2D Matrix Code position may change as per Supplier's m/c requirement

MEROGRAM P1519545

MEROGRAM P1519545

Summary of Product Characteristics

MEROGRAM

Meropenem Powder for Solution for Injection 500 mg/vial & 1000 mg/vial

1. NAME OF THE MEDICINAL PRODUCT: MEROGRAM 500 (Meropenem Powder for Solution for Injection 500 mg/vial).
MEROGRAM 1000 (Meropenem Powder for Solution for Injection 1000 mg/vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Merogram 500:
Each vial contains: Meropenem trihydrate Ph.Eur. equivalent to 500 mg anhydrous meropenem
Sodium carbonate Ph.Eur. 104 mg
Merogram 1000:
Each vial contains: Meropenem trihydrate Ph.Eur. equivalent to 1000 mg anhydrous meropenem
Sodium carbonate Ph.Eur. 208 mg

3. PHARMACEUTICAL FORM
Powder for solution for Injection or infusion
A white to pale yellow crystalline powder

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Meronem IV is indicated for treatment, in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem.
- Pneumonias and Nosocomial Pneumonias
- Urinary Tract Infections
- Intra-abdominal Infections
- Gynaecological Infections, such as endometritis and pelvic inflammatory disease
- Skin and Skin Structure Infections
- Meningitis
- Septicaemia
- Empiric treatment, for presumed infections in adult patients with febrile neutropenia, used as monotherapy or in combination with anti-viral or anti-fungal agents.

Meronem IV has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

There is no experience in paediatric 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, 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 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 120 mg/kg daily given in 3 divided doses) are recommended.

There is limited safety data available to support a dose of above 2g three times daily (or every 8 hours).

Regular sensitivity testing is recommended when treating Pseudomonas aeruginosa infections.

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 haemofiltration; if continued treatment with Meronem IV 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 Meronem IV in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency
No dosage adjustment is necessary in patients with hepatic insufficiency (see "Special warnings and precautions for use").

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 10-20 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 the recommended dose is 40 mg/kg every 8 hours.

There is no experience in children with renal impairment.

Method of Administration
Meronem IV can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes using the specific available presentations.

There is limited safety data available to support the administration of a 40 mg/kg bolus dose.

There is limited safety data available to support the administration of a 2g bolus dose.

Meronem IV to be used for bolus intravenous injection should be constituted with sterile Water for Injections (5 mL per 250 mg Meropenem). This provides an approximate concentration of 50 mg/mL. Constituted solutions are clear, and colourless or yellow.

Meronem IV for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 mL) (see "Incompatibilities and Special precautions for storage").

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any other carbapenem antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

4.4 Special warnings and precautions for use
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 different regions. 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 (see sections 4.3 and 4.8).

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.

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 Meronem IV (See "Undesirable effects"). 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) (see section 4.8).

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 (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 4.5).

Paediatric population

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

Keep all medicines away from children.

Meropenem contains sodium.

Meropenem 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.

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

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. 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/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided (see section 4.4).

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.

4.6 Pregnancy and lactation
Pregnancy
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 (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Breast-feeding
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.

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, paraesthesiae and convulsions have been reported for meropenem.

4.8 Undesirable effects
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 %).

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). 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	thrombocythaemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia
Immune system disorders	Uncommon	angioedema, anaphylaxis (see sections 4.3 and 4.4)
Psychiatric disorders	Rare	delirium
Nervous system disorders	Common	headache
	Uncommon	paraesthesiae
	Rare	convulsions (see section 4.4)
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea, abdominal pain
	Uncommon	antibiotic-associated colitis (see section 4.4)
Hepatobiliary disorders	Common	transaminases 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	urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme.
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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose
Relative overdose may be possible 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 reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8, 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.

Haemodialysis will remove meropenem and its metabolite.

5. Pharmacological properties
5.1 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/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 betalactamases that can hydrolyse carbapenems.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.

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 (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

Black A/s: 254 x 470 mm Booklet Size: 35 x 60 mm

AUROBINDO Packaging Development	Product: Merogram Injection	Component: Leaflet	Item Code: P1519545	Date & Time: 26.08.2021 & 6.00 PM
	Customer / Country: Singapore_Eugia_Unit-2	Version No.: 03	Reason Of Issue: NEW	Reviewed / Approved by
Team Leader: Surender	Dimensions: 254 x 470 mm	No. of Colours : 01		
Initiator: Nagaraju				
Artist: Vision Graphic Designers	2D code: P1519545			
Additional Information :				Sign / Date

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 table of pathogens listed is derived from clinical experience and therapeutic guidelines.

Commonly susceptible species
Gram-positive aerobes
Enterococcus faecalis[$]
*Staphylococcus aureus (*methicillin-susceptible*)*[£]
Staphylococcus species (methicillin-susceptible) including *Staphylococcus epidermidis*
Streptococcus agalactiae (Group B)
Streptococcus milleri group (*S. anginosus*, *S. constellatus*, and *S. intermedius*)
Streptococcus pneumoniae
Streptococcus pyogenes (Group A)

Gram-negative aerobes
Citrobacter freudii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Neisseria meningitides
Proteus mirabilis
Proteus vulgaris
Serratia marcescens

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

Gram-negative anaerobes
Bacteroides caccae
Bacteroides fragilis group
Prevotella bivia
Prevotella disiens

Species for which acquired resistance may be a problem
Gram-positive aerobes
Enterococcus faecium[$†]

Gram-negative aerobes
Acinetobacter species
Burkholderia cepacia
Pseudomonas aeruginosa

Inherently resistant organisms
Gram-negative aerobes
Stenotrophomonas maltophilia
Legionella species

Other micro-organisms
Chlamydophila pneumoniae
Chlamydophila psittaci
Coxiella burnetii
Mycoplasma pneumoniae
$ Species that show natural intermediate susceptibility
£ All methicillin-resistant staphylococci are resistant to meropenem
† Resistance rate ≥ 50% in one or more EU countries.
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.

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.

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. 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 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.

Paediatric population
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
Sodium carbonate, anhydrous

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
24 months

After 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 upto 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.

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 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. If not used immediately in-use storage times and conditions are the responsibility of the user.

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.

6.4 Special precautions for storage
Do not store above 30°C.

This medicinal product does not require any special storage conditions.

Do not freeze the reconstituted solution.

6.5 Nature and contents of container
Meropenem 500 mg:
674.78mg powder in a 30ml Type-I, tubular, clear glass vial with stopper (bromobutyl rubber with aluminum seals having taxim blue colour polypropylene discs).
Meropenem 1000 mg:
1349.56 mg powder in a 40ml Type-I, tubular, clear glass vial with stopper (bromobutyl rubber with aluminum seals having white colour polypropylene discs).

The medicinal product is supplied in pack sizes of 1 vial.

6.6 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.

The product should be inspected visually for particulate matter, damage to the container or discolouration (solution should be colourless to pale yellow) prior to administration. Discard the product if such defects are observed.

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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufactured by:
Eugia Pharma Specialities Limited,
Unit-2, A-1128, RIICO Industrial Area,
Phase-III, Bhiwadi-301 019, District - Alwar,
Rajasthan, India.

8. Distributed in Singapore By:
Apotheca Marketing Pte. Ltd.,
63 Hillview Avenue # 09-16,
Lam Soon Industrial Building,
Singapore 669569.

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