SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

MEROSAN® 0.5

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains

Meropenem Trihydrate equivalent to 0.5 g of Meropenem Anhydrous

3. PHARMACEUTICAL FORM

Sterile Powder for Injection

Before reconstitution : Powder, white to pale yellow

After reconstitution : Clear solution, yellow (Between standard color solution Y_4 and Y_5)

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

MEROSAN® is indicated for the treatment of the following infections in adults and children aged 3 months and older (see sections 4.4 and 5.1):

- Severe pneumonia, including hospital and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

MEROSAN® may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Posology

The tables below provide general recommendations for dosing.

The dose of meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.

A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as infections due to less susceptible

bacterial species (e.g. Enterobacteriaceae Pseudomonas aeruginosa or Acinetobacter spp.) or very severe infections.
Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

Adults and Adolescents

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

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see section 6.2, 6.3 and 6.6).
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 administration 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 (see section 4.4).

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 (see section 5.2).

- **Children from 3 months to 11 years of age and up to 50 kg body weight**
  The recommended dose regimens are shown in the table below:

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

- **Children over 50 kg body weight**
  The adult dose should be administered.
  There is no experience in children with renal impairment.
  Method of administration
  Meropenem 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 a 40 mg/kg dose in children as an intravenous bolus injection.
  For instructions on reconstitution of the medicinal product before administration, see section 6.6.
  Meropenem is a white to pale yellow crystalline powder for solution for injection or infusion in vial.

Product after reconstitution is clear colourless to yellow solution.

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 betalactam antibacterial agent (e.g. penicillins or cephalosporins).

4.4 Special Warnings and Special 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 the European Union. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Hypersensitivity reactions

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported (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 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) (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).
This medicinal product contains 90 mg sodium per dose, equivalent to 4.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
The maximum daily dose of this product is equivalent to ≥ 27% of the WHO recommended maximum daily intake for sodium.
Meropenem is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other FPPs 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 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 normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

Pediatric population

Interaction studies have only been performed in adults.

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.

Breastfeeding

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, paraesthesia 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 %).

Tabulated risk of adverse reactions

In the table below all adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

System Organ Class	Frequency	Event
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	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.
	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)

System Organ Class	Frequency	Event
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

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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 – Meropenem

- 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 antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).

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 µ g/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 µ g.h/ml. After infusion over 5 minutes Cmax values are 52 and 112 µ g/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.
A study of 12 patients administered 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 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

There is no excipient in this product.

6.2 Incompatibility

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

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

The medicinal product does not require any special storage condition.

After reconstitution: The constituted solutions for intravenous injection should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection should not exceed:

- 2 hours when stored at controlled room temperature (15-25^{o}C)
- 12 hours when stored under refrigerated conditions (2-8^{o}C)

6.5 Nature and Contents of Container

Box of 1 vial @ 0.5 g

(Primary packaging : Vial glass type I)

6.6 Special Precautions for Disposal and other Handling

- The constituted solution of **MEROSAN®** should not be frozen
- Discard any unused solutions after these periods.

7. MARKETING AUTHORIZATION HOLDER

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8. MANUFACTURE NAME

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9. DATE OF REVISION OF THE TEXT

August 21th, 2024