

Meropenem for Injection, USP

LEA-020514-00

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEROPENEM FOR INJECTION safely and effectively. See full prescribing information for MEROPENEM FOR INJECTION.

MEROPENEM for injection, for intravenous use

Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Warnings and Precautions, Severe Cutaneous Adverse Reactions (5.2)

6/2018

INDICATIONS AND USAGE

Meropenem for Injection, USP is a penem antibacterial indicated for the treatment of:

- Complicated skin and skin structure infections (adult patients and pediatric patients 3 months of age and older only). (1.1)
- Complicated intra-abdominal infections (adult and pediatric patients). (1.2)
- Bacterial meningitis (pediatric patients 3 months of age and older only). (1.3)

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

DOSAGE AND ADMINISTRATION

- 500 mg every 8 hours by intravenous infusion over 15 to 30 minutes for complicated skin and skin structure infections (cSSSI) for adult patients. When treating infections caused by *Pseudomonas aeruginosa*, a dose of 1 gram every 8 hours is recommended. (2.1)
- 1 gram every 8 hours by intravenous infusion over 15 minutes to 30 minutes for intra-abdominal infections for adult patients. (2.1)
- 1 gram every 8 hours by intravenous bolus injection (5 mL to 20 mL) over 3 minutes to 5 minutes for adult patients. (2.1)
- Dosage should be reduced in adult patients with renal impairment. (2.2)

Recommended Meropenem for Injection, USP 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 to 50	Recommended dose	Every 12 hours
10 to 25	One-half recommended dose	Every 12 hours
Less than 10	One-half recommended dose	Every 24 hours

Pediatric patients 3 months of age and older

Recommended Meropenem for Injection, USP Dosage Schedule for Pediatric Patients 3 Months of Age and Older with Normal Renal Function (2.3)			
Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dosing Interval
Complicated skin and skin structure*	10	500 mg	Every 8 hours
Intra-abdominal	20	1 gram	Every 8 hours
Meningitis	40	2 gram	Every 8 hours

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Meropenem for Injection, USP 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.

1.2 Complicated Intra-abdominal Infections (Adult and Pediatric Patients)

Meropenem for Injection, USP 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.

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

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

Meropenem for Injection, USP has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis.

1.4 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Meropenem for Injection, USP and other antibacterial drugs, Meropenem for Injection, USP 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.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

The recommended dose of Meropenem for Injection, USP 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.

Meropenem for Injection, USP 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.

2.2 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)¹ may be used to estimate creatinine clearance.

$$\text{Males: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x above value

Table 1: Recommended Meropenem for Injection, USP 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 to 50	Recommended dose	Every 12 hours
10 to 25	One-half recommended dose	Every 12 hours
Less than 10	One-half recommended dose	Every 24 hours

There is inadequate information regarding the use of Meropenem for Injection, USP in patients on hemodialysis or peritoneal dialysis.

2.3 Use in Pediatric Patients

Pediatric Patients 3 Months of Age and Older

- For pediatric patients 3 months of age and older, the Meropenem for Injection, USP 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.

- Intravenous infusion is to be given over approximately 15 minutes to 30 minutes.
- Intravenous bolus injection (5 mL to 20 mL) is to be given over approximately 3 minutes to 5 minutes.
- There is no experience in pediatric patients with renal impairment.
*20 mg/kg (or 1 gram for pediatric patients weighing over 50 kg) every 8 hours is recommended when treating complicated skin and skin structure infections caused by <i>P. aeruginosa</i> . (2.3)

Pediatric patients less than 3 months of age

Recommended Meropenem for Injection, USP Dosage Schedule for Pediatric Patients Less Than 3 Months of Age with Complicated Intra-Abdominal Infections and Normal Renal Function (2.3)		
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

- Intravenous infusion is to be given over 30 minutes.
- There is no experience in pediatric patients with renal impairment.
GA: gestational age and PNA: postnatal age

DOSAGE FORMS AND STRENGTHS

500 mg Meropenem for Injection Vial (3)

1 gram Meropenem for Injection Vial (3)

CONTRAINDICATIONS

- Known hypersensitivity to product components or anaphylactic reactions to β-lactams. (4)

WARNINGS AND PRECAUTIONS

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving β-lactams. (5.1)
- Severe cutaneous adverse reactions have been reported in patients receiving Meropenem for Injection, USP. (5.2)
- Seizures and other adverse CNS experiences have been reported during treatment. (5.3)
- Co-administration of Meropenem for Injection, USP with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures. (5.4, 7.2)
- *Clostridium difficile*-associated diarrhea (ranging from mild diarrhea to fatal colitis) has been reported. Evaluate if diarrhea occurs. (5.5)
- In patients with renal dysfunction, thrombocytopenia has been observed. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (2% or less) are: headache, nausea, constipation, diarrhea, anemia, vomiting, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Xellia Pharmaceuticals USA, LLC at safety@xellia.com or 1-833-295-6953, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Co-administration of Meropenem for Injection, USP with probenecid inhibits renal excretion of meropenem and is therefore not recommended. (7.1)
- The concomitant use of Meropenem for Injection, USP and valproic acid or divalproex sodium is generally not recommended. Antibacterial drugs other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. (5.4, 7.2)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Dose adjustment is necessary, if creatinine clearance is 50 mL/min or less. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2021

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

- For pediatric patients weighing over 50 kg administer Meropenem for Injection, USP 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 Meropenem for Injection, USP 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 Meropenem for Injection, USP 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 Meropenem for Injection, USP dose is based on gestational age (GA) and postnatal age (PNA). See dosing table 3 below. Meropenem for Injection, USP should be given as intravenous infusion over 30 minutes.

Table 3: Recommended Meropenem for Injection, USP 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.

2.4 Preparation and Administration of Meropenem for Injection, USP

Important Administration Instructions:

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

For Intravenous Bolus Administration

Re-constitute injection vials (500 mg and 1 gram) with Sterile Water for Injection (see table 4 below). Shake to dissolve and let stand until clear.

Table 4: Volume of Sterile Water for Injection for Reconstitution of Injection Vials

Vial Size	Amount of Diluent Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Average Concentration (mg/mL)
500 mg	10	10	50
1 gram	20	20	50

For Infusion

- Injection vials (500 mg and 1 gram) may be directly re-constituted with a compatible infusion fluid.
- Alternatively, an injection vial may be re-constituted, then the resulting solution added to an intravenous container and further diluted with an appropriate infusion fluid [see *Dosage and Administration* (2.5) and (2.6)].
- Do not use flexible container in series connections.

2.5 Compatibility

Compatibility of Meropenem for Injection, USP with other drugs has not been established. Meropenem for Injection, USP should not be mixed with or physically added to solutions containing other drugs.

2.6 Stability and Storage

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

Intravenous Bolus Administration

Meropenem for Injection, USP vials re-constituted with Sterile Water for Injection for bolus administration (up to 50 mg/mL of Meropenem for Injection, USP) may be stored for up to 3 hours at up to 25°C (77°F) or for 13 hours at up to 5°C (41°F).

Intravenous Infusion Administration

Solutions prepared for infusion (Meropenem for Injection, USP concentrations ranging from 1 mg/mL to 20 mg/mL) reconstituted 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 (Meropenem for Injection, USP concentrations ranging from 1 mg/mL to 20 mg/mL) reconstituted with Dextrose Injection 5% should be used immediately.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Meropenem for Injection, USP 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 (β)-lactams.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with β-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 β-lactam. Before initiating therapy with Meropenem for Injection, USP, it is important to inquire about previous hypersensitivity reactions to penicillins, cephalosporins, other β-lactams, and other allergens. If an allergic reaction to Meropenem for Injection, USP occurs, discontinue the drug immediately.

5.2 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalized exanthematous pustulosis (AGEP) have been reported in patients receiving Meropenem for Injection, USP [see *Adverse Reactions* (6.2)]. If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

5.3 Seizure Potential

Seizures and other adverse CNS experiences have been reported during treatment with Meropenem for Injection, USP. 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* (6.1) and *Drug Interactions* (7.2)]. During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with the overall seizure rate being 1.7% (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* (2.2)].

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, place on anti-convulsant therapy if not already instituted, and re-examine the dosage of Meropenem for Injection, USP to determine whether it should be decreased or discontinued.

5.4 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 Meropenem for Injection, USP is necessary, consider supplemental anti-convulsant therapy [see *Drug Interactions* (7.2)].

5.5 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Meropenem for Injection, USP, and ranges 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.

5.6 Development of Drug-Resistant Bacteria

Preventing Meropenem for Injection, USP 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 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.

5.8 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* (12.3)].

5.9 Potential for Neuromotor Impairment

Alert patients receiving Meropenem for Injection, USP 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 Meropenem for Injection, USP is well tolerated, advise patients not to operate machinery or motorized vehicles [see *Adverse Reactions* (6.1)].

6 ADVERSE REACTIONS

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

- Hypersensitivity Reactions [see *Warnings and Precautions* (5.1)]
- Severe Cutaneous Adverse Reactions [see *Warnings and Precautions* (5.2)]
- Seizure Potential [see *Warnings and Precautions* (5.3)]
- Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid [see *Warnings and Precautions* (5.4)]
- *Clostridium difficile* – associated Diarrhea [see *Warnings and Precautions* (5.5)]
- Development of Drug-Resistant Bacteria [see *Warnings and Precautions* (5.6)]
- Overgrowth of Nonsusceptible Organisms [see *Warnings and Precautions* (5.7)]
- Thrombocytopenia [see *Warnings and Precautions* (5.8)]
- Potential for Neuromotor Impairment [see *Warnings and Precautions* (5.9)]

6.1 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 Meropenem for Injection, USP (500 mg or 1 gram every 8 hours).

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

Meropenem for Injection, USP 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 Meropenem for Injection, USP.

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.

6.2 Post marketing Experience

The following adverse reactions have been identified during post-approval use of Meropenem for Injection, USP. 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.

Skin and Subcutaneous Disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalized exanthematous pustulosis.

7 DRUG INTERACTIONS

7.1 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.

7.2 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 Meropenem for Injection, USP is necessary, then supplemental anti-convulsant therapy should be considered [see *Warnings and Precautions* (5.4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient human data to establish whether there is a drug-associated risk of major birth defects or miscarriages with meropenem in pregnant women.

No fetal toxicity or malformations were observed in pregnant rats and Cynomolgus monkeys administered intravenous meropenem during organogenesis at doses up to 2.4 and 2.3 times the maximum recommended human dose (MRHD) based on body surface area comparison, respectively. In rats administered intravenous meropenem in late pregnancy and during the lactation period, there were no adverse effects on offspring at doses equivalent to approximately 3.2 times the MRHD based on body surface area comparison (see *2.2.2*).

The 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

Meropenem administered to pregnant rats during organogenesis (Gestation Day 6 to Gestation Day 17) in intravenous doses of 240, 500, and 750 mg/kg/day was associated with mild maternal weight loss at all doses, but did not produce malformations or fetal toxicity. The no-observed-adverse-effect-level (NOAEL) for fetal toxicity in this study was considered to be the high dose of 750 mg/kg/day (equivalent to approximately 2.4 times the MRHD of 1 gram every 8 hours based on body surface area comparison). Meropenem administered intravenously to pregnant Cynomolgus monkeys during organogenesis from Day 20 to 50 after mating at doses of 120, 240, and 360 mg/kg/day did not produce maternal or fetal toxicity at the NOAEL dose of 360 mg/kg/day (approximately 2.3 times the MRHD based on body surface area comparison).

In a peri-postnatal study in rats described in the published literature², intravenous meropenem was administered to dams from Gestation Day 17 until Lactation Day 21 at doses of 240, 500, and 1000 mg/kg/day. There were no adverse effects in dams and no adverse effects in the first generation offspring (including developmental, behavioral, and functional assessments and reproductive parameters) except that female offspring exhibited lowered body weights which continued during gestation and nursing of the second generation offspring. Second generation offspring showed no meropenem-related effects. The NOAEL value was considered to be 1000 mg/kg/day (approximately 3.2 times the MRHD based on body surface area comparisons).

Meropenem has been reported to be excreted in human milk. No information is available on the effects of meropenem on the breast-fed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Meropenem for Injection, USP and any potential adverse effects on the breast-fed child from Meropenem for Injection, USP or from the underlying maternal conditions.

8.2 Lactation

Risk Summary

Meropenem has been reported to be excreted in human milk. No information is available on the effects of meropenem on the breast-fed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Meropenem for Injection, USP and any potential adverse effects on the breast-fed child from Meropenem for Injection, USP or from the underlying maternal conditions.

8.4 Pediatric Use

The safety and effectiveness of Meropenem for Injection, USP 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 Meropenem for Injection, USP 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* (1.3), *Dosage and Administration* (2.3), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3) and *Clinical Studies* (14.1)].

Intra-abdominal Infections

Use of Meropenem for Injection, USP 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 Meropenem for Injection, USP 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* (1.2), *Dosage and Administration* (2.3), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3) and *Clinical Studies* (14.2)].

Bacterial Meningitis

Use of Meropenem for Injection, USP 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* (1.3), *Dosage and Administration* (2.3), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3) and *Clinical Studies* (14.3)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Meropenem for Injection, USP, 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 Meropenem for Injection, USP 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* (12.3)].

8.6 Patients with Renal Impairment

Dosage adjustment is necessary in patients with creatinine clearance 50 mL/min or less [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.8), and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

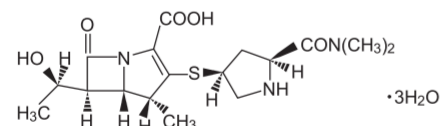
In mice and rats, large intravenous doses of meropenem (2200 mg/kg to 4000 mg/kg) have been associated with ataxia, dyspnea, convulsions, and mortalities.

Intentional overdosing of Meropenem for Injection, USP 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.

11 DESCRIPTION

Meropenem for Injection, USP is a sterile, pyrogen-free, synthetic, carbapenem antibacterial for intravenous administration. It is (4R,5S,6S)-3-[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is C₁₇H₂₀N₂O₆S·3H₂O with a molecular weight of 437.52. Its structural formula is:



Meropenem for Injection, USP 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 Meropenem for Injection, USP vial will deliver 1 gram of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500 mg Meropenem for Injection, USP vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq) [see *Dosage and Administration* (2.4)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meropenem is an antibacterial drug [see *Microbiology* (12.4)].

12.2 Pharmacodynamics

The percentage of time of a dosing interval that unbound plasma concentration of meropenem exceeds the meropenem minimum inhibitory concentration (MIC) against the infecting organism has been shown to best correlate with efficacy in animal and *in vitro* models of infection.

12.3 Pharmacokinetics

Plasma Concentrations

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

Distribution

The plasma protein binding of meropenem is approximately 2%.

After a single intravenous dose of Meropenem for Injection, USP, the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5 hours to 1.5 hours) after the start of infusion, except where indicated in the tissues and fluids listed in Table 5 below.

Table 5: Meropenem Concentrations in Selected Tissues (Highest Concentrations Reported)

Tissue	Intravenous Dose (gram)	Number of Samples	Mean [mcg/mL or mcg/(gram)] ¹	Range [mcg/mL or mcg/(gram)]
Endometrium	0.5	7	4.2	1.7 to 10.2
Myometrium	0.5	15	3.8	0.4 to 8.1
Ovary	0.5	8	2.8	0.6 to 4.8
Cervix	0.5	2	7	5.4 to 8.5
Fallopian tube	0.5	9	1.7	0.3 to 3.4
Skin	0.5	22	3.3	0.5 to 12.6
Interstitial fluid ²	0.5	9	5.5	3.2 to 8.6
Skin	1	10	5.3	1.3 to 16.7
Interstitial fluid ²	1	5	26.3	20.9 to 37.4
Colon	1	2	2.6	2.5 to 2.7
Bile	1	7	14.6 (3 hours)	4 to 25.7
Gall bladder	1	1	-	3.9

Tissue	Intravenous Dose (gram)	Number of Samples	Mean [mcg/mL or mcg/(gram)] ¹	Range [mcg/mL or mcg/(gram)]
Peritoneal fluid	1	9	30.2	7.4 to 54.6
Lung	1	2	4.8 (2 hours)	1.4 to 8.2
Bronchial mucosa	1	7	4.5	1.3 to 11.1
Muscle	1	2	6.1 (2 hours)	5.3 to 6.9
Fascia	1	9	8.8	1.5 to 20
Heart valves	1	7	9.7	6.4 to 12.1
Myocardium	1	10	15.5	5.2 to 25.5
CSF (inflamed)	20 mg/kg ³ 40 mg/kg ⁴	8 5	1.1 (2 hours) 3.3 (3 hours)	0.2 to 2.8 0.9 to 6.5
CSF (uninflamed)	1	4	0.2 (2 hours)	0.1 to 0.3

¹ at 1 hour unless otherwise noted

² obtained from blister fluid

³ in pediatric patients of age 5 months to 8 years

⁴ in pediatric patients of age 1 month to 15 years

Elimination

In subjects with normal renal function, the elimination half-life of meropenem is approximately 1 hour.

Metabolism

There is one metabolite of meropenem that is microbiologically inactive.

Excretion

Meropenem is primarily excreted unchanged by the kidneys. Approximately 70% (50% to 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

Patients with Renal Impairment

Pharmacokinetic studies with Meropenem for Injection, USP 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 for Injection, USP is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage [see *Overdosage* (10)].

Patients with Hepatic Impairment

A pharmacokinetic study with Meropenem for Injection, USP in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Geriatric Patients

A pharmacokinetic study with Meropenem for Injection, USP 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, USP, 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.

The pharmacokinetics of meropenem in patients less than 3 months of age receiving combination antibacterial drug therapy are given below.

Table 6: Meropenem Pharmacokinetic Parameters in Patients Less Than 3 Months of Age^a

	GA less than 32 weeks PNA less than 2 weeks (20 mg/kg every 12 hours)	GA less than 32 weeks PNA 2 weeks or older (20 mg/kg every 8 hours)	GA 32 weeks or older PNA 2 weeks less than 2 weeks (20 mg/kg every 8 hours)	GA 32 weeks or older PNA 2 weeks or older (30 mg/kg every 8 hours)	Overall
CL (L/h/kg)	0.089	0.122	0.135	0.202	0.119
V (L/kg)	0.489	0.467	0.463	0.451	0.468
AUC ₀₋₂₄ (mcg-h/mL)	448	491	445	444	467
C _{max} (mcg/mL)	44.3	46.5	44.9	61	46.9
C _{min} (mcg/mL)	5.36	6.65	4.84	2.1	5.65
T _{1/2} (h)	3.82	2.68	2.33	1.58	2.68

^aValues are derived from a population pharmacokinetic analysis of sparse data

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% [see *Drug Interactions* (7.1)].

12.4 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 bind 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 log₁₀ reduction in cell counts within 12 hours to 24 hours) are typically 1 to 2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes*, against which lethal activity is not observed.

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

Interaction with Other Antimicrobials

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

Antimicrobial Activity

Meropenem has been shown to be active against most isolates of the following microorganisms, 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 thetaiotaomicron

Peptostreptococcus species

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 meropenem against isolates of similar genus or organism group. However, the efficacy of meropenem in treating clinical infections caused by these bacteria 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

Eggerthella perfringens

Fusobacterium lejeune

Fusobacterium species

Parabacteroides distans

Porphyromonas asaccharolytica

Prevotella bivia

Prevotella intermedia

Prevotella melaninogenica

Propionibacterium acnes

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:

Carcinogenesis studies have not been performed.