1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

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1. NAME OF THE MEDICINAL PRODUCT:

COMBIPACK OF MEROPENEM FOR INJECTION USP 1 GM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each combipack contains:

a) Each vial contains:

Meropenem Trihydrate USP

Equivalent to Anhydrous Meropenem 1 gm

Sodium Carbonate (Sodium 90.2 mg)

3. PHARMACEUTICAL FORM

Powder for Solution for Injection or Infusion

4. CLINICAL PARTICULARS

4.1 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 a bacterial infection.

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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.

Paediatric 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity to any other carbapenem antibacterial agent.

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

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.

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported.

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents, including meropenem, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea 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 1.0 g: 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.

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 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.

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.

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.

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.

4.8 UNDESIRABLE EFFECTS

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.

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	Paraesthesiae
	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	Common	rash, pruritis

tissue disorders	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

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: antibacterial 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 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 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 27l.

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 bi-exponential 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.

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.

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.

5.3 PRECLINICAL SAFETY DATA

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None

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

36 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 upto 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

Store below 30°C. Protect from light..

KEEP OUT OF REACH OF CHILDREN

6.5 NATURE AND CONTENTS OF CONTAINER

30 ml Plain Glass Vial packed in a carton along with an insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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.

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. The solutions should be inspected visually for particles and discolouration prior to administration. Only clear colourless to yellow solution, free from particles should be used.

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

7. APPLICANT/MANUFACTURER

MARKETED BY:

EXCEL CHARIS PHARM. CHEM. LTD.

NO. 9 ogungbesan street coker

orile igamu lagos, Nigeria.

Manufactured By:

SWISS PARENTERALS LIMITED

Manufacturing site : Plot No 402, 412-414, Kerala Industrial Estate, GIDC Nr. Bavla,

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