Ropenem® Benta

Meropenem Trihydrate

FORMS AND PRESENTATION
Ropenem® 500 Benta: Injectable: Box of 1vial.
Ropenem® 1000 Benta: Injectable: Box of 1vial.
COMPOSITION
Ropenem® 500 Benta: Each vial contains Meropenem Trihydrate equivalent to Meropenem 500mg.
Ropenem® 1000 Benta: Each vial contains Meropenem Trihydrate equivalent to Meropenem 1000mg.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems.
ATC code: J01DH02.
Mode 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 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 Cmax values of approximately 23, 49 and 115 µg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 µg.h/ml. After infusion over 5 minutes Cmax values are 52 and 112 µg/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, which administered Meropenem 1000 mg 8 hourly post-surgically for intra-abdominal infections, showed a comparable Cmax 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 metabolised 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 ml/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
Pharmacokinetic 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 Cmax 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 t1/2 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
Pharmacokinetic 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
Ropenem® Benta is indicated for the treatment of the following infections in adults and children over 3 months of age:
- Severe pneumonia, including hospital and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

Ropenem® Benta may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.
CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.
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).
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.
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 and pseudomembranous colitis have been reported with nearly all anti-bacterial 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 have infrequently been reported during treatment with carbapenems, including Meropenem.
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. No dose adjustment is necessary.
A positive direct or indirect Coombs test may develop during treatment with Meropenem.
The concomitant use of Meropenem and valproic acid/sodium valproate is not recommended.
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.
PREGNANCY AND LACTATION
There are no or 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.
Small amounts of meropenem have been reported to be excreted in human milk. Meropenem should not be used in breast- feeding women unless the potential benefit for the mother justifies the potential risk to the baby
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 anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant 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 normalised 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 anti-coagulant agent.

ADVERSE EFFECTS

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.
- Infections and infestations: oral and vaginal candidiasis (uncommon)
- Blood and lymphatic system disorders: thrombocythaemia (common); eosinophilia, thrombocytopenia, leucopenia, neutropenia; agranulocytosis, haemolytic anaemia (uncommon)
- Immune system disorders: angioedema, anaphylaxis (uncommon)
- Nervous system disorders: headache (common); paresthesia (uncommon); convulsions (rare)
- Gastrointestinal disorders: diarrhea, vomiting, nausea, abdominal pain (common); antibiotic-associated colitis (uncommon)
- Hepatobiliary disorders: transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased (common); blood bilirubin increased (uncommon)
- Skin and subcutaneous tissue disorders: rash, pruritis (common); urticaria; toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme (uncommon)
- Renal and urinary disorders: blood creatinine increased, blood urea increased (uncommon)
- General disorders and administration site conditions: inflammation, pain (common); thrombophlebitis; pain at the injection site uncommon.

DOSAGE AND ADMINISTRATION

The dose of Ropenem® Benta 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.
Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

Adults and Adolescents

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

Ropenem® Benta 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 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

Ropenem® Benta 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 Ropenem® Benta in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic 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 below:
- Severe pneumonia including hospital and ventilator-associated pneumonia: 10 or 20 mg/kg every 8 hours
- Broncho-pulmonary infections in cystic fibrosis: 40 mg/kg every 8 hours
- Complicated urinary tract infections: 10 or 20 mg/kg every 8 hours
- Complicated intra-abdominal infections: 10 or 20 mg/kg every 8 hours
- Complicated skin and soft tissue infections: 10 or 20 mg/kg every 8 hours
- Acute bacterial meningitis: 40 mg/kg every 8 hours
- Management of febrile neutropenic patients: 20 mg/kg every 8 hours

Children over 50 kg body weight
The adult dose should be administered.
There is no experience in children with renal impairment.
Ropenem® Benta is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, Ropenem® Benta 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.

Intravenous bolus injection administration

A solution for bolus injection is prepared by dissolving the drug product in 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 for 3 hours at up to 25°C or 12 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.
If not used immediately in-use storage times and conditions are the responsibility of the user.

Intravenous infusion administration

A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% 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 3 hours at up to 25°C or 24 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.
If not used immediately in-use storage times and conditions are the responsibility of the user.
Reconstituted solution of the product in 5% dextrose solution should be used immediately.
The constituted solutions should not be frozen.

OVERDOSAGE

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they 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.

STORAGE CONDITIONS

Store below 30ºC. Do not freeze the reconstituted solution.
Keep in original pack in intact conditions.

Date of revision: December 2018.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
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