Summary of Product Characteristics

MEROGRAM

MEROPENEM FOR INJECTION USP 500 mg & 1000 mg

NAME OF DRUG PRODUCT : Meropenem for injection USP 500 mg.
Meropenem for injection USP 1000 mg.

(TRADE) NAME OF PRODUCT: MEROGRAM 500
MEROGRAM 1000

STRENGTH : 500 mg and 1000 mg.

PHARMACEUTICAL DOSAGE FORM : Powder for Injection/ infusion.

QUALITATIVE AND QUANTITATIVE COMPOSITION:

MEROGRAM 500:
Each vial contains: Meropenem Trihydrate USP equivalent to Anhydrous Meropenem 500 mg and Sodium (As Sodium Carbonate) 45.1 mg.
MEROGRAM 1000:
Each vial contains: Meropenem Trihydrate USP equivalent to Anhydrous Meropenem 1000 mg and Sodium (As Sodium Carbonate) 90.2 mg.

PHARMACEUTICAL FORM: A white to off white crystalline powder.

CLINICAL PARTICULARS:

Therapeutic indications:

Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age:
• Pneumonia, including community acquired pneumonia and nosocomial 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
Meropenem may be used in the management of neutropenic patients with fever that is suspected to be due to bacterial infection.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology and method of administration:

Adults:

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.
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**
Pneumonia including community-acquired pneumonia and nosocomial 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 haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis 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 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 in the table below:

Infection	**Dose to be administered every 8 hours**
Pneumonia including community-acquired pneumonia and nosocomial 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.

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 beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

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.

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 enquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If 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. There is no dose adjustment 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.

Meropenem contains sodium.

Meropenem for Injection or Infusion contains approximately 2.0 mEq and 4.0 mEq of sodium per vial for 500 mg and 1000 mg respectively which should be taken into consideration by patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction:

No specific medicinal product interaction studies other than probenecid have been 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 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.

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

It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman.

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects:

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. 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.

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
	Not known	Agranulocytosis, haemolytic anaemia
Immune system disorders	Not known	Angioedema, anaphylaxis
Nervous system disorders	Common	Headache
	Uncommon	Paranesthesia
	Rare	Convulsions
Gastrointestinal disorders	Common	Diarrhoea, vomiting, nausea, abdominal pain
	Not known	Antibiotic-associated colitis
Hepatobiliary disorders	Common	Transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased
	Uncommon	Blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	Rash, pruritis
	Uncommon	Urticaria
	Not known	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
	Not known	Pain at the injection site

Overdose:

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 consistent with the adverse reaction profile, 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

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:

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).

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 includes impermeability and/or an efflux pump(s).

Breakpoints

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below (2009-06-05, v 3.1).

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

1 Meropenem breakpoints for Streptococcus pneumoniae and Haemophilus influenzae in meningitis are 0.25/1 mg/L.

2 Strains with MIC values above the S/I breakpoint are 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 above the current breakpoint (in italics) they should be reported as resistant.

3 Susceptibility of staphylococci to meropenem is inferred from the methicillin susceptibility.

4 Meropenem breakpoints in Neisseria meningitides relates to meningitis only.

5 Non-species related breakpoints have been determined mainly from PK/PD data and are independent of the MIC distributions of specific species. They are for use for species not mentioned in the table and footnotes.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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)£
Stahylococcus species (methicillin-susceptible) including Staphylococcus epidermis
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 meningitidis
Proteus mirablis
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 burnetti
Mycoplasma pneumonia
$ Species that show natural intermediate susceptibility
£ All methicillin-resistant staphylococci are resistant to meropenem
† Resistance rate ≥50% in one or more EU countries.

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 (Cr_{CL} 33-74 ml/min), 5 fold severe impairment (Cr_{CL} 4-23 ml/min) and 10 fold haemodialysis patients (Cr_{CL} <2 ml/min) when compared to healthy subject (Cr_{CL}>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 haemodialysis with clearance during haemodialysis being approximately 4 times higher that in anuric patients.

Hepatic insufficiency:

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.

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 pharomacokinetics 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium Carbonate

Incompatibilities

This medicinal product must not be mixed with other medicinal product.

Shelf life

24 Months

After reconstitution:

The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed one hour.

Special precautions for storage

Store below 30°C.

The container should be kept in the outer carton until immediately before use.

Reconstituted solution of medicinal product should be immediately used after reconstitution.

Directions for use

Injection:

MEROGRAM to be used for bolus I.V Injection should be constituted with sterile water for Injection.

Infusion:

For I.V Infusion MEROGRAM vials may be directly constituted with following diluents:
0.9% Sodium Chloride Injection
5% or 10% Dextrose Injection
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose Injection with 0.225% or 0.45% saline solution
5% Dextrose Injection with 0.15% potassium chloride solution Mannitol 5% and 10%.

Nature and contents of container

MEROGRAM 500: Clear glass vials USP Type I stoppered with Gray bromobutyl rubber stoppers having a diameter of 20mm and sealed with 20mm flip off white color seal.

MEROGRAM 1000: Clear glass vials USP Type I stoppered with Gray bromobutyl rubber stoppers having a diameter of 20mm and sealed with 20mm flip off white color seal.

Special precautions for disposal:

This medicinal product is single use only. Discard any unused contents.

MARKETING AUTHORISATION HOLDER

Eugia Pharma Specialities Limited

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DATE OF PREPARATION OF THIS LEAFLET

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