, 0.4 times the human exposure at a dose of 1 gram every 8 hours) and above in rats.

### 9.2 Nursing Mothers

Meropenem has been reported to be excreted in human milk. Caution should be exercised when PHINPEN IV is administered to a nursing woman.

### 9.3 Pediatric Use

The safety and effectiveness of PHINPEN IV have been established for pediatric patients 3 months of age and older with complicated skin and skin structure infections and bacterial meningitis, and for pediatric patients of all ages with complicated intra-abdominal infections.

### Skin and Skin Structure Infections

Use of PHINPEN IV in pediatric patients 3 months of age and older with complicated skin and skin structure infections is supported by evidence from an adequate and well-controlled study in adults and additional data from pediatric pharmacokinetics studies [see Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology and Clinical Studies].

### Intra-abdominal Infections

Use of PHINPEN IV in pediatric patients 3 months of age and older with intra-abdominal infections is supported by evidence from adequate and well-controlled studies in adults with additional data from pediatric pharmacokinetics studies and controlled clinical trials in pediatric patients. Use of PHINPEN IV in pediatric patients less than 3 months of age with intra-abdominal infections is supported by evidence from adequate and well-controlled studies in adults with additional data from a pediatric pharmacokinetic and safety study [see Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology and Clinical Studies].

### Bacterial Meningitis

Use of PHINPEN IV in pediatric patients 3 months of age and older with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the pediatric population [see Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology and Clinical Studies].

### 9.4 Geriatric Use

Of the total number of subjects in clinical studies of PHINPEN IV, approximately 1100 (30%) were 65 years of age and older, while 400 (11%) were 75 years and older. Additionally, in a study of 511 patients with complicated skin and skin structure infections, 93 (18%) were 65 years of age and older, while 38 (7%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; spontaneous reports and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Meropenem is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with renal impairment. 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.

A pharmacokinetic study with PHINPEN IV in elderly patients has shown a reduction in the plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance [see Clinical Pharmacology].

### 9.5 Patients with Renal Impairment

Dosage adjustment is necessary in patients with creatinine clearance 50 mL/min or less [see Dosage and Administration], Warnings and Precautions, and Clinical Pharmacology.

## 10 OVERDOSAGE

In mice and rats, large intravenous doses of meropenem (2200 mg/kg to 4000 mg/kg) have been associated with ataxia, dyspnea, convulsions, and mortalities.

Intentional overdosing of PHINPEN IV is unlikely, although accidental overdosing might occur if large doses are given to patients with reduced renal function. The largest dose of meropenem administered in clinical trials has been 2 grams given intravenously every 8 hours. At this dosage, no adverse pharmacological effects or increased safety risks have been observed.

Limited postmarketing experience indicates that if adverse events occur following overdosage, they are consistent with the adverse event profile described in the Adverse Reactions section and are generally mild in severity and resolve on withdrawal or dose reduction. Consider symptomatic treatments. In individuals with normal renal function, rapid renal elimination takes place. Meropenem and its metabolite are readily dialyzable and effectively removed by hemodialysis;

however, no information is available on the use of hemodialysis to treat overdosage.

PHINPEN IV is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. The pH of freshly constituted solutions is between 7.3 and 8.3. Meropenem is soluble in 5% monobasic potassium phosphate solution, sparingly soluble in water, very slightly soluble in hydrated ethanol, and practically insoluble in acetone or ether.

When re-constituted as instructed, each 1 gram PHINPEN IV vial will deliver 1 gram of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500 mg PHINPEN IV vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq) [see Dosage and Administration].

## 11 CLINICAL PHARMACOLOGY

### 11.1 Mechanism of Action

Meropenem is an antibacterial drug [see Microbiology]

### 11.2 Pharmacokinetics

#### Plasma Concentrations

At the end of a 30-minute intravenous infusion of a single dose of PHINPEN IV in healthy volunteers, mean peak plasma concentrations of meropenem are approximately 23 mcg/mL (range 14-26) for the 500 mg dose and 49 mcg/mL (range 39-58) for the 1 gram dose. A 5-minute intravenous bolus injection of PHINPEN IV in healthy volunteers results in mean peak plasma concentrations of approximately 45 mcg/mL (range 18-65) for the 500 mg dose and 112 mcg/mL (range 83-140) for the 1 gram dose.

Following intravenous doses of 500 mg, mean plasma concentrations of meropenem usually decline to approximately 1 mcg/mL at 6 hours after administration.

No accumulation of meropenem in plasma was observed with regimens using 500 mg administered every 8 hours or 1 gram administered every 6 hours in healthy volunteers with normal renal function. etabolism

There is one metabolite of meropenem that is microbiologically inactive. Excretion in subjects with normal renal function, the elimination half-life of meropenem is approximately 1 hour.

Meropenem is primarily excreted unchanged by the kidneys. Approximately 70% (50% – 75%) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Fecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Urinary concentrations of meropenem in excess of 10 mcg/mL are maintained for up to 5 hours after a 500 mg dose.

### Specific Populations

#### Renal Impairment

Pharmacokinetic studies with PHINPEN IV in patients with renal impairment have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment (creatinine clearance 50 mL/min or less) [see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].

Meropenem IV is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage [see Overdosage].

#### Hepatic Impairment

A pharmacokinetic study with PHINPEN IV in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

#### Geriatric Patients

A pharmacokinetic study with PHINPEN IV in elderly patients with renal impairment showed a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance.

#### Pediatric Patients

The pharmacokinetics of meropenem for injection IV, in pediatric patients 2 years of age or older, are similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in pediatric patients of age 3 months to 2 years.

#### Drug Interactions

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. Following administration of probenecid with meropenem, the mean systemic exposure increased 56% and the mean elimination half-life increased 38%. Co-administration of probenecid with meropenem is not recommended.

### 11.3 Microbiology

#### Mechanism of Action

The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem penetrates the cell wall of most gram-positive and gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Meropenem binds to PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa*; and PBPs 1, 2 and 4 of *Staphylococcus aureus*. Bactericidal concentrations (defined as a 3 log<sub>10</sub> reduction in cell counts within 12 hours to 24 hours) are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes*, against which lethal activity is not observed.

Meropenem has significant stability to hydrolysis by  $\beta$ -lactamases, both penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria.

Meropenem does not have in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE).

#### Resistance

There are several mechanisms of resistance to carbapenems: 1) decreased permeability of the outer membrane of gram- negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, 2) reduced affinity of the target PBPs, 3) increased expression of efflux pump components, and 4) production of antibacterial drug-destroying enzymes (carbapenemases, metallo- $\beta$ -lactamases).

#### Cross-Resistance

Cross-resistance is sometimes observed with isolates resistant to other carbapenems.

#### Interactions with Other Antibacterial Drugs

In vitro tests show meropenem to act synergistically with aminoglycoside antibacterials against some isolates of *Pseudomonas aeruginosa*.

#### Antimicrobial Activity

Meropenem has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections [see Indications and Usage (1)].

#### Gram-positive bacteria

*Enterococcus faecalis* (vancomycin-susceptible isolates only)  
*Staphylococcus aureus* (methicillin-susceptible isolates only)  
*Streptococcus agalactiae*  
*Streptococcus pneumoniae* (penicillin-susceptible isolates only)  
*Streptococcus pyogenes*  
Viridans group streptococci

#### Gram-negative bacteria

*Escherichia coli*  
*Haemophilus influenzae*  
*Klebsiella pneumoniae*  
*Neisseria meningitidis*  
*Proteus mirabilis*  
*Pseudomonas aeruginosa*

#### Anaerobic bacteria

*Bacteroides fragilis*  
*Bacteroides thetaotaomicron*  
*Peptostreptococcus species*

Greater than 90% of the following microorganisms exhibit activity in vitro with a minimum inhibitory concentration (MIC) less than or equal to the meropenem-susceptible breakpoint for organisms of similar genus shown in Table 7. The safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

#### Gram-positive bacteria

*Staphylococcus epidermidis* (methicillin-susceptible isolates only)

#### Gram-negative bacteria

*Aeromonas hydrophila*  
*Campylobacter jejuni*  
*Citrobacter freundii*  
*Citrobacter koseri*  
*Enterobacter cloacae*  
*Hafnia alvei*  
*Klebsiella oxytoca*  
*Moraxella catarrhalis*  
*Morganella morganii*  
*Pasteurella multocida*  
*Proteus vulgaris*  
*Serratia marcescens*

#### Anaerobic bacteria

*Bacteroides ovatus*  
*Bacteroides uniformis*  
*Bacteroides ureolyticus*  
*Bacteroides vulgatus*  
*Clostridium difficile*  
*Clostridium perfringens*  
*Eggerthella lenta*  
*Fusobacterium species*  
*Parabacteroides distasonis*  
*Porphyromonas asaccharolytica*  
*Prevotella bivia*  
*Prevotella intermedia*  
*Prevotella melaninogenica*  
*Propionibacterium acnes*

#### Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antimicrobial drug product for treatment.

#### Dilution Techniques:

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth or agar) 1,3. The MIC values should be interpreted according to the criteria provided in Table.

#### Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method 2,3 and requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-mcg of meropenem to test the susceptibility of microorganisms to meropenem. The disk diffusion interpretive criteria are provided in Table 7.

#### Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to meropenem as MICs can be determined by a standardized test method 2,4. The MIC values obtained should be interpreted according to the criteria provided in Table 4.

**Table 4: Susceptibility Interpretive Criteria for Meropenem**

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤ 1	2	≥ 4	≥ 23	20-22	≤ 19
<i>Pseudomonas aeruginosa</i> <sup>1</sup>	≤ 2	4	≥ 8	≥ 19	16-18	≤ 15
<i>Haemophilus influenzae</i> <sup>2</sup>	≤ 0.5	—	—	≥ 20	—	—
<i>Neisseria meningitidis</i> <sup>2</sup>	≤ 0.25	—	—	≥ 30	—	—
<i>Streptococcus pneumoniae</i> <sup>3,4,5</sup>	≤ 0.25	0.5	≥ 1	—	—	—
<i>Streptococcus agalactiae</i> and <i>Streptococcus pyogenes</i> <sup>2,4,5</sup>	≤ 0.5	—	—	—	—	—
Viridans group streptococci	≤ 0.5	—	—	—	—	—
Anaerobes <sup>6</sup>	≤ 4	8	≥ 16	—	—	—

S = Susceptible, I = Intermediate, R = Resistant

No interpretive criteria have been established for testing enterococci.

Susceptibility of *Staphylococcus aureus* to meropenem may be deduced from testing either cefoxitin or oxacillin.

1. The interpretive criteria for *P. aeruginosa* are based upon the dosing of 1g every 8 hours.
2. The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If isolates yield MIC
3. results other than susceptible, they should be submitted to a reference laboratory for additional testing.
4. For nonmeningitis isolates of *S. pneumoniae* a penicillin MIC of  $\leq 0.06$  mcg/mL or oxacillin zone  $\geq 20$  mm can predict susceptibility to meropenem. MIC testing should be performed on isolates that do not test as susceptible by either of these methods, and on all meningitis *S. pneumoniae* isolates.
5. Reliable disk diffusion tests for meropenem do not yet exist for testing streptococci.
6. MIC values using either Brucella blood or Wilkins Chalgren agar (former medium medium) are considered equivalent, Both microdilution is only recommended for testing the *B. fragilis* group. MIC values for agar or broth microdilution are considered equivalent for that group.

A report of Susceptible indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. 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 a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches concentrations usually achievable at the infection site; other therapy should be selected.

## 12 NONCLINICAL TOXICOLOGY

### 12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis:

Carcinogenesis studies have not been performed.

#### Mutagenesis:

Genetic toxicity studies were performed with meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.

#### Impairment of Fertility:

Reproductive studies were performed with meropenem in rats at doses up to 1000 mg/kg/day, and cynomolgus monkeys at doses up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 gram every 8 hours). There was no reproductive toxicity seen.

## 13 HOW SUPPLIED/STORAGE AND HANDLING

### PHINPEN IV dry powder Injection 500mg

is available in pack of 1 vial with 10mL Sterile Water for injection.

### PHINPEN IV dry powder Injection 1gm

is available in pack of 1 vial with 20mL Sterile Water for injection.

The dry powder should be stored below 30°C.

## 14 PATIENT COUNSELING INFORMATION

- Counsel patients that antibacterial drugs including PHINPEN IV should only be used to treat bacterial infections.
- They do not treat viral infections (e.g., the common cold). When PHINPEN IV is prescribed to treat a bacterial infection, tell patients that although it is common to feel better early in the course of therapy, take the medication 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 PHINPEN IV or other antibacterial drugs in the future.
- Counsel patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, 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 antibacterial drug. If this occurs, patients should contact their physician as soon as possible [see Warnings and Precautions].
- Counsel patients 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 PHINPEN IV. If treatment with PHINPEN IV is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed [see Warnings and Precautions].
- Patients receiving PHINPEN IV on an outpatient basis must be alerted of adverse events such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that PHINPEN IV is well tolerated, patients should not operate machinery or motorized vehicles [see Warnings and Precautions].

## فن پین اینجکشن

(میریوپینیم)

500 ملی گرام اور 1 گرام وریڈی انجکشن

خودک: ڈاکٹری ہدایت کے مطابق استعمال کریں۔

ہدایت: • تازہ تیار شدہ محلول استعمال کریں۔

• تیار شدہ محلول کو شفافیت دیکھنا استعمال نہ کریں۔

• تیار شدہ محلول کو بوزی استعمال کریں۔

• دو اصراف متھرو ڈاکٹر کے کنٹرول پر فروخت کریں۔

• روشنی اور نمی سے بچائیں۔ • بچوں کی پہنچ سے دور رکھیں۔

• تیار شدہ محلول کو ٹھنڈے ہونے سے بچائیں۔

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