PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE
DAPICUB 500 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 500 mg daptomycin.
One ml provides 50 mg of daptomycin after reconstitution with 10 ml of sodium chloride 9 mg/ml (0,9 %) solution.
Sugar free.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
Before reconstitution
DAPICUB is a pale yellow to light brown lyophilised cake or powder.
After reconstitution (with 10 ml of 0,9 % Sodium chloride injection)
A clear, pale yellow to light brown colour solution free from visible particles.
pH: 4,0 to 5,0.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
DAPICUB is indicated for the following infections in adults:
- Complicated skin and skin structure infections (cSSTI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae* and *Streptococcus dysgalactiae subsp equisimilis*. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.
- *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis (SAB/RIE) caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.
- The efficacy of DAPICUB in patient with left-sided infective endocarditis and in patients with artificial valve endocarditis due to *Staphylococcus aureus* has not been demonstrated. Data of DAPICUB in patient with *Staphylococcus aureus* bloodstream infections with left-sided infective endocarditis is limited and the outcomes for those patients were poor.
- DAPICUB is not indicated for the treatment of pneumonia (see section 4.4).

4.2 Posology and method of administration
Posology
Dosage and administration for adults, 18 years and older
Complicated skin and skin structure infections (cSSTI)
DAPICUB 4 mg/kg is administered once every 24 hours for 7 to 14 days. DAPICUB should not be used more frequently than once a day.
***Staphylococcus aureus* bloodstream infections (bacteremia), including right-sided infective endocarditis (SAB/RIE)**
DAPICUB 6 mg/kg is administered once every 24 hours for 2 to 6 weeks. The duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient. DAPICUB should not be used more frequently than once a day.

Special populations
Renal insufficiency
Daptomycin is eliminated primarily by the kidney.
Due to limited clinical experience (see table and footnotes below) DAPICUB should only be used in adult patients with any degree of renal impairment (CrCl < 80 ml/min) when it is considered that the expected clinical benefit outweighs the potential risk. The response to treatment, renal function and creatine phosphokinase (CPK) levels should be closely monitored in all patients with any degree of renal impairment (see also sections 4.4 and 5.2).
Dose adjustments in adult patients with renal impairment by indication and creatinine clearance

Indication for use	Creatinine clearance	Dose recommendation	Comments
cSSTI without SAB	≥ 30 ml/min	4 mg/kg once daily	See section 5.1
	< 30 ml/min	4 mg/kg every 48 hours	(1, 2)
RIE or cSSTI associated with SAB	≥ 50 ml/min	6 mg/kg once daily	

cSSTI = complicated skin and soft-tissue infections
SAB = *S. aureus* bacteremia
RIE = right-sided infective endocarditis

(1) The safety and efficacy of the dose interval adjustment have not been evaluated in controlled clinical trials and the recommendation is based on pharmacokinetic studies and modelling results (see sections 4.4 and 5.2).
(2) The same dose adjustments, which are based on pharmacokinetic data in volunteers including PK modelling results, are recommended for adult patients on hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, DAPICUB should be administered following the completion of dialysis on dialysis days (see section 5.2).
(3) There are insufficient data to support a dose recommendation for patients with RIE or cSSTI associated with *Staphylococcus aureus* bacteremia who have a creatinine clearance < 50 ml/min. There are no data available to support the efficacy of 4 mg/kg daily in patients with RIE or cSSTI associated with *Staphylococcus aureus* bacteremia whose creatinine clearance is between 30 to 49 ml/min or to support the use of 4 mg/kg every 48 hours in such patient whose creatinine clearance is < 30 ml/min.

Hepatic impairment
No dose adjustment is necessary when administering DAPICUB to patients with mild or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, caution should be exercised if DAPICUB is given to such patients.

Obesity
No dosage adjustment of DAPICUB is warranted in moderately obese (Body Mass Index (BMI) 25 to 39,9 kg/m^2) or extremely obese (BMI ≥ 40 kg/m^2) patients.

Elderly patients
The recommended doses should be used in elderly patients except those with severe renal impairment (see above and section 4.4).

Paediatric population
Safety and efficacy of DAPICUB in patients under the age of 18 have not been established.

Method of administration
In adults, DAPICUB is given by intravenous infusion (see section 6.6) and administered over a 30-minute period.

4.3 Contraindications
- Hypersensitivity to daptomycin or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use
Non-susceptible micro-organisms
The use of antibiotics may promote the overgrowth of non-susceptible micro-organisms. If super-infection occurs during therapy, appropriate measures should be taken.
Clostridium difficile-associated diarrhoea (CDAD)
CDAD has been reported with the use of DAPICUB and may range in severity from mild diarrhoea to fatal colitis (see section 4.8). If CDAD is suspected or confirmed, DAPICUB may need to be discontinued and appropriate treatment instituted as clinically indicated.
Pneumonia
It has been demonstrated that DAPICUB is not effective in the treatment of pneumonia. DAPICUB is therefore not indicated for the treatment of pneumonia.
Eosinophilic pneumonia
Eosinophilic pneumonia has been reported in patients receiving DAPICUB (see section 4.8). In most reported cases associated with DAPICUB, patients developed fever, dyspnoea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organising pneumonia. The majority of cases occurred after more than 2 weeks of treatment with DAPICUB and improved when DAPICUB was discontinued and steroid therapy was initiated. Recurrence of eosinophilic pneumonia upon re-exposure has been reported. Patients who develop these signs and symptoms while receiving DAPICUB should undergo prompt medical evaluation, including, if appropriate, bronchoalveolar lavage, to exclude other causes (e.g. bacterial infection, fungal infection, parasites, and other medicines). DAPICUB should be discontinued immediately and treatment with systemic steroids should be initiated when appropriate.
Renal impairment
Renal impairment has been reported during treatment with DAPICUB. Severe renal impairment may in itself also predispose to elevations in daptomycin levels which may increase the risk of development of myopathy (see below).
An adjustment of DAPICUB dose interval is needed for adult patients whose creatinine clearance is < 30 ml/min (see sections 4.2 and 5.2). The safety and efficacy of the dose interval adjustment have not been evaluated in controlled clinical trials and the recommendation is mainly based on pharmacokinetic modelling data. DAPICUB should only be used in such patients when it is considered that the expected clinical benefit outweighs the potential risk.
Caution is advised when administering DAPICUB to patients who already have some degree of renal impairment (creatinine clearance < 80 ml/min) before commencing therapy with DAPICUB. Regular monitoring of renal function is advised (see also section 5.2).
In addition, regular monitoring of renal function is advised during concomitant administration of potentially nephrotoxic medicines, regardless of the patient's pre-existing renal function (see also section 4.5).
The dosage regimen for DAPICUB in paediatric patients with renal impairment has not been established.
General
If a focus of infection other than cSSTI or RIE is identified after initiation of DAPICUB therapy, consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.
RIE due to Staphylococcus aureus
Data on the use of DAPICUB to treat RIE due to *Staphylococcus aureus* are limited. The safety and efficacy of DAPICUB in children and adolescents aged below 18 years with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* have not been established.
The efficacy of DAPICUB in patients with prosthetic valve infections or with left-sided infective endocarditis due to *Staphylococcus aureus* has not been demonstrated.
Deep-seated infections
Patients with deep-seated infections should receive any required surgical interventions (e.g. debridement, removal of prosthetic devices, valve replacement surgery) without delay.
Creatine phosphokinase and myopathy
Increases in plasma creatine phosphokinase (CPK; MM isoenzyme) levels associated with muscular pains and/or weakness and cases of myositis, myoglobinaemia and rhabdomyolysis have been reported during therapy with DAPICUB (see also sections 4.5 and 4.8). In clinical studies, marked increases in plasma CPK to > 5x Upper Limit of Normal (ULN) without muscle symptoms occurred more commonly in DAPICUB-treated patients than in those that received comparators. Therefore, it is recommended that:
- Plasma CPK should be measured at baseline and at regular intervals (at least once weekly) during therapy in all patients.
- CPK should be measured more frequently (e.g. every 2-3 days at least during the first two weeks of treatment) in patients who are at higher risk of developing myopathy. For example, patients with any degree of renal impairment (creatinine clearance < 80 ml/min; see also section 4.2), including those on hemodialysis or CAPD, and patients taking other medicines known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin).
- It cannot be ruled out that those patients with CPK greater than 5 times upper limit of normal at baseline may be at increased risk of further increases during daptomycin therapy. This should be taken into account when initiating daptomycin therapy and, if daptomycin is given, these patients should be monitored more frequently than once weekly.
- DAPICUB should not be administered to patients who are taking other medicines associated with myopathy.
- Patients should be reviewed regularly while on therapy for any signs or symptoms that might represent myopathy.
- Any patient that develops unexplained muscle pain, tenderness, weakness or cramps should have CPK levels monitored every 2 days. DAPICUB should be discontinued in the presence of unexplained muscle symptoms if the CPK level reaches greater than 5 times upper limit of normal.

Peripheral neuropathy
Patients who develop signs or symptoms that might represent a peripheral neuropathy during therapy with DAPICUB should be investigated and consideration should be given to discontinuation of DAPICUB (see section 4.8).
Obesity
In obese subjects with Body Mass Index (BMI) > 40 kg/m^2 but with creatinine clearance > 70 ml/min, the $AUC_{0-\infty}$ daptomycin was significantly increased compared with non-obese matched controls. There is limited information on the safety and efficacy of daptomycin in the very obese and so caution is recommended. However, there is currently no evidence that a dose reduction is required (see section 5.2).
Persisting or relapsing Staphylococcus aureus bloodstream infection
Repeat blood cultures for patients with persisting or relapsing *S. aureus* bloodstream infections or poor clinical response. If a culture is positive for *S. aureus*, minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardised procedure. Diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical intervention (e.g. debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibiotic regimen may be required.
Laboratory test interactions
False prolongation of prothrombin time (PT) and elevation of international normalised ratio (INR) have been observed when certain recombinant thromboplastin reagents are utilised for the assay (see also section 4.5).

4.5 Interaction with other medicines and other forms of interaction
Daptomycin undergoes little to no Cytochrome P450 (CYP450)-mediated metabolism. It is unlikely that daptomycin will inhibit or induce the metabolism of medicines metabolised by the P450 system.
There is limited experience regarding concomitant administration of daptomycin with other medicines that may trigger myopathy (e.g. HMG-CoA reductase inhibitors). However, some cases of marked rises in CPK levels and cases of rhabdomyolysis occurred in adult patients taking one of these medicines at the same time as DAPICUB. It is recommended that other medicines associated with myopathy should if possible be temporarily discontinued during treatment with DAPICUB unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CPK levels should be measured more frequently than once weekly and patients should be closely monitored for any signs or symptoms that might represent myopathy (see sections 4.4, and 4.8).
Daptomycin had no effect on the pharmacokinetics of warfarin or probenecid, nor did these medicines alter the pharmacokinetics of daptomycin. The pharmacokinetics of daptomycin were not significantly altered by aztreonam.
The interaction between daptomycin and tobramycin with an approved dose of DAPICUB is unknown. Caution is warranted when DAPICUB is co-administered with tobramycin.
Experience with the concomitant administration of DAPICUB and warfarin is limited. Anticoagulant activity in patients receiving DAPICUB and warfarin should be monitored for the first several days after therapy with DAPICUB is initiated.
Daptomycin is primarily cleared by renal filtration and so plasma levels may be increased during co-administration with medicines that reduce renal filtration (e.g. NSAIDs and COX-2 inhibitors). In addition, there is a potential for a pharmacodynamic interaction to occur during co-administration due to additive renal effects. Therefore, caution is advised when daptomycin is co-administered with any other medicine known to reduce renal filtration.
Laboratory tests
Interference between daptomycin and particular reagents used in some assays of prothrombin time/international normalised ratio (PT/INR) have been documented. This interference led to a false prolongation of PT and elevation of INR. If unexplained abnormalities of PT/INR are observed in patients taking daptomycin, consideration should be given to a possible *in vitro* interaction with the laboratory test. The possibility of erroneous results may be minimised by drawing samples for PT or INR testing near the time of trough plasma concentrations of daptomycin (see section 4.4).

4.6 Fertility, pregnancy and lactation
Pregnancy and Breastfeeding
Safety in pregnancy and breastfeeding has not been established.
Fertility
No data is available on fertility

4.7 Effects on ability to drive and use machines
It is unlikely that DAPICUB has an influence on the ability to drive and use machines, however, adverse reactions, such as dizziness has been reported during treatment, patients should ensure that they do not engage in the above activities until they are aware of the measure to which DAPICUB affects them (see section 4.8).

4.8 Undesirable effects
a. Summary of the safety profile
The most frequently reported adverse reactions are: Fungal infections, urinary tract infection, candida infection, anemia, anxiety, insomnia, dizziness, headache, hypertension, hypotension, gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension, liver function tests abnormal (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP)), rash, pruritus, limb pain, serum creatine phosphokinase (CPK) increased, infusion site reactions, pyrexia, asthenia.
Less frequently reported, but more serious, adverse reactions include hypersensitivity reactions, eosinophilic pneumonia (occasionally presenting as organising pneumonia), drug rash with eosinophilia and systemic symptoms (DRESS), angioedema and rhabdomyolysis.

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	Fungal infections, urinary tract infection, candida infection
	Less frequent	Fungaemia, osteomyelitis, oral candidiasis, vaginal candidiasis
	Frequency unknown*	Clostridium difficile-associated diarrhoea (see section 4.4)
Blood and lymphatic system disorders	Frequent	Anaemia
	Less frequent	Thrombocythaemia, eosinophilia, leukocytosis, prothrombin time (PT) prolonged, international normalised ratio (INR) increased, lymphadenopathy
	Frequency unknown*	Thrombocytopaenia
Immune system disorders	Frequency unknown	Hypersensitivity (see section 4.4), manifested by isolated spontaneous reports including, but not limited to angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), pulmonary eosinophilia, vesiculobullous rash with mucous membrane involvement and sensation of oropharyngeal swelling, anaphylaxis (see section 4.4), infusion reactions including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste
Metabolism and nutrition disorders	Less frequent	Decreased appetite, hyperglycaemia, electrolyte imbalance, hypokalaemia, hypomagnesaemia
Psychiatric disorders	Frequent	Anxiety, insomnia
	Less frequent	Hallucinations, mental status change
Nervous system disorders	Frequent	Dizziness, headache
	Less frequent	Paraesthesia, tremor, taste disorder, dyskinesia
	Frequency unknown	Peripheral neuropathy (see section 4.4)
Eye disorders	Less frequent	Eye irritation, vision blurred
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus
Cardiac disorders	Less frequent	Supraventricular tachycardia, extrasystole cardiac arrest, atrial fibrillation, atrial flutter
Vascular disorders	Frequent	Hypertension, hypotension
	Less frequent	Flushing
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea
	Frequency unknown	Eosinophilic pneumonia (see section 4,4), cough
Gastrointestinal disorders	Frequent	Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, distension, bloating, dyspepsia
	Less frequent	Dyspepsia, glossitis, dry mouth, stomatitis, taste disorder, gingival pain, oral hypoaesthesia, epigastric discomfort
Hepatobiliary disorders	Frequent	Liver function tests abnormal (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP))
	Less frequent	Jaundice
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
	Less frequent	Urticaria, eczema
	Frequency unknown	Acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	Frequent	Limb pain, serum creatine phosphokinase (CPK)[2] increased
	Less frequent	Myositis, increased myoglobin, muscular weakness, muscle pain, arthralgia, serum lactate dehydrogenase (LDH) increased, muscle cramps, back pain
	Frequency unknown	Rhabdomyolysis (see section 4.4)
Renal and urinary disorders	Less frequent	Renal impairment, including renal failure and renal insufficiency, serum creatinine increased, proteinuria
Reproductive system and breast disorders	Less frequent	Vaginitis
General disorders and administration site conditions	Frequent	Infusion site reactions, pyrexia, asthenia
	Less frequent	Fatigue, pain, oedema, rigors, jitteriness, chest pain, discomfort (not otherwise specified), weakness

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
In the event of overdose, supportive care is advised. DAPICUB is slowly cleared from the body by hemodialysis (approximately 15 % of the administered dose is removed over 4 hours) or by peritoneal dialysis (approximately 11 % of the administered dose is removed over 48 hours).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Other antibacterials, ATC code: J01XX09

Mechanism of action
Daptomycin is a cyclic lipopeptide natural product that is active against Gram positive bacteria only.
The mechanism of action involves binding (in the presence of calcium ions) to bacterial membranes of both growing and stationary phase cells causing depolarisation and leading to a rapid inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

PK/PD relationship
Daptomycin exhibits rapid, concentration dependent bactericidal activity against Gram positive organisms *in vitro* and in *in vivo* animal models.

Mechanisms of resistance
Strains with decreased susceptibility to daptomycin have been reported especially during the treatment of patients with difficult-to-treat infections and/or following administration for prolonged periods. In particular, there have been reports of treatment failures in patients infected with *Staphylococcus aureus*, *Enterococcus faecalis* or *Enterococcus faecium*, including bacteraemic patients that have been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin during therapy.
The mechanism of daptomycin resistance is not fully understood.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Staphylococci and Streptococci (except *S. pneumoniae*) are Susceptible ≤ 1 mg/l and Resistant > 1 mg/l.

5.2 Pharmacokinetic properties
Daptomycin pharmacokinetics are generally linear and time-independent at doses of 4 to 12 mg/kg administered as a single daily dose by 30 minute intravenous infusion for up to 14 days in healthy adult volunteers. Steady-state concentrations are achieved by the third daily dose.

Distribution
The volume of distribution at steady state of daptomycin in healthy adult subjects was approximately 0,1 l/kg and was independent of dose.
Daptomycin is reversibly bound to human plasma proteins in a concentration independent manner. In healthy adult volunteers and adult patients treated with daptomycin, protein binding averaged about 90 % including subjects with renal impairment, (mean binding range of 90 to 93 %), serum protein binding trended lower (mean binding range of 83,5 to 87,6 %) in subjects with significant renal insufficiency (CLcr <30ml/min or on dialysis). The protein binding of daptomycin in subjects with mild to moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy adult subjects.

Biotransformation
In *in vitro* studies, daptomycin was not metabolised by human liver microsomes. In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of medicines metabolised by the P450 system.
After infusion of ^{14}C-daptomycin in healthy adults, the plasma radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites were detected in urine, as determined by the difference in total radioactive concentrations and microbiologically active concentrations. In a separate study, no metabolites were observed in plasma, and minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

Elimination
Daptomycin is excreted primarily by the kidneys. Concomitant administration of probenecid and daptomycin has no effect on daptomycin pharmacokinetics in humans suggesting minimal to no active tubular secretion of daptomycin.
Following intravenous administration, plasma clearance of daptomycin is approximately 7 to 9 ml/h/kg and its renal clearance is 4 to 7 ml/h/kg.
In a mass balance study using radiolabelled material, 78 % of the administered dose was recovered from the urine based on total radioactivity, whilst urinary recovery of unchanged daptomycin was approximately 52 % of the dose. About 6 % of the administered radiolabel was excreted in the faeces.

Special populations
Renal impairment
Following administration of a single 4 mg/kg or 6 mg/kg intravenous dose of daptomycin over a 30-minute period to adult subjects with various degrees of renal impairment, total daptomycin clearance (CL) decreased and systemic exposure (AUC) increased as renal function (creatinine clearance) decreased. The mean AUC with CL_{Cl} < 30 ml/min and for patients on hemodialysis (post dialysis) was approximately 2 and 3 times higher respectively than for patients with normal renal function (see section 4.2).
Based on pharmacokinetic data and modelling, the daptomycin AUC during the first day after administration of a 6 mg/kg dose to adult patients on HD or CAPD was 2-fold higher than that observed in adult patients with normal renal function who received the same dose. On the second day after administration of a 6 mg/kg dose to HD and CAPD adult patients the daptomycin AUC was approximately 1.3-fold higher than that observed after a second 6 mg/kg dose in adult patients with normal renal function. On this basis, it is recommended that adult patients on HD or CAPD receive daptomycin once every 48 hours at the dose recommended for the type of infection being treated (see section 4.2).

Hepatic impairment
The pharmacokinetics of daptomycin is not altered in subjects with moderate hepatic impairment (Child-Pugh B classification of hepatic impairment) compared with healthy volunteers matched for gender, age and weight following a single 4 mg/kg dose. No dosage adjustment is necessary when administering daptomycin in patients with moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh C classification) have not been evaluated.

Obesity
Relative to non-obese subjects daptomycin systemic exposure measured by AUC was about 28 % higher in moderately obese subjects (Body Mass Index of 25 to 40 kg/m^2) and 42 % higher in extremely obese subjects (Body Mass Index of > 40 kg/m^2). However, no dose adjustment is considered to be necessary based on obesity alone.

Elderly
Following administration of a single 4 mg/kg intravenous dose of daptomycin over a 30-minute period, the mean total clearance of daptomycin was approximately 35 % lower and the mean $AUC_{0-\infty}$ was approximately 58 % higher in elderly subjects (≥ 75 years of age) compared with those in healthy young subjects (18 to 30 years of age). There were no differences in C_{max}. The differences noted are most likely due to the normal reduction in renal function observed in the geriatric population.
No dose adjustment is necessary based on age alone. However, renal function should be assessed, and the dose should be reduced if there is evidence of severe renal impairment.

Gender
No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium hydroxide (E524) (pH adjustment)

6.2 Incompatibilities
DAPICUB is not compatible with dextrose-containing diluents. This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life
Unopened vial: 24 months, store in a refrigerator (2°C – 8°C).
After reconstituted: The reconstituted solution should be used immediately.
Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25 ºC and up to 48 hours at 2 ºC to 8 ºC. Chemical and physical stability of the diluted solution in infusion bags is established as 12 hours at 25 ºC or 24 hours at 2 ºC to 8 ºC.
The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) should not exceed 12 hours at room temperature or 48 hours under refrigeration.

6.4 Special precautions for storage
Store in a refrigerator (2 ºC to 8 ºC)
For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container
DAPICUB is supplied in single-use clear glass vials with rubber stoppers and aluminium flip top seal.
The vials are packed in single units.

6.6 Special precautions for disposal and other handling
Reconstitution
- DAPICUB is reconstituted with 10 ml of 0,9 % sodium chloride injection to yield a concentration of 50 mg/ml.
- The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of DAPICUB range in colour from pale yellow to light brown.
- Transfer the reconstituted solution to 50 ml of 0,9 % sodium chloride or Lactated Ringer's Injection infusion bags to yield a concentration of 10 mg/ml.

As no preservatives or bacteriostatic medicines are present in this product, aseptic techniques must be used.
Limited data is available on the compatibility of DAPICUB with other IV substances. Additives or other medicines should not be added to the DAPICUB single-use vial or infused simultaneously through the same IV line. If the same IV line is used for sequential infusion of several different medicines, the line should be flushed with 0,9 % sodium chloride or Lactated Ringer's solution before and after infusion with DAPICUB.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Kahma Biotech (Pty) Ltd
106, 16th Road
Midrand

8 REGISTRATION NUMBER
55/20.1/0096

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14 March 2023

10 DATE OF REVISION OF THE TEXT
14 March 2023