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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DABUCOR 350

DABUCOR 500

Powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DABUCOR 350

Each vial contains 350 mg daptomycin as a sterile, lyophilised powder.

One ml provides 50 mg of daptomycin after reconstitution with 7 ml of sodium chloride 9 mg/ml (0.9 %) solution.

DABUCOR 500

Each vial contains 500 mg daptomycin as a sterile, lyophilised powder.

One ml provides 50 mg of daptomycin after reconstitution with 10 ml of sodium chloride 9 mg/ml (0.9 %) solution

Sugar-free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion

A pale yellow to light brown lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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DABUCOR is indicated for the following infections in adults:

Complicated skin and skin structure infections (cSSSI) caused by susceptable isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant isolates), *Sreptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus dysgalactiae subsp.equismilis*. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

***Staphylococcus aureus* bloodstream infecions (bacteraemia), including those with right-sided infective endocarditis (SAB/RIE)**, caused by methcillin-susceptable and methicllin-resistant isolates. Combination therapy may be clinically indiacted if the document or presumed pathogens including Gram-negative or anaerobicorganisms.

The efficacy of DABUCOR in patients with left-sided infective endocarditis and in patients with artificial valve endocarditis due to *Staphylococcus aureus* has not been demonstrated. The clinical trial of DABUCOR in patients with *Staphylococcus aureus* blood stream infections included limited data from patients with left-sided infective endocarditis, outcomes in these patients were poor.

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

4.2 Posology and method of administration

Posology

Dosage and administration pertain to adults 18 years and over

Complicated Skin and Skin Structure Infections (cSSSI):

DABUCOR 4 mg/kg should be administered once daily over a 30-minute period by IV infusion in 0.9 % sodium chloride injection once every 24 hours for 7 – 14 days. DABUCOR should not be dosed more frequently than once a day.

Staphylococcus aureus bloodstream infections (Bacteraemia), including Right-Sided Endocarditis:

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DABUCOR 6 mg/kg should be 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 treatment may be longer than 14 days in accordance with the perceive risk of complications in the individual patients. DABUCOR should not be dosed 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) DABUCOR should only be used in patients with any degree of renal insufficiency (cr Cl < 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) should be monitored closely in all patients with any degree of renal insufficiency (see section 4.4).

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

Indications for use (1)	**Creatine clearance (1)**	**Dose recommendation (1)**	**Comments**
cSSTI without *S.aureus* bacteraemia	≥ 30 ml/min	4 mg/kg once daily	Refer to 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)

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1. The safety and efficacy of the dose interval adjustment have not been clinically evaluated and the recommendation is based on pharmacokinetic modelling data (see section 4.4).
2. The same dose adjustments which are also based solely on modelling are recommended for patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, DABUCOR should be administered following the completion of dialysis on dialysis days.
3. There are insufficient data to support a dose recommendation for patients with RIE or cSSTI associated with Staphylococcus aureus bacteraemia who have creatine 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 bacteraemia who have creatine clearance is between 30-49 ml/min or to support the use of 4 mg/kg every 48 hours in such patients whose creatine clearance is < 30 ml/min.

Hepatic insufficiency

No dosage adjustment is warranted when administering DABUCOR to patients with mild-moderate hepatic impairment (Child-Pugh Class B). The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency have not been evaluated.

Obesity

No dosage adjustment of DABUCOR is warranted in moderately obsess (Body Mass Index (BMI)) 25-39,9 kg/m^2 patients.

Elderly patients

No dosage adjustments are warranted for elderly with normal renal function.

Children and adolescents (< 18 years old)

Safety and efficacy of DABUCOR in patients under the age of 18 have not been established.

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Method of administration

DABUCOR is indicated for parenteral use only.

Preparation and administration for DABUCOR

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

4.3 Contraindications

DABUCOR is contraindicated in patients with known hypersensitivity to daptomycin or to any of the ingredients of DABUCOR listed in section 6.1.

4.4 Special warnings and precautions for use

General

If a focus of infection other than cSSTI or RIE is identified after initiation of DABUCOR 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.

Anaphylaxis/hypersensitivity reactions

Anaphylaxis/hypersensitivity reactions have been reported with DABUCOR. If an allergic reaction to DABUCOR occurs, discontinue use and institute appropriate therapy.

Pneumonia

It has been demonstrated in clinical studies that DABUCOR is not effective in the treatment of pneumonia. DABUCOR is therefore not indicated for the treatment of pneumonia.

RIE due to *Staphylococcus aureus*

Clinical data on the use of DABUCOR to treat right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* are limited to 19 adult patients (see “Clinical efficacy in adults” in section 5.1). The safety and efficacy of DABUCOR in children and adolescents aged below 18years with right-sided infective endocarditis (RIE) due to Staphylococcus aureus have not been established.

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The efficacy of DABUCOR 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.

Enterococcal infections

There is insufficient evidence to be able to draw any conclusions regarding the possible clinical efficacy of DABUCOR against infections due to enterococci, including Enterococcus faecalis and Enterococcus faecium. In addition, dose regimens of daptomycin that might be appropriate for the treatment of enterococcal infections, with or without bacteraemia, have not been identified. 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 antibacterial may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken.

***Clostridioides difficile*-associated diarrhoea**

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

Drug/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).

Creatine phosphokinase and myopathy

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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 DABUCOR (see also sections 4.5, 4.8 and 5.3). In clinical studies, marked increases in plasma CPK to > 5x Upper Limit of Normal (ULN) without muscle symptoms occurred more commonly in DABUCOR-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) inpatients 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 haemodialysis or CAPD, and patients taking other medicinal products 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.

• DABUCOR should not be administered to patients who are taking other medicines associated with myopathy unless it is considered that the benefit to the patient outweighs the risk.

• 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. DABUCOR should be discontinued in the presence of unexplained muscle symptoms if the CPK level reaches greater than 5 times upper limit of normal.

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Peripheral neuropathy

Patients who develop signs or symptoms that might represent a peripheral neuropathy during therapy with DABUCOR should be investigated and consideration should be given to discontinuation of daptomycin (see sections 4.8 and 5.3).

Paediatric population

Paediatric patients below the age of one year should not be given DABUCOR due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs (see section 5.3).

Eosinophilic pneumonia

Eosinophilic pneumonia has been reported in patients receiving DABUCOR (see section 4.8). In most reported cases associated with DABUCOR, 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 DABUCOR and improved when DABUCOR 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 DABUCOR should undergo prompt medical evaluation, including, if appropriate, bronchoalveolar lavage, to exclude other causes (e.g. bacterial infection, fungal infection, parasites, other medicinal products). DABUCOR should be discontinued immediately and treatment with systemic steroids should be initiated when appropriate.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and vesiculobullous rash with or without mucous membrane involvement (Stevens-Johnson Syndrome (SJS)or Toxic Epidermal Necrolysis (TEN)), which could be life-threatening or fatal, have been reported with daptomycin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, DABUCOR should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a severe cutaneous adverse

reaction with the use of daptomycin, treatment with daptomycin must not be restarted in this patient at any time.

Tubulointerstitial nephritis

Tubulointerstitial nephritis (TIN) has been reported in post-marketing experience with daptomycin. Patients who develop fever, rash, eosinophilia and/or new or worsening renal impairment while receiving DABUCOR should undergo medical evaluation. If TIN is suspected, DABUCOR should be discontinued promptly and appropriate therapy and/or measures should be taken.

Renal impairment

Renal impairment has been reported during treatment with DABUCOR. Severe renal impairment may in itself also pre-dispose to elevations in daptomycin levels which may increase the risk of development of myopathy (see above).

An adjustment of DABUCOR 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. DABUCOR 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 DABUCOR to patients who already have some degree of renal impairment (creatinine clearance < 80 ml/min) before commencing therapy with DABUCOR. 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 DABUCOR in paediatric patients with renal impairment has not been established.

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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 (mean 42 % higher) 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).

4.5 Interaction with other medicinal products and other forms of interaction

CYP P450 enzymes

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. Interaction studies for DABUCOR were performed with aztreonam, tobramycin, warfarin and probenecid. Daptomycin had no effect on the pharmacokinetics of warfarin or probenecid, nor did these medicinal products alter the pharmacokinetics of daptomycin.

Aztreonam

The pharmacokinetics of daptomycin were not significantly altered by aztreonam.

Tobramycin

Although small changes in the pharmacokinetics of daptomycin and tobramycin were observed during co-administration by intravenous infusion over a 30-minute period using a DABUCOR dose of 2 mg/kg, the changes were not statistically significant. The interaction between daptomycin and tobramycin with an approved dose of DABUCOR is unknown. Caution is warranted when DABUCOR is co-administered with tobramycin.

Warfarin

Experience with the concomitant administration of DABUCOR and warfarin is limited. Studies of DABUCOR with anticoagulants other than warfarin have not been conducted. Anticoagulant activity in patients receiving DABUCOR and warfarin should be monitored for the first several days after therapy

with DABUCOR is initiated.

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 DABUCOR. It is recommended that other medicinal products associated with myopathy should if possible be temporarily discontinued during treatment with DABUCOR 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, 4.8 and 5.3).

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 medicines known to reduce renal filtration.

Laboratory test interactions

During post–marketing surveillance, cases of interference between daptomycin and particular 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 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

Safety in pregnancy has not been established.

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Breast-feeding

Safety in lactation has not been established.

Fertility

No clinical data on fertility are available for daptomycin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, adverse reactions such as headache, insomnia and dizziness have been reported (see section 4.8), therefore patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

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), drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema and rhabdomyolysis.

b. Tabulated list of adverse reactions

Table 1 below contains adverse reactions associated with daptomycin treatment

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Table 1: ADRs reported in patients with MDS or AML treated with azacitidine (clinical studies and postmarketing)

SYSTEM ORGAN CLASS	INCIDENCE	ADVERSE REACTION
Infections and infestations	Frequent	Fungal infections, urinary tract infection, candida infection
	Less frequent	Fungaemia
	Frequency unknown	*Clostridioides difficile* -associated diarrhoea**
Blood and lymphatic system disorders	Frequent	Anaemia
	Less frequent	Thrombocythaemia, eosinophilia, international normalisedratio (INR) increased, leukocytosis
	Less frequent	Prothrombin time (PT) prolonged
	Frequency unknown	Thrombocytopaenia
Immune system disorders	Frequency unknown	Hypersensitivity**, manifested by isolated spontaneous reports including, but not limited to angioedema, pulmonaryeosinophilia, sensation of oropharyngeal swelling, anaphylaxis**, infusion reactions including the followingsymptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste

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Metabolism and nutrition disorders	Less frequent	Decreased appetite, hyperglycaemia, electrolyte imbalance	
Psychiatric disorders	Frequent	Anxiety, insomnia	
Nervous system disorders	Frequent	Dizziness, headache	
	Less frequent	Paraesthesia, taste disorder, tremor, eye irritation	
	Frequency unknown	Peripheral neuropathy**	
Ear and labyrinth disorders	Less frequent	Supraventricular tachycardia, extrasystole	
Vascular disorders	Frequent	Hypertension, hypotension	
	Less frequent	Flushes	
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Eosinophilic pneumonia**, cough	
Gastro-intestinal disorders	Frequent	Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension	
	Less frequent	Dyspepsia, glossitis	

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Hepatobiliary disorders	Frequent	Liver function tests abnormal (increased alanineaminotransferase (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 (AGEP), drugreaction with eosinophilia and systemic symptoms(DRESS)**, vesiculobullous rash with or without mucousmembrane involvement (SJS or TEN)**	
Musculo-skeletal and connective tissue disorders	Frequent	Limb pain, serum creatine phosphokinase (CPK) increased	
	Less frequent	Myositis, increased myoglobin, muscular weakness, musclepain, arthralgia, serum lactate dehydrogenase (LDH) increased, muscle cramps	
	Frequency unknown	Rhabdomyolysis**	
Renal and urinary disorders	Less frequent	Renal impairment, including renal failure and renal insufficiency, serum creatinine increased	
	Frequency unknown	Tubulointerstitial nephritis (TIN)**	

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Reproductive system and breast disorders	Less frequent	Vaginitis
General disorders and administration site conditions	Frequent	Infusion site reactions, pyrexia, asthenia
	Less frequent	Fatigue, pain

* Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it isnot possible to reliably estimate their frequency which is therefore categorised as not known.

** See section 4.4.

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 professionals 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. 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 % ofthe administered dose is removed over 48 hours).

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 20.1 Antibiotic and antibiotic combinations.

Pharmacotherapeutic group: Antibacterials for systemic use, Other antibacterials, ATC code: J01XX09

Mechanism of action

Daptomycin is a cyclic lipopeptide natural medicine 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.

Interactions with other antibiotics

In vitro studies have investigated daptomycin interactions with other antibiotics. Antagonism, as determined by kill curve studies, has not been observed. *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).

PK/PD relationship

Daptomycin exhibits rapid, concentration dependent bactericidal activity against Gram positive organisms *in vitro* and in i*n vivo* animal models. In animal models AUC/MIC and C max/MIC correlate with efficacy and predicted bacterial kill in vivo at single doses equivalent to human adult doses of 4 mg/kg and 6 mg/kg once daily.

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 bacteraemia patients, that have been

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associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin during therapy.

The mechanism(s) of daptomycin resistance is (are) not fully understood.

Breakpoints

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

Susceptibility

The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly Susceptible Species
*Staphylococcus aureus**
Staphylococcus haemolyticus
Coagulase negative staphylococci
*Streptococcus agalactiae**
*Streptococcus dysgalactiae subsp equisimilis **
*Streptococcus pyogenes **
Group G streptococci
Clostridium perfringens
Peptostreptococcus spp
Inherently resistant organisms
Gram negative organisms

* denotes species against which it is considered that activity has been satisfactorily demonstrated in clinical studies.

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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.

Daptomycin administered as a 2-minute intravenous injection also exhibited dose proportional pharmacokinetics in the approved therapeutic dose range of 4 to 6 mg/kg. Comparable exposure (AUC and Cmax) was demonstrated in healthy adult subjects following administration of daptomycin as a 30-minute intravenous infusion or as a 2-minute intravenous injection.

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. Tissue distribution studies in rats showed that daptomycin appears to only minimally penetrate the blood-brain barrier and the placental barrier following single and multiple doses.

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.

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.

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.

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Following intravenous administration, plasma clearance of daptomycin is approximately 7 to 9 ml/hr/kg and its renal clearance is 4 to 7 ml/hr/kg.

Special populations

Elderly

No dose adjustment is necessary for elderly patients with normal renal function. Renal function should be assessed and the dose should be reduced if there is evidence of severe renal impairment.

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).

Obesity

The $AUC^{0-\infty}$ of daptomycin is approximately 30 – 31 % higher in extremely obese patients than in non-obese controls. No adjustment of daptomycin dosage is warranted in obese patients.

Renal impairment

Following administration of a single 4 mg/kg or 6 mg/kg dose of daptomycin to subjects with various degrees of renal insufficiency, daptomycin clearance was reduced and systemic exposure (AUC) was increased. The mean AUC for patients with CL_{cr} < 30 ml/min and for patients on haemodialysis (post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function. Refer to section 4.2.

The dosage regimen for DABUCOR in paediatric patients with renal impairment has not been established.

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.

5.3 Preclinical safety data

Reproductive toxicity testing showed no evidence of effects on fertility, embryofoetal, or postnatal development. However, daptomycin can cross the placenta in pregnant rats (see section 5.2). Excretion of daptomycin into milk of lactating animals has not been studied.

Long-term carcinogenicity studies in rodents were not conducted. Daptomycin was not mutagenic or clastogenic in a battery of *in vivo* and *in vitro* genotoxicity tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (does not exist as such in the finished product)

Water for injection

Nitrogen

6.2 Incompatibilities

DABUCOR is not physically or chemically compatible with glucose-containing solutions.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Compatible intravenous solutions

DABUCOR is compatible with 0.9 % sodium chloride injection and Lactated Ringer's injection.

Because only limited data are available on the compatibility of DABUCOR with other IV substances, additives or other medications should not be added to DABUCOR single-use vials or infused simultaneously through the same IV line.

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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 DABUCOR.

6.3 Shelf life

2 years

Store in a refrigerator (2 °C – 8 °C).

After reconstitution

Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25 °C and up to 48 hours at 2 °C – 8 °C. Chemical and physical stability of the diluted solution in infusion bags is established as 12 hours at 25 °C or 24 hours at 2 °C – 8 °C.

For the 30-minute intravenous infusion, the combined storage time (reconstituted solution in vial and diluted solution in infusion bag; see section 6.6) at 25 °C must not exceed 12 hours (or 24 hours at 2 °C – 8 °C).

For the 2-minute intravenous injection, the storage time of the reconstituted solution in the vial (see section 6.6) at 25 °C must not exceed 12 hours (or 48 hours at 2 °C – 8 °C).

However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. If not used immediately, in-use storage times are the responsibility of the user and would not normally be longer than 24 hours at 2 °C – 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

For storage conditions after reconstitution and after reconstitution and dilution of the medicinal product see section 6.3.

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6.5 Nature and contents of container

DABUCOR 350: 20 ml clear lyo glass vial with 20 mm dark grey bromobutyl FM460 RFS lyo stopper and 20 mm flip off plain yellow seal.

DABUCOR 500: 20 ml clear lyo glass vial with 20 mm dark grey bromobutyl FM460 RFS lyo stopper and 20 mm flip off plain royal blue seal.

Pack size: 1 vial per carton.

6.6 Special precautions for disposal and other handling

In adults, daptomycin may be administered intravenously as an infusion over 30 minutes or as an injection over 2 minutes. Daptomycin should not be administered as a 2-minute injection to paediatric patients. Paediatric patients 7 to 17 years old should receive daptomycin infused over 30 minutes. In paediatric patients under 7 years old receiving a 9-12 mg/kg dose, daptomycin should be administered over 60 minutes (see sections 4.2 and 5.2). Preparation of thesolution for infusion requires an additional dilution step as detailed below.

DABUCOR given as 30 or 60-minute intravenous infusion

A 50 mg/ml concentration of DABUCOR 350 mg powder for infusion is obtained by reconstituting the lyophilised product with 7 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection.
A 50 mg/ml concentration of DABUCOR 500 mg powder for infusion is obtained by reconstituting the lyophilised product with 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection.

The lyophilised product takes approximately 15 minutes to dissolve. The fully reconstituted product will appear clear andmay have a few small bubbles or foam around the edge of the vial.

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DABUCOR 350 mg powder for solution for injection or infusion

To prepare DABUCOR for intravenous infusion, please adhere to the following instructions:

Aseptic technique should be used throughout to reconstitute or dilute lyophilised DABUCOR.

For Reconstitution

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top ofthe rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch therubber stopper or allow it to touch any other surface. Draw 7 ml of sodium chloride 9 mg/ml (0.9 %) solution for injectioninto a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then slowlyinject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial.

2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.

3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution.Vigorous shaking/agitation should be avoided to prevent foaming of the product.

4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspectedfor the absence of particulates prior to use. Reconstituted solutions of DABUCOR range in colour from pale yellow to lightbrown.

5. The reconstituted solution should then be diluted with sodium chloride 9 mg/ml (0.9 %) (typical volume 50 ml).

For Dilution

1. Slowly remove the appropriate reconstituted liquid (50 mg daptomycin/ml) from the vial using a new sterile needle thatis 21 gauge or smaller in diameter by inverting the vial in order to allow the solution to drain towards the stopper. Using asyringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of thesolution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plungerall the way back to the end of the syringe barrel in order to remove the required solution from the inverted vial.

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2. Expel air, large bubbles, and any excess solution in order to obtain the required dose.

3. Transfer the required reconstituted dose into 50 ml sodium chloride 9 mg/ml (0.9 %).

4. The reconstituted and diluted solution should then be infused intravenously over 30 or 60 minutes as directed insection 4.2.

DABUCOR 500 mg powder for solution for injection or infusion

To prepare DABUCOR for intravenous infusion, please adhere to the following instructions:

Aseptic technique should be used throughout to reconstitute or dilute lyophilised DABUCOR.

For Reconstitution

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top ofthe rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch therubber stopper or allow it to touch any other surface. Draw 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injectioninto 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.

2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.

3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution.Vigorous shaking/agitation should be avoided to prevent foaming of the product.

4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspectedfor the absence of particulates prior to use. Reconstituted solutions of DABUCOR range in colour from pale yellow to lightbrown.

5. The reconstituted solution should then be diluted with sodium chloride 9 mg/ml (0.9 %) (typical volume 50 ml).

For Dilution

FINAL PROFESSIONAL INFORMATION

1. Slowly remove the appropriate reconstituted liquid (50 mg daptomycin/ml) from the vial using a new sterile needle thatis 21 gauge or smaller in diameter by inverting the vial in order to allow the solution to drain towards the stopper. Using asyringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of thesolution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plungerall the way back to the end of the syringe barrel in order to remove the required solution from the inverted vial.
2. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
3. Transfer the required reconstituted dose into 50 ml sodium chloride 9 mg/ml (0.9 %).
4. The reconstituted and diluted solution should then be infused intravenously over 30 or 60 minutes as directed insection 4.2.

The following have been shown to be compatible when added to DABUCOR containing infusion solutions: aztreonam,ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin and lidocaine.

DABUCOR given as 2-minute intravenous injection (adult patients only)

Water should not be used for reconstitution of DABUCOR for intravenous injection. DABUCOR should only be reconstituted with sodium chloride 9 mg/ml (0.9 %).

A 50 mg/ml concentration of DABUCOR 350 mg powder for injection is obtained by reconstituting the lyophilised productwith 7 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection.

A 50 mg/ml concentration of DABUCOR 500 mg powder for injection is obtained by reconstituting the lyophilised productwith 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection.

The lyophilised product takes approximately 15 minutes to dissolve. The fully reconstituted product will appear clear andmay have a few small bubbles or foam around the edge of the vial.

DABUCOR 350 mg powder for solution for injection or infusion

To prepare DABUCOR for intravenous injection, please adhere to the following instructions:

FINAL PROFESSIONAL INFORMATION

Aseptic technique should be used throughout to reconstitute lyophilised

DABUCOR.

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top ofthe rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch therubber stopper or allow it to touch any other surface. Draw 7 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.

2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.

3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution.Vigorous shaking/agitation should be avoided to prevent foaming of the product.

4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspectedfor the absence of particulates prior to use. Reconstituted solutions of DABUCOR range in colour from pale yellow to lightbrown.

5. Slowly remove the reconstituted liquid (50 mg daptomycin/ml) from the vial using a sterile needle that is 21 gauge orsmaller in diameter.

6. Invert the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle intothe inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial whendrawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

7. Replace needle with a new needle for the intravenous injection.

8. Expel air, large bubbles, and any excess solution in order to obtain the required dose.

9. The reconstituted solution should then be injected intravenously slowly over 2 minutes as directed in section 4.2.

FINAL PROFESSIONAL INFORMATION

DABUCOR 500 mg powder for solution for injection or infusion

To prepare DABUCOR for intravenous injection, please adhere to the following instructions:

Aseptic technique should be used throughout to reconstitute lyophilised DABUCOR.

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top ofthe rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch therubber stopper or allow it to touch any other surface. Draw 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injectioninto a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then slowlyinject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution.Vigorous shaking/agitation should be avoided to prevent foaming of the product.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspectedfor the absence of particulates prior to use. Reconstituted solutions of DABUCOR range in colour from pale yellow to lightbrown.
5. Slowly remove the reconstituted liquid (50 mg daptomycin/ml) from the vial using a sterile needle that is 21 gauge orsmaller in diameter.
6. Invert the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle intothe inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial whendrawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to theend of the syringe barrel in order to remove all of the solution from the inverted vial.
7. Replace needle with a new needle for the intravenous injection.
8. Expel air, large bubbles, and any excess solution in order to obtain the required dose.

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9. The reconstituted solution should then be injected intravenously slowly over 2 minutes as directed in section 4.2.

DABUCOR vials are for single-use only.

From a microbiological point of view, the product should be used immediately after reconstitution (see section 6.3).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park

6 Coombe Place

Rivonia

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

DABUCOR 350: 53/20.1/0604

DABUCOR 500: 53/20.1/0605

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 February 2023

10. DATE OF REVISION OF THE TEXT

To be confirmed