Adcock Ingram Critical Care (Pty) Ltd.
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SCHEDULING STATUS: **S4**

1 NAME OF THE MEDICINE

ADCO MEROPENEM 500 mg IV powder for solution for intravenous injection

ADCO MEROPENEM 1 000 mg IV powder for solution for intravenous injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

ADCO MEROPENEM 500 mg IV:

Each vial contains meropenem trihydrate equivalent to 500 mg meropenem.

ADCO MEROPENEM 1 000 mg IV:

Each vial contains meropenem trihydrate equivalent to 1 000 mg meropenem.

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder: White to light yellow powder in a vial.

4 CLINICAL PARTICULARS

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4.1 Therapeutic indications

ADCO MEROPENEM is indicated for the treatment, in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem and as empiric therapy prior to the identification of the causative organism.

Acute exacerbation of chronic bronchitis and pneumonia due to:

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pneumoniae

Streptococcus spp.

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Pseudomonas aeruginosa

Branhamella catarrhalis

Klebsiella pneumoniae

Klebsiella spp.

Enterobacter cloacae

Enterobacter spp.

Acinetobacter

Pneumonia in children due to:

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pneumoniae

Haemophilus influenzae

Pseudomonas aeruginosa

Urinary tract infections in adults and children, including complicated infections due to:

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Escherichia coli *Pseudomonas aeruginosa*

Enterobacter cloacae *Morganella morganii*

Proteus mirabilis *Serratia marcescens*

Citrobacter freundii

Pelvic inflammatory disease (including tubo-ovarian abscess) and endometritis due to:

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus haemolyticus

Staphylococcus spp. (methicillin-susceptible strains only)

Staphylococcus spp. (coagulase negative) (methicillin susceptible strains only) *Streptococcus agalactiae Group B*

Pseudomonas aeruginosa *Streptococcus* spp.

Streptococcus viridians *Acinetobacter anitratus*

Acinetobacter lwoffii *Enterobacter aerogenes*

Enterobacter cloacae *Escherichia coli*

Gardnerella vaginalis *Klebsiella pneumoniae*

Neisseria gonorrhoeae *Proteus mirabilis*

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Skin and skin structure infections in adults due to:

Escherichia coli *Klebsiella pneumoniae*

Proteus mirabilis *Pseudomonas aeruginosa*

Staphylococcus aureus (methicillin susceptible strains only)

Coagulase negative Staphylococcus (methicillin susceptible strains only)

Streptococcus agalactiae *Group A Streptococcus*

Streptococcus viridans *Bacteroides fragilis*

Peptostreptococcus spp.

Meningitis in adults and children due to:

Streptococcus pneumoniae *Haemophilus influenzae*

Neisseria meningitidis

Septicaemia in adults and children due to:

Streptococcus pneumoniae *Escherichia coli*

Klebsiella pneumoniae

Empiric treatment, including initial monotherapy, for presumed bacterial infections in host-compromised neutropenic patients due to:

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Streptococcus sanguis *Escherichia coli*

Pseudomonas aeruginosa *Streptococcus epidermidis*

Intra-abdominal abscess and peritonitis due to:

Streptococcus milleri *Streptococcus mitior*

Enterococcus faecalis *Escherichia coli*

Klebsiella pneumonia *Pseudomonas aeruginosa*

Bacteroides fragilis *Bacteroides ovatus*

Bacteroides distasonis *Klebsiella oxytoca*

Clostridium perfringens

Polymicrobial infections

4.2 Posology and method of administration

Posology

Adults:

Usual dose:

500 mg to 1 g by intravenous administration every 8 hours depending on the type and severity of infection, the known or expected susceptibility of the pathogen(s), and the condition of the patient.

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Exceptions:

Febrile episodes in neutropenic patients - the dose should be 1 g every 8 hours.

Meningitis - the dose should be 2 g every 8 hours.

Caution may be required in using beta-lactam antibiotics in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infections. Concomitant use of an aminoglycoside is recommended.

Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa*.

Use in adults with impaired renal function:

Adults with impaired renal function/ with creatinine clearance less than 51 mL/min may require a reduction in dose as given below:

Creatinine clearance	**Dose (based on "unit" dose range of 500 mg to 2 g every 8 hours)**	**Frequency**
26 to 50 mL/min	One unit dose	Every 12 hours
10 to 25 mL/min	One-half unit dose	Every 12 hours
< 10 mL/min	One-half unit dose	Every 24 hours

ADCO MEROPENEM is cleared by haemodialysis. If continued treatment is necessary, the unit dose based on the infection type and severity is recommended at the completion of the haemodialysis procedure to re-institute effective treatment.

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There is no experience with peritoneal dialysis.

Use in adults with hepatic insufficiency:

No dosage adjustment is required in patients with impaired hepatic metabolism.

Elderly:

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

Paediatrics population:

Under 3 months of age: Efficacy and tolerability have not been established.

3 months to 12 years of age: the IV dose is 10 to 40 mg/kg every 8 hours depending on type and severity of infection, the known or suspected susceptibility of the pathogen(s), and the condition of the patient.

In children over 50 kg weight, adult dosage should be used.

Exceptions:

Meningitis - the dose should be 40 mg/kg every 8 hours.

Method of administration

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ADCO MEROPENEM should be given as an as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6.

4.3 CONTRAINDICATIONS

ADCO MEROPENEM is contraindicated in patients who have demonstrated hypersensitivity to meropenem or any ingredient of **ADCO MEROPENEM**.

Patients who have a history of hypersensitivity to carbapenems, penicillins, or other beta-lactam antibiotics may also be hypersensitive to **ADCO MEROPENEM**.

4.4 SPECIAL WARNINGS AND PRECATIONS FOR USE

Hypersensitivity reactions:

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8)

Patients who have a history of hypersensitivity to carbapenems, penicillins or other 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 medicine should be discontinued and appropriate measures taken.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).

Overgrowth of non-susceptible organisms such as Enterococcus faecium, strains of Pseudomonas aeruginosa, and Candida species may occur. Prescribers are advised to consider the local prevalence of resistance in these bacteria to penem antibiotics.

Skin reactions:

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, beta-lactam antibiotics should be discontinued.

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.

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Concomitant use with valproic acid/sodium valproate/valpromide:

The concomitant use of ADCO MEROPENEM and valproic acid/sodium valproate/valpromide is not recommended (see section 4.5).

Use in patients with renal insufficiency:

ADCO MEROPENEM should be given with caution in patients with renal impairment (See section 4.2), and the dose reduced appropriately.

Geriatric use:

Elderly patients are more likely to have an age-related decrease in renal function, which may require a reduction in dosage in these patients.

Use in patients with central nervous system disorders:

Particular care is necessary in patients with epilepsy or brain lesions (see section 4.5).

Paediatric use:

Efficacy and tolerability in infants under 3 months old have not been established, therefore **ADCO MEROPENEM** is not recommended for use below this age.

ADCO MEROPENEM contains sodium:

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ADCO MEROPENEM 500 mg IV contains 45 mg sodium (main component of cooking/table salt) in each 500 mg dose. This is equivalent to 2,25 % of the recommended maximum daily dietary intake of sodium for an adult.

ADCO MEROPENEM 1 000 mg IV contains 90 mg sodium (main component of cooking/table salt) in each 1 000 mg dose. This is equivalent to 4,5 % of the recommended maximum daily dietary intake of sodium for an adult. **ADCO 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 medicines and other forms of interaction

Probenecid inhibits the renal excretion of meropenem thereby increasing its plasma concentrations and prolonging its elimination half-life. Concurrent administration is not recommended.

ADCO MEROPENEM may reduce serum valproic acid levels. Sub-therapeutic levels may cause loss of seizure control (see section 4.4).

Oral anti-coagulants

Simultaneous administration of meropenem trihydrate 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 medicines including warfarin in patients who are concomitantly receiving antibacterial medicines. 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 coadministration of antibiotics with an oral anti-coagulant medicine.

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4.6 Fertility, pregnancy, and lactation

Pregnancy

The safety of **ADCO MEROPENEM** in human pregnancy has not been established.

Breastfeeding

ADCO MEROPENEM is detectable at very low concentrations in animal breast milk. It is not known whether **ADCO MEROPENEM** is distributed into human breast milk and therefore should not be used in breast-feeding women.

4.7 Effects on ability to drive and use machinery:

ADCO MEROPENEM is not known to interfere with the ability to drive and operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

In a review of patients treated with meropenem, the most frequently reported meropenem related adverse reactions were diarrhoea, nausea/vomiting and injection site inflammation. The most commonly reported meropenem related laboratory adverse events were thrombocytosis and increased hepatic enzymes.

b. Tabulated risk of adverse reactions

In the table below all adverse reactions are listed by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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System Organ Class	Frequency	Event
Infections and Infestations	Less frequent	Pharyngitis, oral and vaginal candidiasis
Blood and lymphatic disorders	Frequent	Anaemia, thrombocythemia
	Less frequent	Eosinophilia, leucopenia, neutropenia, thrombocytopenia, agranulocytosis, haemolytic anaemia, decreased haematocrit and haemoglobin
Immune system disorders	Less frequent	Systemic allergic reactions which may include angioedema and manifestations of anaphylaxis
Endocrine disorders	Less frequent	Hypoglycaemia
Nervous system disorders	Less frequent	Headache, convulsions, paraesthesia
Cardiac disorders	Frequency not known	Kounis syndrome
Vascular disorders	Less frequent	Shock, visceral vascular disorder
Respiratory, thoracic and mediastinal disorders	Less frequent	Apnoea, pneumonia
Gastrointestinal disorders	Frequent	Diarrhoea, nausea and vomiting
	Less frequent	Constipation, bleeding, bleeding events (black, bloody stools; black, bloody vomit; nosebleed), gastrointestinal haemorrhage, haemoperitoneum, pseudomembranous colitis (see section 4.4).

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Hepatobiliary disorders	Frequent	Increases in serum transaminases, alanine amino transferase (ALT), aspartate amino transferase (ASI), bilirubin, alkaline phosphatase and lactic dehydrogenase.
Skin and subcutaneous tissue disorders	Less frequent	Skin rash, pruritus, urticaria
	Frequency not known	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome), acute generalised exanthematous pustulosis (AGEP), erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN) and linear IgA disease.
Renal and urinary system disorders	Less Frequent	Increased serum creatinine, blood urea increased
General disorders and administration site conditions	Frequent	Inflammation at site of injection
	Less frequent	Thrombophlebitis, pain at site of injection
Investigations	Frequency not known	Partial thromboplastin time and prothrombin time (INR) may be prolonged or shortened Positive direct or indirect antiglobulin (Coombs') test

Paediatric population

ADCO MEROPENEM may be used in 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.

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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (Who-umc.org) found on SAHPRA website.

For reporting side effects directly to the holder of the certificate of registration, contact +27 11635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose

Accidental overdosage could occur during therapy particularly in patients with renal impairment.

In the event of an overdose, the medication should be discontinued and symptomatic and supportive care administered until **ADCO MEROPENEM** can be eliminated through the kidneys.

In patients with renal impairment, haemodialysis will remove **ADCO MEROPENEM** and its metabolite.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Other beta-lactam antibacterials, Carbapenems

ATC code: J01DH02

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Meropenem is a carbapenem antibiotic for parenteral use, that exerts its bactericidal action by interfering with vital bacterial cell wall synthesis. It is relatively stable to human dehydropeptidase-1 (DHP-1) and therefore does not need to be given with an inhibitor of this enzyme.

In vitro tests show that meropenem acts synergistically with various antibiotics. It has been demonstrated both *in vitro* and *in vivo* that meropenem has a post-antibiotic effect.

Resistant organisms:

Stenotrophomonas maltophilia, Enterococcus faecium and methicillin resistant Staphylococci have been found to be resistant to meropenem.

5.2 Pharmacokinetic properties

Absorption

After intravenous bolus injection of meropenem 500 mg and 1 000 mg over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL respectively.

Intravenous infusions of 1 g of meropenem over 2 minutes, 3 minutes and 5 minutes resulted in peak plasma levels of 110, 91 and 94 microgram/mL, respectively.

After an IV dose of 500 mg, plasma levels of meropenem declined to values of 1 microgram/mL or less, in 6 hours after administration.

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No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

When multiple doses are administered, the concentrations at steady state are approximately 20 % higher than after a single dose.

Biotransformation:

Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite.

Elimination

Meropenem has a plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children.

About 70 % of the dose is recovered unchanged in the urine over a 12 hour period. Urinary concentrations above 10 micrograms/ml are maintained for up to 5 hours after a 500 mg dose.

Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.

Distribution

Meropenem is widely distributed into body tissues and fluids including the cerebro-spinal fluid and bile. Plasma protein binding of meropenem is approximately 2 %.

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In patients with bacterial meningitis, meropenem achieves concentrations in excess of those required to inhibit most bacteria.

Special population

Children

Studies in children have shown that the pharmacokinetics of meropenem in children are similar to those in adults. The elimination half-life for meropenem was approximately 1,5 hours in children under the age of 2 years and the pharmacokinetics are linear over the dose range of 10 to 40 mg/kg.

Renal impairment

Pharmacokinetic studies in patients with renal insufficiency have shown the plasma clearance of meropenem correlates with creatinine clearance. Doses of meropenem should be reduced in subjects with renal impairment.

The elderly

Pharmacokinetic studies in the elderly have shown a reduction in plasma clearance of meropenem which correlated with age associated reduction in creatinine clearance.

Liver impairment

Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of ADCO MEROPENEM is sodium carbonate as a solubiliser and buffering agent.

6.2 Incompatibilities

ADCO MEROPENEM should not be mixed with or physically added to solutions containing other medicines except those mentioned in section 6.6.

6.3 Shelf life

36 months

Reconstituted solutions: Refer also to section 4.2.

It can be stored for a maximum of 24 hours at 2 to 8 °C unless it has been prepared under controlled aseptic conditions.

Solvent	CONCENTRATION (mg/ml)	SHELF LIFE (hours)	
		25 ºC	4 ºC
WFI	50	2	12
0.9 % NaCl	1 to 20	4	24
5 % Glucose	1 to 20	1	4
10 % Glucose	1 to 20	1	2
5 % Glucose + 0.9 % NaCl	1 to 20	1	4
5 % Glucose + 0.02% Sodium Bicarbonate	1 to 20	1	6

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2.5 % Mannitol	1 to 20	2	16
10 % Mannitol	1 to 20	1	8
5 % Glucose + 0.15 % KCL	20	1	6
5 % Glucose + Normasol®-M	20	1	8

6.4 Special precautions for storage

ADCO MEROPENEM powder vials should be stored in a cool dry place and are stable at or below 25 °C.

For storage conditions after reconstitution and dilution of the medicine, see section 6.3

6.5 Nature of contents of container

ADCO MEROPENEM 500 mg IV: A 20 ml uncoloured, type III, glass vial, sealed with a bromobutyl rubber stopper and packed in a printed carton box.

ADCO MEROPENEM 1 000 mg IV: A 20 ml uncoloured, type III, glass vial, sealed with a bromobutyl rubber stopper and packed in a printed carton box.

6.6 Special precaution for disposal and other handling

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

Constitution, compatibility and stability:

Bolus intravenous injection:

ADCO MEROPENEM 500 mg IV should be constituted with 10 ml sterile water for injection.

ADCO MEROPENEM 1 000 mg IV should be constituted with 20 ml sterile water for injection.

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This provides an approximate available concentration of 50 mg/ml.

Intravenous infusion:

ADCO MEROPENEM vials may be directly constituted with a compatible infusion fluid (as listed below) and then further diluted with the compatible infusion fluid, as needed.

Freshly prepared solutions of **ADCO MEROPENEM** should be used whenever possible. However, reconstituted solutions are chemically and physically stable under the conditions and for the periods indicated in the table below. On microbiological grounds, it should preferably be used immediately after preparation (see table in section 6.3).

ADCO MEROPENEM should not be mixed with or physically added to solutions containing other medicines.

Constituted solutions are white to light yellow powder in a vial.

Reconstituted solution: The solution is clear and varies from colourless to yellow depending on the concentration.

Solutions of **ADCO MEROPENEM** should not be frozen.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road, Aeroton

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Johannesburg

2013

South Africa

8 REGISTRATION NUMBER

ADCO MEROPENEM 500 mg IV: 44/20.1.1/0206

ADCO MEROPENEM 1 000 mg IV: 44/20.1.1/0303

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 06 March 2014

10 DATE OF REVISION OF THE TEXT

18 June 2025

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