Meropenem Trihydrate

Morfenexx 1000

1 g Powder for Injection (I.V.)
ANTIBACTERIAL
(CARBAPENEM)

℞

FORMULATION:
Each vial contains:
Meropenem trihydrate USP
eq. to Meropenem ..... 1 g
Sodium Carbonate ..... 90.2 mg

PRODUCT DESCRIPTION:
White to off white crystalline powder.

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems.
Mechanism of Action
Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).
Pharmacokinetic/Pharmacodynamic (PK/PD) relationship
Similar to other beta-lactam antibacterial agents, the time that Meropenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy. In preclinical models Meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40 % of the dosing interval. This target has not been established clinically.
Mechanism of Resistance
Bacterial resistance to Meropenem may result from:
1) Decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins).
2) Reduced affinity of the target PBPs.
3) Increased expression of efflux pump components.
4) Production of beta-lactamases that can hydrolyse carbapenems.
Localized clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union.
There is no target-based cross-resistance between Meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).
Breakpoints
European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.
EUCAST clinical MIC breakpoints for Meropenem (2015-01-01, v5)

Organism	Susceptible (S) (mg/L)	Resistant (R) (mg/L)
Enterobacteriaceae	≤ 2	> 8
Pseudomonas spp.	≤ 2	> 8
Acinetobacter spp.	≤ 2	> 8
Streptococcus groups A, B, C, G	note 6	note 6
Streptococcus pneumoniae [1]	≤ 2	> 2
Viridans group streptococci [2]	≤ 2	> 2
Enterococcus spp.	--	--
Staphylococcus spp.	note 3	note 3
Haemophilus influenzae [1,2] *and Moraxella catarrhalis* [2]	≤ 2	> 2
Neisseria meningitidis [2,4]	≤ 0.25	> 0.25
Gram-positive anaerobes except *Clostridium difficile*	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
Listeria monocytogenes	≤ 0.25	> 0.25
Non-species related breakpoints [5]	≤ 2	> 8

PHARMACOKINETIC PROPERTIES:
In healthy subjects, the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 L/kg (11-27 L) and the mean clearance is 287 mL/min at 250 mg falling to 205 mL/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean C_{max} values of approximately 23, 49 and 115 g/mL respectively, corresponding AUC values were 39.3, 62.3 and 153 g h/mL. After infusion over 5 minutes C_{max} values are 52 and 112 g/mL after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of Meropenem does not occur.
A study of 12 patients administered with Meropenem 1000 mg 8 hourly post-surgically for intra-abdominal infections showed a comparable C_{max} and half-life to normal subjects but a greater volume of distribution 27 L.
Distribution
The average plasma protein binding of Meropenem was approximately 2% and was independent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynecological tissues, skin, fascia, muscle, and peritoneal exudates.
Metabolism
Meropenem is metabolized by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. *In vitro* Meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor.
Elimination
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.
Renal insufficiency
Renal impairment results in higher plasma AUC and longer half-life for Meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCl 33-74 mL/min), 5 fold in severe impairment (CrCl 4-23 m/min) and 10 fold in hemodialysis patients (CrCl <2 mL/min) when compared to healthy subjects (CrCl >80 mL/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment.
Meropenem is cleared by hemodialysis with clearance during hemodialysis being approximately 4 times higher than in anuric patients.
Hepatic insufficiency
A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of Meropenem after repeated doses.
Adult patients
Pharmacokinetics studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.
Pediatrics
The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C_{max} values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months $t_{1/2}$ 1.6 hours). The mean Meropenem clearance values were 5.8 mL/min/kg (6-12 years), 6.2 mL/min/kg (2- 5 years), 5.3 mL/min/kg (6-23 months) and 4.3 mL/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as Meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter- individual variability.
The pharmacokinetics of Meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 %T>MIC for *P. aeruginosa* in 95 % of pre-term and 91 % of full term neonates.
Elderly
Pharmacokinetics studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

INDICATIONS:
Meropenem is indicated in adults and children over 3 months of age in the:
• Treatment of infections caused by susceptible organism, including pneumonia, respiratory tract infections (including cystic fibrosis), urinary tract infections, intra-abdominal infections, intra and post-partum infections, skin and soft tissue infections, and bacterial meningitis.
• Management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

DOSAGE AND ADMINISTRATION:
Posology
The tables below provide general recommendations for dosing.
The dose of Meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.
A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter spp.* or very severe infections.
Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).
Adults and adolescents

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia.	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g
Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes.
Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.
Renal impairment
The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 mL/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

Creatinine clearance (mL/min)	Dose (based on "unit" dose range of 500 mg or 1 g or 2 g, see table above)	Frequency
26-50	one unit dose	every 12 hours
10-25	half of one unit dose	every 12 hours
<10	half of one unit dose	every 24 hours

Meropenem is cleared by hemodialysis and hemofiltration. The required dose should be administered after completion of the hemodialysis cycle.
There are no established dose recommendations for patients receiving peritoneal dialysis.

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment.

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 mL/min.

Pediatric population
Children under 3 months of age
The safety and efficacy of Meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetics data suggest that 20 mg/kg every 8 hours may be an appropriate regimen.
Children from 3 months to 11 years of age and up to 50 kg body weight
The recommended dose regimens are shown in the table below:

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

Children over 50 kg body weight
The adult dose should be administered.
There is no experience in children with renal impairment.

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, Meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.
Meropenem is a white to off white crystalline powder for solution for injection or infusion in vial.
Product after reconstitution is a clear solution.

MEROPENEM FOR INJECTION USP for intravenous infusion maybe directly constituted with a compatible infusion fluid and then further diluted (50 to 200 mL) with the compatible infusion fluid, as needed.

MEROPENEM FOR INJECTION USP is compatible with the following infusion fluids:
0.9% sodium chloride intravenous infusion
5% or 10% glucose intravenous
5% glucose intravenous infusion with 0.02% sodium bicarbonate
5% glucose and sodium chloride intravenous infusion
5% glucose with 0.225% sodium chloride intravenous infusion
5% glucose with 0.15% potassium chloride intravenous infusion
2.5% and 10% mannitol intravenous infusion
normosol-M in 5% glucose intravenous infusion.

DIRECTION FOR RECONSTITUTION:
Intravenous bolus injection administration
A solution for bolus injection is prepared by dissolving the drug product Meropenem in sterile water for injection to a final concentration of 50 mg/mL.
Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated up to 3 hours at controlled room temperature (15-25°C) or up to 8 hours under refrigerated conditions (2-8°C). From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.

Intravenous infusion administration
A solution for infusion is prepared by dissolving the drug product Meropenem in either 0.9% sodium chloride solution for infusion or 5% glucose (dextrose) solution for infusion to a final concentration of 1 to 20 mg/mL.
Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 6 hours at controlled room temperature (15-25°C) or upto12 hours under refrigerated conditions (2-8°C). In this case, the prepared solution if stored under refrigeration (i.e., 2-8°C) should be used within 1 hour after it has left the refrigerator.
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. Reconstituted solution of Meropenem in 5% glucose (dextrose) solution should be used immediately, i.e., within 30 minutes following reconstitution.
Do not freeze the reconstituted solution.

Special precautions for disposal and other handling:
Injection
Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection.
Infusion
For intravenous infusion, Meropenem vial may be directly constituted with 0.9% sodium chloride or 5% glucose (dextrose) solutions for infusion.
Each vial is for single use only.
Standard aseptic techniques should be used for solution preparation and administration.
The solution should be shaken before use. The solutions should be inspected visually for particles and discoloration prior to administration.

CONTRAINDICATIONS:
Hypersensitivity to the active substance.
Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of betalactam antibacterial agent (e.g., penicillins or cephalosporins).

WARNINGS AND PRECAUTIONS:
The selection of Meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.
Enterobacteriaceae, Pseudomonas aeruginosa and *Acinetobacter spp.* resistance
Resistance to penems of *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter* spp. varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.
Hypersensitivity reactions
As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported.
Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to Meropenem. Before initiating therapy with Meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.
If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.
Antibiotic-associated colitis
Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents, including Meropenem, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of Meropenem.
Discontinuation of therapy with Meropenem and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.
Seizures
Seizures have infrequently been reported during treatment with carbapenems, including Meropenem.
Hepatic function monitoring
Hepatic function should be closely monitored during treatment with Meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis).
Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with Meropenem. There is no dose adjustment necessary.
Direct antiglobulin test (Coombs test) seroconversion
A positive direct or indirect Coombs test may develop during treatment with Meropenem.
Concomitant use with valproic acid/ sodium valproate/ valpromide
The concomitant use of Meropenem and valproic acid/sodium valproate is not recommended.
Pediatric population
Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.
Meropenem contains sodium.
This medicinal product contains approximately 2.0 mmol (or 45 mg) of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.

PREGNANCY:
There are limited amount of data from the use of Meropenem in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Meropenem during pregnancy.

LACTATION:
Small amounts of Meropenem have been reported to be excreted in human milk. Meropenem should not be used in breastfeeding women unless the potential benefit for the mother justifies the potential risk to the baby.

Effects on ability to drive and use machines:
No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that headache, paraesthesia and convulsions have been reported for Meropenem.

DRUG INTERACTIONS:
No specific medicinal product interaction studies other than probenecid were conducted.
Probenecid competes with Meropenem for active tubular secretion and thus inhibits the renal excretion of Meropenem with the effect of increasing the elimination half-life and plasma concentration of Meropenem. Caution is required if probenecid is co-administered with Meropenem.
The potential effect of Meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.
Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided.
Oral anticoagulants
Simultaneous administration of antibiotics with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anticoagulant agent.

ADVERSE DRUG REACTIONS:
In a review of 4,872 patients with 5,026 Meropenem treatment exposures, Meropenem-related adverse reactions most frequently reported were diarrhea (2.3 %), rash (1.4 %), nausea/vomiting (1.4 %) and injection site inflammation (1.1 %). The most commonly reported Meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5-4.3 %).
Adverse reactions listed in the table with a frequency of "not known" were not observed in the 2,367 patients who were included in pre-authorisation clinical studies with intravenous and intramuscular Meropenem but have been reported during the post-marketing period.
Tabulated risk of adverse reactions
In the table below all adverse reactions are listed by system organ class and frequency: very common (⩾ 1/10); common (⩾ 1/100 to <1/10); uncommon (⩾ 1/1,000 to <1/100); rare (⩾ 1/10,000 to <1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Table 1

System Organ Class	Frequency	Event
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	thrombocythemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, hemolytic an emia
Immune system disorders	Uncommon	angioedema, anaphylaxis
Nervous system disorders	Common	headache
	Uncommon	paresthesia
	Rare	convulsions
Gastrointestinal disorders	Common	diarrhea, vomiting, nausea, abdominal pain
	Uncommon	antibiotic-associated colitis
Hepatobiliary disorders	Common	increased transaminases increased blood alkaline phosphatase increased blood lactate dehydrogenase.
	Uncommon	increased blood bilirubin
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme.
	Unknown	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome)
Renal and urinary disorders	Uncommon	increased blood creatinine , increased blood urea
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	Thrombophlebitis, pain at the injection site

Pediatric population
Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

OVERDOSE AND TREATMENT:
Relative overdose may be possible in patients with renal impairment. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.
In individuals with normal renal function, rapid renal elimination will occur.
Hemodialysis will remove Meropenem and its metabolite.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Storage at temperatures not exceeding 30°C.

To reduce microbiological hazard, solutions of Meropenem for Injection USP should be used as soon as practicable after reconstitution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours, or the period shown in the following table, which ever is the lesser.

Diluent	Hours stable	
	Up to 25°C.	4°C
Vials constituted with Water for Injections for bolus injection	8	48
Solutions 1 to 20 mg/mL prepared with 0.9% sodium chloride	8	48
5% glucose	3	14
5% glucose and 0.225% sodium chloride	3	14
5% glucose and 0.9% sodium chloride	3	14
5% glucose and 0.15% potassium chloride	3	14
2.5% or 10% mannitol intravenous infusion	3	14
normosol-M in 5% glucose intravenous infusion	3	14
10% glucose	2	8
5% glucose and 0.02% sodium bicarbonate intravenous infusion	2	8

Keep all medicines out of reach of children.

AVAILABILITY:
USP Type I Clear and Tubular Glass vial with grey bromo butyl rubber stopper and sky blue plain flip-off aluminum seal x 30 mL (Box of 1's)

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