SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Daptomycin Equity, 500 mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Daptomycin Equity is sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Solution for Infusion

Before reconstitution: pale yellow to light brown lyophilised cake or powder.

After reconstitution: clear, pale yellow to light brown colour solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Daptomycin Equity is indicated for the following infections in adults:

Complicated skin and skin structure infections (cSSSI) 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 (bacteraemia), 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 daptomycin, as contained in Daptomycin Equity, 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 daptomycin in patients with *Staphylococcus aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor.

Daptomycin Equity is not indicated for the treatment of pneumonia (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):

Daptomycin Equity 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. Daptomycin Equity should not be dosed more frequently than once a day.

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

Daptomycin Equity 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 perceived risk of complications in the individual patients. Daptomycin Equity should not be dosed more frequently than once a day.

Special populations

Renal insufficiency:

Daptomycin is eliminated primarily by the kidneys. Due to limited clinical experience (see table and

footnotes below) Daptomycin Equity should only be used in patients with any degree of renal insufficiency (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) should be monitored closely in all patients with any degree of renal insufficiency (see sections 4.4. and 5.2)

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

Indication for use (1)	***Creatinine 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)

(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 sections 4.4 and 5.2).

(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, Daptomycin Equity 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* 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 *Staphylococcus 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 insufficiency:

No dosage adjustment is warranted when administering Daptomycin Equity to patients with mild-to-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 Daptomycin Equity is warranted in moderately obese (Body Mass Index [BMI] 25-39,9 kg/m^2) or extremely obese (BMI ≥ 40 kg/m^2) patients.

Elderly patients:

No dosage adjustment is warranted for the elderly with normal renal function.

Children and adolescents (< 18 years old):

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

Method of administration

In adults, Daptomycin Equity is given by intravenous infusion and administered over a 30-minute period, or by intravenous injection and administered over a 2-minute period (see section 6.6).

4.3 Contraindications

- Hypersensitivity to daptomycin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

Prescribers must adhere to the principles of antibiotic stewardship.

The use of antibiotics may promote the selection of non-susceptible organisms. If super-infection occurs during therapy, appropriate measures should be taken.

If a focus of infection other than cSSTI or RIE is identified after initiation of Daptomycin Equity 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 daptomycin. If an allergic reaction to Daptomycin Equity occurs, discontinue use and institute appropriate therapy.

Pneumonia

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

RIE due to Staphylococcus aureus

The safety and efficacy of Daptomycin Equity 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 Daptomycin Equity 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 Daptomycin Equity against infections due to enterococci, including *Enterococcus faecalis* and *Enterococcus faecium*. In addition, dose regimens of Daptomycin Equity 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).

Clostridium difficile-associated diarrhoea

Clostridium difficile-associated diarrhoea (CDAD) has been reported with daptomycin (see section 4.8). If

CDAD is suspected or confirmed, Daptomycin Equity may need to be discontinued and appropriate treatment instituted as clinically indicated.

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

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 daptomycin, as contained in Daptomycin Equity (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 daptomycin-treated patients (1,9 %) than in those that received comparators (0,5 %). 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 haemodialysis 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 Equity therapy. This should be taken into account when initiating Daptomycin Equity therapy and, if Daptomycin Equity is given, these patients should be monitored more frequently than once weekly.
- Daptomycin Equity 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. Daptomycin Equity 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 Daptomycin Equity should be investigated and consideration should be given to discontinuation of Daptomycin Equity (see sections 4.8 and 5.3).

Eosinophilic pneumonia

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

Renal impairment

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

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

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).

Persisting or relapsing *Staphylococcus aureus* bloodstream infection.

Patients with persisting or relapsing *S.aureus* bloodstream infection or poor clinical response should have repeat blood cultures. 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.

Severe cutaneous adverse reactions (SCARs)

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, Daptomycin Equity 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 Equity, treatment with Daptomycin Equity must not be restarted in this patient at any time.

Tubulointerstitial nephritis (TIN)

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 Daptomycin Equity should undergo medical evaluation. If TIN is suspected, Daptomycin Equity should be discontinued promptly and appropriate therapy and/or measures should be taken.

Paediatric population

Safety and efficacy of Daptomycin Equity in patients under the age of 18 have not been established (see section 4.2).

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.

Interaction studies for daptomycin were performed with aztreonam, tobramycin, warfarin and probenecid. 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.

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

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

There is limited experience regarding concomitant administration of Daptomycin Equity 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 daptomycin. It is recommended that other medicines associated with myopathy should if possible be temporarily discontinued during treatment with Daptomycin Equity 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 as contained in Daptomycin Equity 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 Equity is co-administered with any other medicine known to reduce renal filtration.

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

Daptomycin Equity should not be used during pregnancy because safety has not been established.

Breastfeeding

Safety has not been established and therefore Daptomycin Equity should not be used during breastfeeding.

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

Dizziness and vertigo have been reported (see section 4.8). Caution is advised when driving or operating machinery. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of 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 rash with eosinophilia and systemic symptoms (DRESS), angioedema and rhabdomyolysis.

Tabulated list of adverse reactions

Table 1 Adverse reactions from clinical studies and post-marketing reports

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	*Frequent*	Fungal infections, urinary tract infection, candida infection
	Less frequent	Fungaemia, oral and vaginal candidiasis, osteomyelitis, fungal urinary tract infection
	Unknown frequency	*Clostridium difficile*-associated diarrhoea**
Blood and lymphatic system disorders	*Frequent*	Anaemia
	Less frequent	Thrombocythaemia, eosinophilia, increased international normalised ratio (INR), leucocytosis, prolonged prothrombin time (PT), lymphadenopathy
	Unknown frequency	Thrombocytopaenia
Immune system disorders	*Unknown frequency*	Hypersensitivity**, manifested by isolated spontaneous reports including, but not limited to angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), pulmonary eosinophilia, vesicobullous rash with mucous membrane

		involvement and sensation of oropharyngeal swelling, anaphylaxis**, infusion reactions including the following symptoms: tachycardia, pyrexia, wheezing, rigors, systemic flushing, vertigo, syncope and metallic taste
Metabolism and nutrition disorders	*Less frequent*	Decreased appetite, hyperglycaemia, electrolyte imbalance, hypokalaemia, hypomagnesaemia
Psychiatric disorders	*Less frequent*	Anxiety, insomnia, hallucination, mental status change
Nervous system disorders	*Frequent*	Dizziness, headache
	Less frequent	Paraesthesia, taste disorder, tremor, dyskinesia
	Unknown frequency	Peripheral neuropathy**
Ear and labyrinth disorders	*Less frequent*	Vertigo, tinnitus
Eye disorders	*Less frequent*	Eye irritation, blurred vision
Cardiac disorders	*Less frequent*	Supraventricular tachycardia, extrasystole, atrial flutter, atrial fibrillation, cardiac arrest
Vascular disorders	*Frequent*	Hypertension, hypotension
	Less frequent	Flushes
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea
	Unknown frequency	Eosinophilic pneumonia[1]**, cough

Gastrointestinal disorders	*Frequent*	Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension
	Less frequent	Dyspepsia, glossitis, dry mouth, epigastric discomfort, gingival pain, oral hypoaesthesia, loose stools, stomatitis
Hepato-biliary disorders	*Frequent*	Liver function tests abnormal[2] (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, heat rash, rash vesicular
	Unknown frequency	Acute generalised exanthematous pustulosis (AGEP), medicine reaction with eosinophilia and systemic symptoms (DRESS)**, vesiculobullous rash with or without mucous membrane involvement (SJS or TEN)**
Musculoskeletal and connective tissue disorders	*Frequent*	Limb pain, serum creatine phosphokinase (CPK)[2] increased
	Less frequent	Myositis, increased myoglobin, muscular weakness, muscle pain,

		arthralgia, increased serum lactate dehydrogenase (LDH), muscle cramps, myalgia, back pain
	Unknown frequency	Rhabdomyolysis[3] **
Renal and urinary disorders	*Less frequent*	Renal impairment, including renal failure and renal insufficiency, increased serum creatinine, renal failure acute, proteinuria
	*Unknown frequency**	Tubulointerstitial nephritis (TIN)**
Reproductive system and breast disorders	*Less frequent*	Vaginitis
General disorders and administration site conditions	*Frequent*	Infusion site reactions, pyrexia, asthenia
	Less frequent	Fatigue, pain, chest pain, discomfort (not otherwise specified), oedema, jitteriness, rigors, weakness
Investigations	*Less frequent*	Increased blood bicarbonate, increased blood phosphorus, increased lactate dehydrogenase (LDH)

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

** See section 4.4.

[1] While the exact incidence of eosinophilic pneumonia associated with daptomycin is unknown, to date the reporting rate of spontaneous reports is very low (< 1/10 000).

[2] 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. The majority of transaminase elevations were of Grade 1-3 toxicity and resolved upon discontinuation of treatment.

[3] 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 medicinal products known to cause rhabdomyolysis.

The safety data for the administration of daptomycin via 2-minute intravenous injection are derived from two pharmacokinetic studies in healthy adult volunteers. Based on these study results, both methods of Daptomycin Equity administration, the 2-minute intravenous injection and the 30-minute intravenous infusion, had a similar safety and tolerability profile. There was no relevant difference in local tolerability or in the nature and frequency of adverse reactions.

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

In overdose, side effects can be precipitated and/or be of increased severity (see 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 and class:

A 20.1 Antibiotic and antibiotic combinations

Mechanism of action

Daptomycin binds to bacterial membranes and causes a rapid depolarisation of membrane potential in both growing and stationary phase bacteria. This loss of membrane potential causes inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death.

Microbiology

Daptomycin is a cyclic lipopeptide. 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.

Mechanism of resistance

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

PK/PD relationship

Daptomycin exhibits rapid, concentration dependent bactericidal activity against Gram positive organisms *in vitro.*

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).

5.2 Pharmacokinetic properties

Absorption

Daptomycin pharmacokinetics were generally linear and time-independent at doses of 4 to 12 mg/kg administered as a single daily dose. Steady-state concentrations were 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 C_{max}) 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.

After infusion of 14C-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 50 % of the dose. About 5 % of the administered radiolabel was excreted in the faeces.

Special populations

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.

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

Relative to non-obese subjects daptomycin systemic exposure measured by AUC was about 28 % higher in moderately obese subjects (Body Mass Index of 25-40 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.

Gender

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

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.

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. See section 4.2 for dose adjustments in patients with renal impairment by indication and creatinine clearance.

The dosage regimen for Daptomycin Equity 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (to adjust pH)

6.2 Incompatibilities

Daptomycin Equity is not physically or chemically compatible with glucose-containing solutions. Daptomycin Equity must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

2 years

After reconstitution:

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, 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).

Do not freeze.

For storage conditions after reconstitution and dilution of Daptomycin Equity see section 6.3.

6.5 Nature and contents of container

Daptomycin Equity powder for solution for infusion is filled in a 10 ml Type I glass vial sealed with a lyophilisation type I, grey butyl rubber closure and an aluminium cap with a blue plastic flip-off seal, packed into cartons as single units.

6.6 Special precautions for disposal and other handling

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

The contents of a Daptomycin Equity vial should be reconstituted to 50 mg/ml using aseptic technique as follows:

Note: To minimise foaming, AVOID vigorous agitation or shaking of the vial during or after reconstitution.

1. Remove the polypropylene flip-off cap from the Daptomycin Equity vial to expose the central portion of the rubber stopper.
2. Slowly transfer 10 ml of 0,9 % sodium chloride injection through the centre of the rubber stopper into the Daptomycin Equity vial, pointing the transfer needle toward the wall of the vial.
3. Ensure that the entire Daptomycin Equity product is wetted by gently rotating the vial.
4. Allow the product to stand undisturbed for 10 minutes.
5. Gently rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution.

For IV injection over a period of 2 minutes, reconstituted Daptomycin Equity is administered at a concentration of 50 mg/ml.

The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) at room temperature should not exceed 12 hours; the combined storage time (reconstituted solution in vial and diluted solution in infusion bag) under refrigeration should not exceed 48 hours. Parenteral medicines should be inspected visually for particulate matter prior to administration.

Compatible intravenous solutions:

Daptomycin Equity is compatible with 0,9 % sodium chloride injection and Lactated Ringer's injection.

Daptomycin Equity is not compatible with dextrose-containing diluents.

Because only limited data are available on the compatibility of Daptomycin Equity with other IV substances, additives or other medications should not be added to Daptomycin Equity 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 Daptomycin Equity.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

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Irene

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0157

8 REGISTRATION NUMBER(S)

54/20.1/0841

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 March 2023

10 DATE OF REVISION OF THE TEXT