Size : 600x260 mm

60gsm with fold

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Mero-Avenir 500 mg
Mero-Avenir 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Mero-Avenir 500 mg:
Each vial contains Meropenem trihydrate 570.5 mg equivalent to 500 mg Anhydrous Meropenem.

Mero-Avenir 1000 mg:
Each vial contains Meropenem trihydrate 1141 mg equivalent to 1000 mg Anhydrous Meropenem.

Excipients:
Each 500 mg vial contains 104 mg sodium carbonate which equates to approximately 2.0 mEq of sodium (approximately 45 mg)
Each 1000 mg vial contains 208 mg sodium carbonate which equates to approximately 4.0 mEq of sodium (approximately 90 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder for Solution for injection or infusion.
A white to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mero-Avenir is indicated for treatment in adults and children of the following severe infections caused by single or multiple susceptible bacteria sensitive to meropenem:
- Pneumonias and nosocomial pneumonias.
- Pulmonary infections in patients with cystic fibrosis.
- Urinary tract infections.
- Intra-abdominal infections.
- Gynecological infections such as endometritis and pelvic inflammatory disease.
- Skin and skin structure infections.
- Meningitis.
- Septicemia.

Mero-Avenir has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

There is no experience in pediatric patients with neutropenia or primary or secondary immunodeficiency.

4.2 Posology and method of administration

Adults
The dosage and duration of therapy shall be established depending on type and severity of infection and the condition of the patient.

The recommended daily dosage is as follows:
500 mg IV every 8 hours in the treatment of pneumonia, UTI, gynaecological infections such as endometritis, pelvic inflammatory disease, skin and skin structure infections.

1 g IV every 8 hours in the treatment of nosocomial pneumonias, peritonitis, presumed infections in neutropenic patients, septicaemia.

In cystic fibrosis, doses up to 2 g every 8 hours have been used; most patients have been treated with 2 g every 8 hours.

In meningitis the recommended dosage is 2 g every 8 hours.
When treating infections known or suspected to be caused by Pseudomonas aeruginosa, a dose of at least 1g every 8 hours in adults (maximum approved dose is 6g daily given in 3 divided doses) and a dose of at least 20mg/kg every 8 hours in children (maximum approved dose is 120mg/kg/ daily given in 3 divided doses) are recommended.

Regular sensitivity testing is recommended when treating Pseudomonas aeruginosa infection.
There are limited safety data available to support the administration of a 2g bolus dose in adults as an intravenous bolus injection.

Dosage Schedule for Adults with Impaired Renal Function
Dosage should be reduced in patients with creatinine clearance less than 51 ml/min, as scheduled below.

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

Meropenem is cleared by haemodialysis and hemofiltration; if continued treatment with Mero-Avenir is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with the use of Mero-Avenir in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency
No dosage adjustment is necessary in patients with hepatic insufficiency (see Section 4.4).

Elderly Patients
No dosage adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 ml/min.

Children
For children over 3 months and up to 12 years of age the recommended dose is 10 to 20 mg /kg every 8 hours depending on type and severity of infection, susceptibility of the pathogen and the condition of the patient. In children over 50 kg weight, adult dosage should be used.

In meningitis and cystic fibrosis the recommended dose is 40 mg/kg every 8 hours.

There is no experience in children with renal impairment.

Method of Administration
Mero-Avenir is usually given by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2, 6.3 and 6.6). 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 40 mg/kg dose in children as an intravenous bolus injection. There is limited safety data available to support the administration of a 2g bolus dose (in adults).

Appearance of Reconstituted Solution
The reconstituted solution should be clear to slight yellow transparent and should be free of any visible particles.

4.3 Contraindications
Mero-Avenir is contraindicated in patients who have demonstrated:
- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to any other carbapenem antibacterial agents.
- Severe hypersensitivity (e.g anaphylactic reactions, severe skin reactions) to any other type of beta-lactam antibacterial agents (e.g. penicillins or cephalosporins).

4.4 Special warnings and precautions for use
There is some clinical and laboratory evidence of partial cross-allergenicity between other carbapenems and beta-lactam antibiotics, penicillins and cephalosporins.

The selection of Mero-Avenir 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 Mero-Avenir of Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to Mero-Avenir.

Hypersensitivity reactions
As with all beta-lactam antibiotics, (serious and occasionally fatal) hypersensitivity reactions have been reported (see Section 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other betalactam antibiotics may also be hypersensitive to Mero-Avenir. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.
Mero-Avenir should be used with caution in patients with such a history. If an allergic reaction to meropenem occurs, the drug should be discontinued and appropriate measures taken.

If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken. 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 generalised exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem (see Section 4.8).

If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Antibiotic - associated colitis

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 diarrhoea during or subsequent to the administration of meropenem (see section 4.8).

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 (see section 4.8).

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 of Mero-Avenir in patients with hepatic disease should be made with careful monitoring of transaminase and bilirubin levels.

Patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary (see section 4.2).

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/valpromide is not recommended (see section Interactions with other medicinal products and other forms of interaction).
Mero-Avenir may reduce serum valproic acid levels. Sub-therapeutic levels may be reached in some patients.

As with other antibiotics, overgrowth of non-susceptible organisms may occur and, therefore, continuous monitoring of each patient is necessary.

Use in infections caused by methicillin resistant staphylococci is not recommended.

The co-administration of Mero-Avenir with potentially nephrotoxic drugs should be considered with caution. For dosage see Section 4.2.

Mero-Avenir contains sodium.
Mero-Avenir 500 mg: This medicinal product contains approximately 2.0 mEq of sodium per 500 mg dose which should be taken into

consideration by patients on a controlled sodium diet.
Mero-Avenir 1000 mg: This medicinal product contains approximately 4.0 mEq of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.

Paediatric use
Efficacy and tolerability in infants under 3 months old have not been established; therefore, Mero-Avenir is not recommended for use below this age. There is no experience in children with altered hepatic or renal function.

4.5 Interaction with other medicinal products and other forms of interaction

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. As the potency and duration of action of Mero-Avenir dosed without probenecid are adequate, the co-administration of probenecid with Mero-Avenir is not recommended.
Caution is required if probenecid is co-administered with meropenem.

The potential effect of Mero-Avenir on the protein binding of other medicinal products or metabolism has not been studied. The protein binding of Mero-Avenir is low (approximately 2%) and therefore no interactions with other compounds based on displacement from plasma proteins would be expected.

Mero-Avenir may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.
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 Mero-Avenir in patients stabilised on valproic acid/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided (see Special Warnings and Precautions for use).

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 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 normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after coadministration of antibiotics with an oral anti-coagulant agent.

Mero-Avenir has been administered concomitantly with many other medications without apparent adverse interaction. However, no specific drug interaction studies other than probenecid were conducted.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy

The safety of Mero-Avenir in human pregnancy has not been evaluated. Animal studies have not shown any adverse effect on the developing foetus. The only adverse effect observed in animal reproductive studies was an increased incidence of abortions in monkeys at 13 times the expected exposure in man.
As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.
Mero-Avenir should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus. In every case, it should be used under the direct supervision of the physician.

Lactation
Meropenem has been reported to be excreted in small amounts in human milk. Mero-Avenir should not be used in breast-feeding women unless the potential benefit for the mother justifies the potential risk to the baby.

4.7 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 Mero-Avenir.

4.8 Undesirable effects

Mero-Avenir is generally well tolerated. Adverse reactions rarely lead to cessation of treatment. Serious adverse reactions are rare.

Summary of the safety profile in a review of 4,872 patients with 5,026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhoea (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%). Tabulated risk of adverse reactions in the table below all adverse reactions are listed by system organ class and frequency.

The following adverse reactions have been identified following clinical studies with Mero-Avenir. Their frequency is presented in Table 1 Frequency of Adverse Reactions (data derived from clinical trial data sources) using CIOMS III frequency classification and then listed by MedDRA SOC and at the preferred level. Frequencies of occurrence of undesirable effects are defined as: very common (≥1/10; ≥10%); common (≥1/100 to <1/10; ≥1% to <10%); uncommon (≥1/1,000 to <1/100; ≥0.1% to <1%); rare (≥1/10,000 to <1/1,000; ≥0.01% to <0.1%); very rare (<1/10,000; <0.01%) ; not known (cannot be estimated from the available data).

Table 1: Frequency of Adverse Reactions (data derived from clinical trial data sources)

System Organ Class	Frequency	Reaction
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	thrombocythaemia
	Uncommon	agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropenia leucopenia eosinophilia,

Immune system disorders	Uncommon	anaphylaxis (see sections 4.3 and 4.4), angioedema
Psychiatric disorders	Rare	delirium
Nervous system disorder	Common	headache
	Uncommon	paraesthesia
	Rare	convulsions
Gastrointestinal disorders	Common	diarrhea, vomiting, nausea, abdominal pain.
	Uncommon	antibiotic associated colitis
Hepato-biliary disorders	Common	transaminases increased: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased.
	Uncommon	blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme. (see section 4.4), urticaria
	Not known	drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis (see section 4.4)
Renal and urinary disorders	Uncommon	blood creatinine increased, blood urea increased
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis, pain at the injection site

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose
Accidental overdosage could occur during therapy, particularly in patients with renal impairment if the dose is not adjusted as described in section 4.2. Limited post-marketing experience indicates that if adverse events occur following over dosage, they are consistent with the adverse event profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction . Treatment of overdosage should be symptomatic. In normal individuals, rapid renal elimination will occur ; in subjects with renal impairment, haemodialysis will remove meropenem and its metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antibacterials for systemic use, carbapenems, ATC code: J01DH02

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, and (4) production of beta-lactamases that can hydrolyse carbapenems.
Localised 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 antibacterial 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 (2013-02-11, v 3.1)

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 and 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

1. Meropenem breakpoints for Streptococcus pneumoniae and Haemophilus influenzae in meningitis are 0.25 mg/l (Susceptible) and 1 mg/l (Resistant).

2. Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.

3. Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.

4. Breakpoints relate to meningitis only.

5. Non-species related breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Non species related breakpoints are based on the following dosages: EUCAST breakpoints apply to meropenem 1000 mg x 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g x 3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.

6. The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.
-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug. Isolates may be reported as R without prior testing.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.
The following list of pathogens is derived from clinical experience and therapeutic guidelines.

Commonly susceptible species: Gram-positive aerobes:
Enterococcus faecalis (note that E. faecalis can naturally display intermediate susceptibility), Staphylococcus aureus (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSA are resistant to meropenem), Staphylococcus species including Staphylococcus epidermidis (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSE are resistant to meropenem), Streptococcus agalactiae (Group B streptococcus), Streptococcus milleri group (S. anginosus, S. constellatus, and S. intermedius), Streptococcus pneumoniae, Streptococcus pyogenes (Group A streptococcus)

Commonly susceptible species: Gram-negative aerobes:
Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Serratia marcescens

Commonly susceptible species: Gram-positive anaerobes Clostridium perfringens, Peptoniphilus asaccharolyticus, Peptostreptococcus species (including P. micros, P anaerobius, P. magnus)

Commonly susceptible species: Gram-negative anaerobes Bacteroides caccae, Bacteroides fragilis, Prevotella bivia, Prevotella disiens

Species for which acquired resistance may be a problem: Gram-positive aerobes
Enterococcus faecium (E. faecium can naturally display intermediate susceptibility even without acquired resistance mechanisms;

Species for which acquired resistance may be a problem: Gram-negative aerobes
Acinetobacter species, Burkholderia cepacia, Pseudomonas aeruginosa

Inherently resistant organisms: Gram-negative aerobes
Stenotrophomonas maltophilia, Legionella species

Other inherently resistant organisms
Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii, Mycoplasma pneumonia

The published medical microbiology literature describes in-vitro meropenem-susceptibilities of many other bacterial species. However

the clinical significance of such in-vitro findings is uncertain. Advice on the clinical significance of in-vitro findings should be obtained from local infectious diseases and clinical microbiology experts and local professional guidelines.

Meropenem is active in vitro against many strains resistant to other β-lactam antibiotics. This is explained in part by enhanced stability to β-lactamases. Activity in vitro against strains resistant to unrelated classes of antibiotics such as aminoglycosides or quinolones is common. The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Glanders and melioidosis: Use of meropenem in humans is based on in vitro B.mallei and B. pseudomallei susceptibility data and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis.

5.2 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 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, gynaecological tissues, skin, fascia, muscle, and peritoneal exudates.

Biotransformation
Meropenem is metabolised by hydrolysis of the β-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 coadminister 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. Faecal 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 haemodialysis 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 (see section 4.2).

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.

Hepatic insufficiency
A study in patients with alcoholic cirrhosis has shown 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.

Paediatrics
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 (see section 4.2).

5.3 Preclinical safety data

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above after a single administration and above and in monkeys at 500 mg/kg in a 7-day study. Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg.

The IV LD50 of meropenem in rodents is greater than 2000 mg/kg.

In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters in dogs. There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including

teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.
There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies.
The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mero-Avenir 500 mg : anhydrous sodium carbonate.
Mero-Avenir 1000 mg : anhydrous sodium carbonate.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.
After reconstitution:

Chemical and physical in-use stability for a prepared solution has been demonstrated that the product remains stable at concentration of 50 mg/ml for 2 hours at up to 25°C when reconstituted with water for injection and that the product remains stable at concentration of 5-20 mg/ml for 3 hours at up to 25°C or for 24 hours under refrigerated conditions (2-8°C) when reconstituted and diluted with 0.9% Sodium chloride solution .
The reconstituted solution in 5% glucose should be used immediately.
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.

6.4 Special precautions for storage
Store below 30°C.
Store in the original container.
Do not freeze the reconstituted solution.

6.5 Nature and contents of container
Mero-Avenir 500 mg
674.5 mg powder in a 10 ml Type 1 glass vial with stopper (grey butyl rubber with an aluminium caps.)
Mero-Avenir 1000 mg
1349 mg powder in a 20 ml Type 1 glass vial with stopper (grey butyl rubber with an aluminium caps.)

The medicinal product is supplied in pack sizes of 10 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

How to prepare this medicine

i. Wash your hands and dry them very well. Prepare a clean working area.

ii. Remove the Meropenem bottle (vial) from the packaging. Check the vial and the expiry date printed on the box and the vial label. Check that the vial is intact and has not been damaged.

iii. Remove the coloured cap and clean the grey rubber stopper with an alcohol wipe. Allow the rubber stopper to dry.

iv. Connect a new sterile needle to a new sterile syringe, without touching the ends.

v. Draw up the recommended amount of sterile 'Water for Injections' into the syringe. The amount of liquid that you need is shown below:

Meropenem 500 mg Powder for Solution for injection or infusion, vial has a size of 10 ml and can be reconstituted with 10 ml Water for Injections.

Meropenem 1000 mg Powder for Solution for injection or infusion, vial has a size of 20 ml and can be reconstituted with 20 ml Water for Injections.

Dose of Meropenem	Amount of 'Water for Injections' needed for dilution
500 mg (milligrams)	10 ml (millilitres)
1 g (gram)	20 ml
1.5 g	30 ml
2 g	40 ml

Please note: If your prescribed dose of Mero-Avenir is more than 1g, you will need to use more than 1 vial of Mero-Avenir. You can then draw the liquid in the vials into the one syringe.

vi. Put the needle of the syringe through the center of the grey rubber stopper and inject the recommended amount of Water for Injections into the vial or vials of Mero-Avenir.
vii. Remove the needle from the vial and shake the vial well for about 5 seconds, or until all the powder has dissolved. Clean the grey rubber stopper once more with a new alcohol wipe and allow the rubber stopper to dry.
viii. With the plunger of the syringe pushed fully into the syringe, put the needle back through the grey rubber stopper. You must then hold both the syringe and the vial and turn the vial upside down.
ix. Keeping the end of the needle in the liquid, pull back the plunger and draw all the liquid in the vial into the syringe.
x. Remove the needle and syringe from the vial and throw the empty vial away in a safe place.
xi. Hold the syringe upright, with the needle pointing upwards. Tap the syringe so that any bubbles in the liquid rise to the top of the syringe.
xii. Remove any air in the syringe by gently pushing the plunger until all the air has gone.

xiii. If you are using Mero-Avenir at home, dispose of any needles and infusion lines that you have used in an appropriate way. If your doctor decides to stop your treatment, dispose of any unused Mero-Avenir in an appropriate way.

Please note:
An Intravenous infusion of Mero-Avenir may be prepared by directly constituting the contents of the vials with 0.9 % sodium chloride or 5% glucose solutions for infusion. Please follow the instructions that stated below:

1. To Mero-Avenir 500 mg add 10 ml of the infusion diluent, then shake well to reconstitute and then add this to the Diluent infusion bag.

2. To Mero-Avenir 1000 mg add 20 ml of the infusion Diluent, then shake well to reconstitute and then add this to the Diluent infusion bag.

The following concentration is achieved in the infusion bag when the infusion is prepared:

Dose of Meropenem	Infusion Diluent	Resulting concentration of infusion
500 mg	100 ml 0.9% NaCl	5 mg/ ml
500 mg	100 ml 5% Glucose	5 mg/ ml
1 gram	100 ml 0.9% NaCl	10 mg/ ml
1 gram	100 ml 5% Glucose	10 mg/ ml

Appearance of Reconstituted Solution
The reconstituted solution should be clear to slight yellow transparent and should be free of any visible particles.

The re-constituted solution in the vial should be shaken to dissolve the entire contents of the vial.

Injection
Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection as mentioned above.

Infusion
For intravenous infusion, meropenem vials may be directly constituted with 0.9 % sodium chloride or 5% glucose solutions for infusion as described above.

Each vial is for single use only.

Standard aseptic techniques should be used for solution preparation and administration.
Any unused product or waste material should be disposed of in accordance with local requirements.

Mero-Avenir should not be mixed with or physically added to solutions containing other drugs. Solutions of Mero-Avenir should not be frozen.

7. LICENSE HOLDER ABROAD:
VENUS PHARMA GmbH, Germany
Werne, Germany

8. MANUFACTURER
VENUS REMEDIES LIMITED, INDIA
Hill Top Industrial Estate, Jharmajri, EPIP, Phase-I (extension),
Bhatoli Kalan, Baddi, Himachal Pradesh, 173205, India

9. REGISTRATION HOLDER
Bio-Avenir Ltd.
1 David Hamelech ST., Herzelia Pituach 4666101, Israel

10. REGISTRATION No.
MERO-AVENIR 500 MG 156 44 34151 00
MERO-AVENIR 1000 MG 156 45 34109 00

Revised in 05/2021 according to MOH guidelines
MERO 500 & 1000 -SPC-0521-01

C4\SM\M500\0146-02, C4\SM\M1000\0147-02