Clean Copy Amended Proposed Professional Information for Medicines for Human Use

MERCARB 500

MERCARB 1 000

(Powder for solution for injection or infusion)

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

MERCARB 500; MERCARB 1 000 (Powder for solution for injection or infusion)

COMPOSITION

MERCARB 500

Meropenem (as trihydrate) 570 mg, equivalent to meropenem anhydrous 500 mg/vial.

MERCARB 1 000

Meropenem (as trihydrate) 1 140 mg, equivalent to meropenem anhydrous 1 000 mg/vial.

The other ingredient is sodium carbonate.

Sugar free.

THE CATEGORY AND CLASS

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Meropenem is a carbapenem antibiotic for parenteral use, that is stable to human dehydropeptidase-I (DHP-I). It is structurally similar to imipenem.

Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis. Bactericidal concentrations are commonly the same as the minimum inhibitory

concentrations (MICs).

Meropenem has a high degree of stability to almost all beta-lactamases produced by Gram-positive and Gram-negative bacteria. Meropenem is stable in susceptibility test systems.

Susceptibility tests can be performed using routine methods.

In vitro, meropenem can act synergistically with various antibiotics.

A post-antibiotic effect has been demonstrated *in vitro* and *in vivo*.

Meropenem may be active *in vitro* against imipenem-resistant strains of *Pseudomonas aeruginosa.*

Species for which acquired resistance may be a problem

Gram-positive anaerobes: *Enterococcus faecium.*

Gram-negative aerobes: *Acinetobacter* species, *Burkholderia cepacia*, *Pseudomonas aeruginosa.*

Inherently resistant organisms

Gram-negative aerobes: *Stenotrophomonas maltophilia*, *Legionella* species.

Other micro-organisms: *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Coxiella burnetii*, *Mycoplasma pneumoniae.*

All methicillin-resistant staphylococci are resistant to meropenem.

Pharmacokinetic properties

After intravenous injection of **MERCARB** 500 mg and 1 000 mg over 5 minutes, peak plasma concentrations of about 50 and 112 microgram/mL respectively are attained.

The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 microgram/mL, respectively.

MERCARB is widely distributed into body tissues and fluids including the cerebro-spinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria. It is about 2 % bound to plasma proteins.

Approximately 70 % of a dose is recovered unchanged in the urine over a 12 hour period

and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours at the 500 mg dose. 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.

There is 1 metabolite, which is microbiologically inactive.

When multiple doses are administered at 8 hourly intervals to patients the concentrations at steady-state are approximately 20 % higher than after a single dose.

MERCARB has a plasma elimination half-life of about 1 hour in subjects with normal renal function.

Special populations

Children

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

Renal impairment

In patients with renal insufficiency the plasma clearance of meropenem correlated with age-associated reduction in creatinine clearance.

Liver impairment

In patients with liver disease no effects of liver disease have been observed on the pharmacokinetics of meropenem.

Elderly

A reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, was observed in the elderly.

No dose adjustment is required in the elderly patients, except in cases of moderate to severe renal impairment with creatinine clearance below 50 mL/minute.

INDICATIONS

MERCARB is indicated for treatment of the following infections, caused by single or multiple susceptible bacteria and as empiric therapy prior to the identification of the causative organisms:

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*, *Moraxella (Branhamella) catarrhalis*, *Klebsiella* spp., *Enterobacter cloacae*, *Enterobacter* spp., *Acinetobacter* spp.

Pneumonia in children due to:

Staphylococcus aureus (methicillin-susceptible strains only), *Streptococcus pneumoniae*, *Haemophilus influenza, Pseudomonas aeruginosa.*

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

Enterobacter cloacae, Escherichia coli, Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens, Citrobacter freundii.

Pelvic Inflammatory Disease (including tubo-ovarian abscess) and endometritis due to:

Enterococus faecalis, Staphylococcus aureus (methicillin-susceptible strains only) coagulase-negative *Staphylococcus* spp. (methicillin-susceptible strains only), *Streptococcus agalactiae* (Group B), *Streptococcus viridans, Streptococcus* spp., *Escherichia coli, Neisseria gonorrhoeae, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Proteas mirabilis, Acinetobacter anitratus, Acinetobacter lwoffii, Gardnerella vaginalis, Bacteroides fragilis* group, *Peptostreptococcus anaerobius, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus.*

Skin and skin structure infections in adults due to:

Staphylococcus aureus (methicillin-susceptible strains only), coagulase-negative *Staphylococcus* spp. (methicillin-susceptible strains only), *Streptococcus pyogenes*

(Group A), *Streptococcus agalactiae, Streptococcus viridans, Enterococcus faecalis, Escherichia coli, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Peptostreptococcus* spp.

Meningitis in adults and children due to:

Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides.

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:

Streptococcus epidermidis, Streptococcus mitis, Streptococcus sanguinis, Escherichia coli.

Intra-abdominal abscess and peritonitis due to:

Streptococcus milleri, Enterococcus faecalis, Escherichia coli, Klebsiella pneumonia, Klebsiella oxytoca, Pseudomonas aeruginosa, Bacteroides fragilis group (including *Bacteroides distasonis, Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides vulgatus), Clostridium perfringens, Streptococcus mitior.*

Polymicrobial infections

CONTRAINDICATIONS

MERCARB is contraindicated in patients who have demonstrated hypersensitivity to meropenem or any of the excipients of **MERCARB**.

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

WARNINGS AND SPECIAL PRECAUTIONS

The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial medicine (such as meropenem) based on factors such as severity of the infection, prevalence of resistance to other

suitable antibacterial medicines and the risk of selecting for carbapenem-resistant bacteria.

Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. resistance to penems such as meropenem has been reported. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Paediatric use

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

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported with meropenem. Before initiating therapy with **MERCARB**, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If a severe allergic reaction occurs with **MERCARB** treatment, it should be discontinued, and appropriate measures taken.

Antibiotic-associated colitis

Overgrowth of non-susceptible organisms may occur and repeated evaluation of each patient is necessary. Pseudomembranous colitis has been reported with **MERCARB**, therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with **MERCARB** use. Medicines that inhibit peristalsis should not be given.

Seizures

Seizures have been reported during treatment with meropenem, such as **MERCARB**.

Use in patients with liver disease

Patients with pre-existing liver disorders must have liver function monitored during treatment with **MERCARB**, due to the risk of hepatotoxicity such as cholestasis and cytolysis.

Direct antiglobulin test seroconversion

A positive direct or indirect antiglobulin test may develop.

Effects on ability to drive and use machines

No data are available, but it is not anticipated that **MERCARB** will affect the ability to drive.

Excipients of MERCARB

MERCARB contains sodium and this should be taken into consideration by patients on a controlled sodium diet.

INTERACTIONS

MERCARB may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.

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. As the potency and duration of action of **MERCARB** dosed without probenecid are adequate the co-administration of probenecid with **MERCARB** is not recommended.

The potential effect of **MERCARB** on the protein binding of other medicines or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected.

MERCARB has been administered concomitantly with many other medicines without apparent adverse interaction.

However, no specific data regarding other interactions are available.

HUMAN REPRODUCTION

Pregnancy

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

Lactation

Meropenem is detectable at very low concentrations in animal breast milk.

MERCARB should not be used in breastfeeding women.

DOSAGE AND DIRECTIONS FOR USE

Intravenous administration:

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 suspected susceptibility of the pathogen(s), and the condition of the patient.

Exceptions:

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

(2) 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.*

MERCARB should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 - 30 minutes.

(see Constitution, compatibility, and stability section for constitution details).

Dosage schedule for adults with impaired renal function:

Dosage should be reduced in patients with creatinine clearance less than 51 mL/minute, as scheduled below.

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

< 10	One-half unit dose	Every 24 hours

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

There is no experience with peritoneal dialysis.

Use in adults with hepatic insufficiency:

No dosage adjustment is necessary 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/minute.

Children:

For infants and children over 3 months and up to 12 years of age the IV dose is 10 – 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.

MERCARB should be given as an IV bolus over approximately 5 minutes or by intravenous infusion over approximately 15 – 30 minutes (see Constitution, compatibility and stability section for details).

There is no experience in children with renal impairment.

Constitution, compatibility and stability:

Intravenous bolus injection administration

MERCARB to be used for bolus intravenous injection should be constituted with sterile water for injection (10 mL/500 mg and 20 mL/1 000 mg).

This provides an approximate available concentration of 50 mg/mL. Constituted solutions are clear or pale yellow.

Dose of Meropenem (50 mg/mL)	Amount of "Water for Injections" needed for dilution
500 mg	10 mL
1 g	20 mL

Intravenous infusion administration

For intravenous infusion **MERCARB** vials may be directly constituted with 0,9 % sodium chloride or 5 % dextrose solutions for infusion.

MERCARB infusion vials constituted with 0,9 % sodium chloride injection (2,5 mg/mL of meropenem concentration) were stable for up to 4 hours at 30 °C and for up to 36 hours at 4 °C. Infusion vials constituted with 5 % dextrose injection (2,5 mg/mL of meropenem concentration) were stable for up to 2 hours at 30 °C and for up to 8 hours at 4 °C. Freshly prepared solutions of **MERCARB** should be used whenever possible.

Dose of Meropenem (2,5 mg/mL)	Amount of "0,9 % sodium chloride or 5 % Dextrose"
500 mg	200 mL
1 g	400 mL

Infusion vials (500 mg and 1 g) may be directly constituted with a compatible infusion fluid. Alternatively an injection vial may be constituted as above, then the resulting solution added to an I.V. container and further diluted with an appropriate infusion fluid (see table below). Solutions prepared for infusion (Meropenem concentrations ranging from 1 to 20 mg/mL; e.g. 500 mL/500 mg to 25 mL/500 mg or 1 000 mL/1 000 mg to 50 mL/1 000 mg) may be stored in plastic intravenous bags at temperatures and with diluents as shown below:

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

Diluent Infusions (1 – 20 mg/mL) prepared with:	Hours stable at 30 °C	Hours stable at 4 °C
0,9% NaCl	4	36
5 % dextrose	2	16
10 % dextrose	2	4
5 % dextrose and 0,9 % sodium chloride	2	4
5 % dextrose and 0,2 % sodium chloride	2	8
5 % dextrose and 0,15 % potassium chloride	2	12
5 % dextrose and 0,02 % sodium bicarbonate solution	2	12
5 % Dextrose in Normosol-M	2	16
5 % dextrose in Ringer's lactate	2	8
2,5 % dextrose and 0,45 % sodium chloride	6	24
2,5 % Mannitol	3	32
Ringer's	8	48
Ringer's lactate	8	24

Although chemical and physical in-use stability has been demonstrated as indicated in the table, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C,

unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Solutions of **MERCARB** should not be frozen.

SIDE EFFECTS

The following adverse reactions have been reported in patients treated with **MERCARB.**

Infections and infestations

Less frequent: Oral and vaginal candidiasis

Blood and lymphatic system disorders

Frequent: Thrombocythaemia

Less Frequent: Eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia

Immune system disorders

Less frequent: Angioedema, anaphylaxis

Nervous system disorders

Frequent: Headache

Less frequent: Paraesthesiae, convulsions

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, abdominal pain

Less frequent: Antibiotic-associated colitis

Hepato-biliary disorders

Frequent: Increases in serum transaminases, alkaline phosphatase, lactate dehydrogenase

Less frequent: Increased blood bilirubin

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus

Less [F]frequent: Urticaria, erythema multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis

Frequency not known: Drug reactions with eosinophilia and systemic symptoms (DRESS)

Renal and urinary disorders

Less frequent: Increased blood creatinine, increased blood urea

General disorders and administrative site conditions

Frequent: Inflammation, pain

Less frequent: Thrombophlebitis, pain at the injection site

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENTS

Over-dosing could occur particularly in patients with renal impairment. Limited post-marketing experience indicates that if adverse events occur following over dosage, they are consistent with the adverse event profile described in "SIDE EFFECTS", are generally mild in severity and resolve on withdrawal or dose reduction.

Symptomatic treatment should be considered.

In normal individuals rapid renal elimination will occur.

Haemodialysis will remove **MERCARB** and its metabolite.

IDENTIFICATION

Powder:

Clear glass vial containing a white to light yellow powder.

Reconstituted solution:

The solution is clear and varies from colourless to yellow depending on the concentration. The solution is free of any visible particles.

PRESENTATION

MERCARB 500

The 20 mL vials are USP Type 1 glass (colourless), with a chlorobutyl rubber closure, flip-off aluminium seal with a polypropylene cap (blue colour). The vials are packed in a hard paper box, single or in packs of 10.

MERCARB 1 000

The 20 mL vials are USP Type 1 glass (colourless), with a chlorobutyl rubber closure, flip-off aluminium seal with a polypropylene cap (red colour). The vials are packed in a hard paper box, single or in packs of 10.

STORAGE INSTRUCTIONS

Store at or below 30 °C. For storage of the reconstituted solution(s) see under DOSAGE AND DIRECTIONS FOR USE.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN.

Diluent	Hours stable at 30 °C	Hours stable at 4 °C
0,9 % NaCl	8	48
5 % dextrose	2	8
10 % dextrose	2	4
5 % dextrose and 0,9 % sodium chloride	2	4
5 % dextrose and 0,2 % sodium chloride	2	8
5 % dextrose and 0,15% potassium chloride	2	12
5 % dextrose and 0,02 % sodium bicarbonate solution	2	12
5 % Dextrose in Normosol-M	2	16
5 % dextrose in Ringer's lactate	2	8
2,5 % dextrose and 0,45 % sodium chloride	6	24
2,5 % Mannitol	3	32
Ringer's	8	48

Ringer's lactate	8	24

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REGISTRATION NUMBER

Will be allocated by Council upon registration.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd.

52 Mineral Crescent

Crown Mines, Ext 3

Johannesburg, 2092

South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

To be confirmed by Council

References (included in 1.5.5.1):

Reference no.	Reference	Divider
1	**Annotated Amended Proposed Professional Information for Medicines for Human Use:** **MERCARB 500** **MERCARB 1 000** (Powder for solution for injection or infusion)	1.5.5.1