PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

CUBACT™, 500 mg, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of CUBACT contains 500 mg daptomycin.

One ml provides 50 mg of daptomycin after reconstitution with 10 ml of 9 mg/ml (0,9 %) sodium chloride for injection.

For the full list of excipients, see section 6.1.

Sugar free.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

A pale yellow to light brown, sterile lyophilised powder.

Refer to sections 4.2 and 6.6 for appearance after reconstitution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CUBACT is indicated for the following infections in adults:

Complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive micro-organisms: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae* and *Streptococcus dysgalactiae* subspecies *equisimilis*.

Combination therapy may be indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

***Staphylococcus aureus* bloodstream (SAB) infections (bacteraemia)**, including those with right-sided infective endocarditis (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 CUBACT in patients with left-sided infective endocarditis and in patients with artificial valve endocarditis due to *Staphylococcus aureus* has not been demonstrated.

CUBACT is not indicated for the treatment of pneumonia (see section 4.4).

4.2 Posology and method of administration

Dosage and directions for use pertain to adults ≥ 18 years.

Posology

Complicated skin and skin structure infections (cSSSI)

CUBACT 4 mg/kg is administered once daily over a 30-minute period by IV infusion in 0,9 % sodium chloride injection, every 24 hours, for 7 - 14 days. CUBACT should not be dosed more frequently than once a day.

S. aureus bloodstream infections (bacteraemia), including right-sided infective endocarditis (SAB/RIE)

CUBACT 6 mg/kg is administered once daily over a 30-minute period by IV infusion in 0,9 % sodium chloride injection, once every 24 hours, for a minimum of 2 - 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. CUBACT should not be dosed more frequently than once a day.

Special populations

Renal impairment

Daptomycin is eliminated primarily by the kidney.

CUBACT should only be used in 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 section 5.2, *Special populations*, *Creatine phosphokinase and myopathy* and section 4.4).

Dose adjustments in patients with renal impairment by indication and creatinine clearance:

Indication for use [1]	**Creatinine clearance**[1]	**Dose** [1] **recommendation**	**Comments**
cSSTI without *S. aureus* bacteraemia	≥ 30 ml/min	4 mg/kg once daily	See section 5.2
	< 30 ml/min	4 mg/kg every 48 hours	[1, 2]
RIE or cSSTI associated with *S. aureus* bacteraemia	≥ 50 ml/min	6 mg/kg once daily	[3]

[1] The recommendation is based on pharmacokinetic modelling data only (see section 4.4 and 5.2 *Special populations*).

[2] The same dose adjustments, which are also based on modelling, are recommended for patients on haemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, CUBACT should be administered following the completion of dialysis on dialysis days (see section 5.2 *Special populations*).

[3] There are insufficient data to support a dose recommendation for patients with RIE or cSSTI associated with *S. aureus* bacteraemia 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 *S. aureus* bacteraemia whose creatinine clearance is between 30 - 49 ml/min or to support the use of 4 mg/kg every 48 hours in such patients whose creatinine clearance is < 30 ml/min.

Hepatic impairment

No dose adjustment is necessary when administering CUBACT to patients with mild or moderate hepatic impairment (Child-Pugh Class B).

Patients with severe hepatic impairment (Child-Pugh Class C) have not been investigated.

Obesity

No dose adjustment of CUBACT is required in moderately obese (Body Mass Index [BMI] 25 - 39,9 kg/m^2) or extremely obese (BMI $\geq$ 40 kg/m^2) patients.

Elderly patients

No dose adjustment of CUBACT is warranted for the elderly with normal renal function.

Children and adolescents (< 18 years old)

Safety and efficacy of CUBACT in patients under the age of 18 have not been established (see section 4.4).

Method of administration

In adults, CUBACT is given by intravenous infusion and administered over a 30-minute period. See section 6.6 for instruction for preparation of the infusion solution.

Because only limited data are available on the compatibility of CUBACT with other IV substances, additives or other medications should not be added to CUBACT single-use vials 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 a compatible infusion solution before and after infusion with CUBACT. See section 6.2.

The reconstituted solution is dark yellow to light brown, free of visible particles.

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

CUBACT is contraindicated:

- in patients with known hypersensitivity to daptomycin or to any of the ingredients of CUBACT;
- for the treatment of pneumonia (see section 4.4).

4.4 Special warnings and precautions for use

If a focus of infection other than cSSTI or RIE is identified after initiation of treatment with CUBACT, it should be considered to institute alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Anaphylaxis/hypersensitivity reactions

Anaphylaxis/hypersensitivity reactions have been reported with CUBACT (see section 4.8). If an allergic reaction to CUBACT occurs, its use should be discontinued and appropriate therapy should be instituted.

Pneumonia

CUBACT is not effective in the treatment of pneumonia. CUBACT is therefore not indicated for the treatment of pneumonia (see section 4.3).

RIE due to Staphylococcus aureus

The efficacy of CUBACT in patients with prosthetic valve infections or with left-sided infective endocarditis due to *Staphylococcus aureus* has not been demonstrated (see section 4.1 and 5.1 *Resistance*).

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.

Enterococcal infections

There is insufficient evidence regarding the possible clinical efficacy of CUBACT against infections due to enterococci, including *Enterococcus faecalis* and *Enterococcus faecium*. Failures with daptomycin in the treatment of enterococcal infections that were mostly accompanied by bacteraemia have been reported. In some instances, treatment failure has been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin (see section 5.1).

Non-susceptible micro-organisms

The use of antibiotics, including CUBACT, may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Clostridium difficile-associated diarrhoea (CDAD)

Clostridium difficile-associated diarrhoea (pseudomembranous colitis) has been reported with CUBACT (see section 4.8). If CDAD is suspected or confirmed, CUBACT may need to be discontinued and appropriate treatment instituted as clinically indicated.

Medicine/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 section 4.5).

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 CUBACT (see section 4.8). 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 section 4.2), including those on haemodialysis or CAPD, and patients taking other medicines known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin).
- CUBACT should not be administered to patients who are also taking other medicines associated with myopathy, unless it is considered that the benefit to the patient outweighs the risk.

  It is recommended that other medicines associated with myopathy should if possible be temporarily discontinued during treatment with CUBACT. 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 section 4.5 and 4.8.
- Patients with CPK greater than 5 times the upper limit of normal at baseline may be at increased risk of further increases during therapy with CUBACT. This should be considered when initiating therapy with CUBACT and, if it is given, these patients should be monitored more frequently than once weekly.
- Patients should be reviewed regularly while on therapy for any signs or symptoms that might represent myopathy.
- CPK levels should be monitored every 2 days in any patient that develops unexplained muscle pain, tenderness, weakness or cramps. CUBACT should be discontinued in the presence of unexplained muscle symptoms if the CPK level reaches greater than 5 times the upper limit of normal.

Peripheral neuropathy

Patients who develop signs or symptoms that might represent a peripheral neuropathy during therapy with CUBACT should be investigated and consideration should be given to discontinuation of CUBACT (see section 4.8).

Eosinophilic pneumonia

Eosinophilic pneumonia has been reported in patients receiving CUBACT (see section 4.8). In most cases fever, dyspnoea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates have been reported in association with CUBACT. These symptoms mostly occur after more than 2 weeks of treatment with CUBACT. Recurrence of eosinophilic pneumonia upon re-exposure has been reported.

Patients who develop these signs and symptoms while receiving CUBACT should undergo prompt medical evaluation, including, if appropriate, bronchoalveolar lavage, to exclude other causes (e.g. bacterial infection, fungal infection, parasites, other medicines). CUBACT should be discontinued immediately and treatment with systemic steroids should be initiated when appropriate.

Renal impairment

Renal impairment has been reported during treatment with CUBACT. Severe renal impairment may increase the risk of development of myopathy (see *Creatine phosphokinase and myopathy* above).

An adjustment of CUBACT dose interval is needed for patients whose creatinine clearance is < 30 ml/min (see *Creatine phosphokinase and myopathy* above, section 5.2 *Renal impairment* and section 4.2). The safety and efficacy of the dose interval adjustment have not been evaluated. CUBACT 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 CUBACT to patients who already have some degree of renal impairment (creatinine clearance < 80 ml/min) before commencing therapy with CUBACT.

Regular monitoring of renal function is advised. Regular monitoring of renal function is also advised during concomitant administration of potentially nephrotoxic substances, regardless of the patient's pre-existing renal function (see section 4.5).

Paediatric population

Safety and efficacy of CUBACT have not been established in patients under the age of 18 years. CUBACT is therefore not recommended in this age group.

Obesity

The mean systemic exposure (AUC) is significantly increased in obese patients (see section 5.2, *Special populations: Obesity*). However, there is no evidence that a dose reduction is required.

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 may be an increased risk of myopathy if CUBACT is given concomitantly with other medicines known to have this side effect (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin). It is recommended that other medicines associated with myopathy should if possible be temporarily discontinued during treatment with CUBACT unless the benefits of concomitant administration outweigh the risk. See sections 4.4 and 4.8.

Anti-inflammatory medicines

Daptomycin is mainly excreted by renal filtration and caution is advised if CUBACT is given with any other medicine known to reduce renal filtration (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors), since plasma levels of daptomycin may be increased.

Warfarin

Experience with the concomitant administration of CUBACT and warfarin is limited. Studies of daptomycin with anticoagulants other than warfarin have not been conducted. Anticoagulant

activity in patients receiving CUBACT and warfarin should be monitored for the first several days after therapy with CUBACT is initiated.

Other antibiotics

In vitro synergistic interactions of daptomycin with aminoglycosides, beta-lactam antibiotics, and rifampicin have been shown against some isolates of staphylococci (including some methicillin-resistant isolates).

During co-administration of CUBACT and tobramycin, changes in the pharmacokinetics of daptomycin and tobramycin may occur. The interaction between daptomycin and tobramycin with an approved dose of CUBACT is unknown. Caution is warranted when CUBACT is co-administered with tobramycin.

The pharmacokinetics of daptomycin are not significantly altered by aztreonam.

Laboratory tests

Cases of interference between daptomycin and reagents used in some assays of prothrombin time/international normalised ratio (PT/INR) have been reported. This interference led to a false prolongation of PT and elevation of INR. If unexplained abnormalities of PT/INR are observed in patients taking CUBACT, 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 lactation

Safety in pregnancy and lactation has not been established.

Fertility

No clinical data on fertility are available for daptomycin.

4.7 Effects on ability to drive and use machines

Dizziness is a frequent side effect of CUBACT. Patients should be advised not to drive or use machinery if they feel dizzy after being on treatment with CUBACT.

4.8 Undesirable effects

a. Summary of the safety profile

During clinical studies, adverse reactions (i.e. considered by the investigator to be possibly, probably, or definitely related to the medicine) were reported at similar frequencies for daptomycin and comparator regimens.

The most frequently reported adverse reactions are:

Fungal infections, urinary tract infection, candida infection, anaemia, 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), DRESS (drug rash with eosinophilia and systemic symptoms), angioedema and rhabdomyolysis.

b. Tabulated summary of adverse reactions

System organ class	
Frequency	**Adverse reaction**
Infections and infestations	
Frequent:	Fungal infections, urinary tract infection, candida infection
Less frequent:	Fungaemia
Frequency unknown:	*Clostridium difficile*-associated diarrhoea (see section 4.4)
Blood and lymphatic system disorders	

Frequent:	Anaemia
Less frequent:	Thrombocythaemia, eosinophilia, increased international normalised ratio (INR), leukocytosis, prolonged prothrombin time (PT), lymphadenopathy
Frequency unknown:	Thrombocytopaenia

Immune system disorders

Frequency unknown:	Hypersensitivity (including angioedema, DRESS, pulmonary eosinophilia, vesicobullous rash with mucous membrane involvement and sensation of oropharyngeal swelling, anaphylaxis) (see section 4.4), infusion reactions (including tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste)

Metabolism and nutrition disorders

Less frequent:	Decreased appetite, hyperglycaemia, electrolyte imbalance

Psychiatric disorders

Frequent:	Anxiety, insomnia
Less frequent:	Hallucinations

Nervous system disorders

Frequent:	Dizziness, headache
Less frequent:	Paraesthesia, taste disorder, tremor, eye irritation
Frequency unknown:	Peripheral neuropathy (see section 4.4)

Ear and labyrinth disorders

Frequency unknown:	Vertigo

Cardiac disorders

Frequency unknown:	Supraventricular tachycardia, extrasystoles
Less frequent:	Atrial fibrillation, atrial flutter, cardiac arrest

Vascular disorders

Frequent:	Hypertension, hypotension

Less frequent: Flushes

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Eosinophilic pneumonia (see section 4.4), cough

Gastrointestinal disorders

Frequent: Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension

Less frequent: Dyspepsia, glossitis

Hepatobiliary disorders

Frequent: Abnormal liver function test results (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

Frequency unknown: Acute generalised exanthematous pustulosis

Musculoskeletal and connective tissue disorders

Frequent: Limb pain, serum creatine phosphokinase (CPK)[1] increased

Less frequent: Myositis, myopathy, increased myoglobin, muscular weakness, muscle pain, arthralgia, serum lactate dehydrogenase (LDH) increased, muscle cramps

Frequency unknown: Rhabdomyolysis (see section 4.4) [2]

Renal and urinary disorders

Less frequent: Renal impairment, including renal failure and renal insufficiency, increased serum creatinine, 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, weakness, chest pain

[1] In some cases of myopathy involving raised CPK and muscle symptoms, the patients also presented with elevated transaminases. These transaminase increases were likely to be related to the skeletal muscle effects. Most transaminase elevations were of Grade 1-3 toxicity and resolved upon discontinuation of treatment.

[2] When clinical information on the patients was available to make a judgement, approximately 50 % of the cases occurred in patients with pre-existing renal impairment, or in those receiving concomitant medicines known to cause rhabdomyolysis.

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. Healthcare 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

Refer to section 4.8.

In the event of overdose, supportive care is advised. Daptomycin is slowly cleared from the body by haemodialysis (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

Category A 20.1.1 Broad and medium spectrum antibiotics.

Daptomycin is a cyclic lipopeptide, which binds to bacterial cell membranes. This causes depolarisation of membrane potential in both growing and stationary phase bacteria, whereby protein, DNA and RNA synthesis are inhibited and results in bacterial cell death.

Microbiology

The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria.

In vitro susceptibility does not necessarily imply clinical efficacy.

In vitro synergistic interactions of daptomycin with aminoglycosides, beta-lactam antibiotics and rifampicin have been shown against some isolates of staphylococci (including some methicillin-resistant isolates).

Resistance

The mechanism of resistance of daptomycin has not been identified. Emergent decreases in susceptibility have been observed in *Staphylococcus aureus* isolates following daptomycin therapy.

5.2 Pharmacokinetic properties

Absorption

Steady-state concentrations are achieved by the third daily dose.

Distribution

Daptomycin is reversibly bound to human plasma proteins (mean binding range 90 – 93 %) in a concentration independent manner. Serum protein binding tends to be lower (83,5 – 87,6 %) in patients with significant renal impairment (CL_{cr} < 30 ml/min or on dialysis). The protein binding of daptomycin in patients with mild-to-moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy adult persons.

The volume of distribution at steady state in healthy persons is about 0,1 litres/kg and is independent of dose.

Biotransformation

In vitro, daptomycin is not metabolised by human liver microsomes and 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.

No metabolites have been observed in plasma. Inactive metabolites have been detected in urine. Minor amounts of three oxidative metabolites and one unidentified compound have been detected in urine. The site of metabolism has not been identified.

Elimination

Daptomycin is excreted primarily by the kidneys; 78 % of the administered dose is recovered from the urine and about 6 % in the faeces. Approximately 52 % of the dose is excreted in the urine as unchanged daptomycin.

Linearity/non-linearity

Daptomycin pharmacokinetics are generally linear and time-independent at doses of 4 to 12 mg/kg, administered as a single daily dose.

Special populations

Renal impairment

Total daptomycin clearance (CL) decreases and systemic exposure (AUC) increases as renal function (creatinine clearance) decreases.

The mean system exposure (AUC) for patients with CL_{cr} < 30 ml/min and for patients on haemodialysis (post-dialysis) is approximately 2 and 3-fold higher, respectively, than that observed in patients with normal renal function (see section 4.2).

Hepatic impairment

The pharmacokinetics of daptomycin is not altered in patients with moderate hepatic impairment (Child-Pugh B) compared with healthy volunteers matched for gender, age and weight. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh C classification) have not been evaluated.

Obesity

The AUC increases about 30 % in moderately obese patients (body mass index [BMI] of 25 - 39,9 kg/m^2) and 31 % in extremely obese patients (BMI of $\geq$ 40 kg/m^2) compared with non-obese persons. However, no dose adjustment is warranted in moderately or extremely obese patients. See section 4.2.

Elderly

No dosage adjustment is warranted for elderly patients with normal renal function; see section 4.2.

Children and adolescents (< 18 years of age)

The pharmacokinetics of daptomycin in children and adolescent populations (< 18 years of age) have not been established. See section 4.2.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

6.2 Incompatibilities

CUBACT is not compatible with dextrose-containing diluents (see section 4.5). As limited data are available on the compatibility of CUBACT with other IV substances, it should not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Shelf life (unopened product):

24 months

Prepared solution (reconstituted and diluted):

Stability studies on the prepared solutions have shown that:

- **the reconstituted solution** of CUBACT powder for solution for infusion is physically and chemically stable when reconstituted with 10 ml of sodium chloride 9 mg/ml (0,9 %) during 12 hours at 25 ºC and during 48 hours at 2 - 8 ºC;
- **the diluted solution** of CUBACT powder for solution for infusion is physically and chemically stable when reconstituted with 10 ml of sodium chloride 9 mg/ml (0,9 %) solution for injection and then diluted with sodium chloride 9 mg/ml (0,9 %) up to 50 ml during 12 hours at 25 ºC and during 24 hours at 2 - 8 ºC.

The combined storage time for the 30-minute intravenous infusion (reconstituted solution in the vial and diluted solution in infusion bag) at room temperature (at or below 25 °C) should not exceed 12 hours; the combined storage time (reconstituted solution in the vial and diluted solution in infusion bag) under refrigeration (2 - 8 °C) should not exceed 24 hours.

However, from a microbiological point of view the product should be used immediately as it does not contain a preservative or bacteriostatic substance. If not used immediately, in-use storage times are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Storage of the unopened product:

Store in the refrigerator, at 2 - 8 °C. Do not freeze.

Storage of the reconstituted and diluted product:

See section 6.3.

6.5 Nature and contents of the container

CUBACT is packed in 15 or 20 ml type I clear glass vials with grey bromobutyl rubber stoppers, closed with an aluminium/polypropylene flip-off seal.

Available in cartons containing 1 vial or 5 vials.

Not all packing sizes may be marketed.

6.6 Special precautions for disposal and other handling

In adults, CUBACT is given by intravenous infusion (see section 4.2) and administered over a 30-minute period.

Preparation of CUBACT for administration

CUBACT is supplied in single-use vials containing 500 mg daptomycin as a sterile, lyophilised powder.

The contents of a CUBACT vial should be reconstituted to 50 mg/ml, using aseptic technique throughout the process, as described below.

The appropriate volume of the solution should be further diluted, using aseptic technique, into an IV infusion bag containing 0,9 % sodium chloride injection (typical volume 50 ml). To minimise foaming, **avoid** vigorous shaking/agitation of the vial during or after reconstitution.

Preparation of the solution for infusion requires an additional dilution step as detailed below.

1. The polypropylene flip-off cap should be removed to expose the central portions of the rubber stopper.
2. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.
3. Draw 10 ml of sodium chloride 9 mg/ml (0,9 %) solution for injection into a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device,

then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial.

4. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
5. Finally, the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution.
6. 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 CUBACT range in colour from dark yellow to light brown, free of visible particles.
7. Slowly remove the reconstituted liquid (50 mg daptomycin/ml) from the vial using a sterile needle that is 21 gauge or smaller in diameter.
8. The reconstituted solution should then be further diluted with sodium chloride 9 mg/ml (0,9 %) (typical volume 50 ml).
9. Invert the vial to allow the solution to drain towards the stopper. Using a new syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger back to the end of the syringe barrel, to completely remove the solution from the inverted vial.
10. Replace needle with a new needle for the intravenous infusion.
11. Expel air, large bubbles, and any excess solution, to obtain the required dose. To minimise foaming, **avoid** vigorous shaking/agitation of the vial during or after reconstitution.
12. This reconstituted and diluted solution should then be infused intravenously over 30 minutes as directed (see section 4.2).

Storage of the prepared solution

CUBACT vials are for single use only. From a microbiological point of view, the product should be used immediately after reconstitution (see section 6.3). If not used immediately, in-use storage times are the responsibility of the user.

Any unused portion of CUBACT or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

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8 REGISTRATION NUMBER

CUBACT: 53 / 20.1.1 / 0433

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 October 2022

10 DATE OF REVISION OF THE TEXT

15 September 2023