

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DRYMRED 500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Lyophilised powder for IV infusion.

A pale yellow to light brown lyophilised cake or powder.

When reconstituted: A pale yellow to light brown coloured, clear solution with no visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DRYMRED 500 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 (bacteremia), including those with right-sided infective endocarditis (SAB/RIE)**, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

The efficacy of DRYMRED 500 in patients with left-sided infective endocarditis and in patients with artificial

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valve endocarditis due to *Staphylococcus aureus* has not been demonstrated.

In a clinical trial of daptomycin in patients with *Staphylococcus aureus* bloodstream infections, limited data from patients with left-sided infective endocarditis was included and outcomes in these patients were poor. DRYMRED 500 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):

DRYMRED 500 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. DRYMRED 500 should not be dosed more frequently than once a day.

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

DRYMRED 500 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. DRYMRED 500 should not be dosed more frequently than once a day.

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 <i>S. aureus</i> 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 <i>S. aureus</i> 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 section 4.4 and section 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).

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Whenever possible, DRYMRED 500 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* bacteremia 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.

Special populations

Renal insufficiency:

Daptomycin is eliminated primarily by the kidney.

Due to limited clinical experience (see table and footnotes below), DRYMRED 500 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 5.2 and section 4.4).

Hepatic insufficiency:

No dosage adjustment is warranted when administering DRYMRED 500 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 DRYMRED 500 is warranted in moderately obese (Body Mass Index [BMI] 25 – 39,9 kg/m²) or extremely obese (BMI ≥ 40 kg/m²) patients.

Elderly patients:

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

Paediatric population

Children and adolescents (< 18 years old): Safety and efficacy of DRYMRED 500 in patients under the age of 18 have not been established.

Method of administration

For intravenous administration over a 30-minute period

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For instructions on reconstitution and dilution before administration of DRYMRED 500, see section 6.6.

4.3 Contraindications

Known hypersensitivity to daptomycin or to any of the excipients of DRYMRED 500.

4.4 Special warnings and precautions for use

General

If a focus of *Staphylococcus aureus* infection other than cSSTI or RIE is identified after initiation of DRYMRED 500 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 such as in DRYMRED 500. If an allergic reaction to DRYMRED 500 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. DRYMRED 500 is therefore not indicated for the treatment of pneumonia.

In Phase III studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardio-respiratory adverse events were higher in DRYMRED 500 treated patients than in comparator treated patients. These differences were due to lack of therapeutic effectiveness of DRYMRED 500 in the treatment of CAP in patients experiencing these adverse events.

RIE due to *Staphylococcus aureus*

Clinical data on the use of daptomycin to treat RIE due to *Staphylococcus aureus* are limited to 19 patients. The efficacy of DRYMRED 500 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. valve replacement surgery, removal of prosthetic devices, debridement) without delay.

Enterococcal infections

There is insufficient evidence regarding the possible clinical efficacy of DRYMRED 500 against infections due to enterococci, including *Enterococcus faecalis* and *Enterococcus faecium*. In addition, dose regimens

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

Prescribing DRYMRED 500 in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

***Clostridium difficile*-associated diarrhoea**

Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of DRYMRED 500, and may range in severity from mild diarrhoea to fatal colitis. If CDAD is suspected or confirmed, DRYMRED 500 may need to be discontinued. Appropriate fluid and electrolyte management, antibiotic treatment of *C. difficile*, protein supplementation, and surgical evaluation should be instituted as clinically indicated.

Drug-laboratory test interactions

Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalised Ratio (INR) when certain recombinant thromboplastin reagents are utilised for the assay.

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 DRYMRED 500 (see section 4.8). In clinical studies, marked increases in plasma CPK to > 5 x Upper Limit of Normal (ULN) without muscle symptoms occurred.

- 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 medications known to be associated

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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.

DRYMRED 500 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. DRYMRED 500 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 DRYMRED 500 should be investigated and consideration should be given to discontinuation of DRYMRED 500 (see section 4.8).

Eosinophilic pneumonia

Eosinophilic pneumonia has been reported in patients receiving DRYMRED 500. In most reported cases associated with DRYMRED 500, patients developed fever, dyspnoea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates. In most of the cases this occurred after more than 2 weeks of treatment with DRYMRED 500 and improved when DRYMRED 500 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 DRYMRED 500 should undergo prompt medical evaluation, including, if appropriate, bronchoalveolar lavage, to exclude other causes (e.g. bacterial infection, fungal infection, parasites, other medicines). DRYMRED 500 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,

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

Renal impairment

Renal impairment has been reported during treatment with DRYMRED 500. 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).

Dose adjustment is needed for patients whose creatinine clearance is < 30 ml/min (see section 4.2 and section 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. DRYMRED 500 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 DRYMRED 500 to patients who have some degree of renal impairment (creatinine clearance < 80 ml/min) before commencing therapy with DRYMRED 500. Regular monitoring of renal function is advised (see section 5.2).

In addition, regular monitoring of renal function is advised during concomitant administration of potentially nephrotoxic agents, regardless of the patient's pre-existing renal function.

Obesity

In obese subjects with Body Mass Index (BMI) > 40 kg/m² but with creatinine clearance > 70 ml/min, the AUC_{0-∞} 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.

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Paediatric population

Safety and efficacy of DRYMRED 500 have not been established in patients under the age of 18 years.

DRYMRED 500 is therefore not recommended in this age group.

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.

4.5 Interactions with other medicinal products and other forms of interaction

Daptomycin does not induce or inhibit the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4. In *in vitro* studies, daptomycin was not metabolised by human liver microsomes. It is unlikely that daptomycin will induce or inhibit the metabolism of medicines metabolised by the P450 system.

Interaction studies with aztreonam, tobramycin, warfarin, simvastatin and probenecid showed 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 co-administration, the changes were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of DRYMRED 500 is unknown. Caution is warranted when DRYMRED 500 is co-administered with tobramycin.

Because experience with the concomitant administration of DRYMRED 500 and warfarin is limited, anticoagulant activity in patients receiving DRYMRED 500 and warfarin should be monitored during therapy with DRYMRED 500.

There is limited experience regarding concomitant administration of daptomycin with other medicines that may trigger myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin). However, some cases of marked rises in CPK levels and cases of rhabdomyolysis occurred in patients taking one of these

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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 DRYMRED 500 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 section 4.4).

Daptomycin is primarily cleared by renal filtration and so plasma levels may be increased during co-administration with medicines that reduce renal filtration (e.g. NSAIDs and COX-2 inhibitors). In addition, there is a potential for a pharmacodynamic interaction to occur during co-administration due to additive renal effects. Therefore, caution is advised when daptomycin is co-administered with any other medicine known to reduce renal filtration.

Laboratory tests

Clinically relevant plasma levels of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalised Ratio (INR) when certain recombinant thromboplastin reagents are utilised for the assay. The possibility of an erroneously elevated PT/INR result due to interaction with a recombinant thromboplastin reagent may be minimised by drawing specimens for PT or INR testing near the time of trough plasma concentrations of daptomycin. However, sufficient daptomycin levels may be present at trough to cause interaction.

If confronted with an abnormally high PT/INR result in a patient being treated with DRYMRED 500, it is recommended that healthcare practitioners:

1. Repeat the assessment of PT/INR; request that a specimen be drawn just prior to the next DRYMRED 500 dose (i.e. at trough concentration). If the PT/INR value drawn at trough remains substantially elevated over what would otherwise be expected, consider evaluating PT/INR using an alternative method.
2. Evaluate for other causes of abnormally elevated PT/INR results.

Pharmaceutical incompatibilities

DRYMRED 500 is not compatible with dextrose-containing diluents (refer to section 6.6).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

No clinical data on pregnancies are available for daptomycin. Animal studies do not indicate direct or

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indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnasal development.

DRYMRED 500 should not be used during pregnancy.

Breastfeeding

In a single human case study, DRYMRED 500 was intravenously administered daily for 28 days to a nursing mother at a dose of 500 mg/day, and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of daptomycin in the breast milk was 0,045 mcg/ml, which is a low concentration.

Therefore, until more experience is gained, breast-feeding should be discontinued when DRYMRED 500 is administered to nursing women.

Fertility

No clinical data on fertility are available for daptomycin.

4.7 Effects on ability to drive and use machines

On the basis of reported adverse reactions, DRYMRED 500 may cause dizziness or vertigo. Patients are advised not to drive or use machinery until their individual susceptibility is known.

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

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b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse effect
Infections and infestations	Frequent	Fungal infections, urinary tract infection, candida infection
	Less frequent	Fungaemia
	Frequency unknown	<i>Clostridium difficile</i> -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)

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Ear and labyrinth disorders	Frequency unknown	Vertigo
Cardiac disorders	Less frequent	Atrial fibrillation, atrial flutter, cardiac arrest
	Frequency unknown	Supraventricular tachycardia, extrasystoles
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 (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), vesiculobullous rash with or without mucous membrane involvement (SJS or TEN) (see section 4.4)
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

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		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
	Frequency unknown	Tubulointerstitial nephritis (TIN) (see section 4.4)
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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms of overdose may be exaggerated.

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

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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

Pharmacological classification: A 20.1 Antibiotic and antibiotic combinations

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

5.1 Pharmacodynamic properties

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 inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

Daptomycin is a cyclic lipopeptide. The *in vitro* spectrum of activity of daptomycin encompasses only Gram-positive pathogenic bacteria. *In vitro* susceptibility does not necessarily imply clinical efficacy.

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 *Enterococcus faecalis* or *Enterococcus faecium*, including bacteraemic patients, that have been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin during therapy.

Emergent decreases in susceptibility have been observed in *Staphylococcus aureus* isolates following daptomycin therapy. Daptomycin is inherently resistant against Gram-negative organisms.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

Daptomycin exhibits rapid, concentration dependent bactericidal activity against susceptible 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 are generally linear and time-independent at doses of 4 to 12 mg/kg administered as a single daily dose. Steady-state concentrations are achieved by the third daily dose.

Distribution

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

The volume of distribution at steady-state of daptomycin in healthy adult subjects was approximately 0,1 litres/kg and was independent of dose. Tissue distribution studies in rats showed that daptomycin appears to only minimally penetrate across the blood-brain barrier following single and multiple doses.

Metabolism

In vitro studies with human hepatocytes indicate that daptomycin does not induce or inhibit the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4. Daptomycin was not metabolised by human liver microsomes in *in vitro* studies. It is unlikely that daptomycin will induce or inhibit the metabolism of medicines metabolised by the P450 system.

After infusion of ^{14}C -daptomycin, 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. In a mass balance study using radiolabeled daptomycin, 78 % of the administered dose was recovered from the urine based on total radioactivity, while urinary recovery of unchanged daptomycin was approximately 52 % of the dose. About 6 % of the administered dose was excreted in the faeces based on total radioactivity.

Special populations

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Renal insufficiency

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.

Hepatic insufficiency

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, weight and age. The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency (Child-Pugh C classification) have not been evaluated.

Obesity

The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 – 39,9 kg/m²) and 6 extremely obese (BMI ≥ 40 kg/m²) subjects. The AUC increased approximately 30 % in moderately obese subjects and 31 % in extremely obese subjects compared with non-obese controls. However, no dosage adjustment of daptomycin is warranted in moderately or extremely obese patients.

Elderly

No dosage adjustment is necessary for elderly patients with normal renal function. The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (> 75 years of age) and 11 healthy young controls (18 to 30 years of age). Following administration of a single 4 mg/kg IV dose, the mean total clearance of daptomycin was reduced approximately 35 % and the mean AUC_{0-∞} increased approximately 58 % in elderly subjects compared with young healthy subjects. There were no differences in C_{max}. Refer to 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. Refer to section 4.2.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

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6.2 Incompatibilities

DRYMRED 500 is not compatible with dextrose-containing diluents (see section 4.5). As limited data are available on the compatibility of DRYMRED 500 with other IV substances, it should not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store original packages in a refrigerator (2 – 8 °C). Avoid excessive heat.

After reconstitution/dilution: Although chemical and physical in-use stability for the reconstituted and diluted product has been demonstrated for 12 hours at 25 °C or 48 hours stored refrigerated at 2 – 8 °C 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 12 hours at 2 to 8 °C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

Do not freeze the reconstituted/diluted infusion solution.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

DRYMRED 500 powder for solution for infusion is filled in a clear 15 ml Type I glass vial sealed with a grey bromobutyl rubber stopper 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

Preparation of DRYMRED 500 for administration:

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

The contents of a DRYMRED 500 vial should be reconstituted to 50 mg/ml using aseptic technique as follows:

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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 DRYMRED 500 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 DRYMRED 500 vial, pointing the transfer needle toward the wall of the vial.
3. Ensure that the entire DRYMRED 500 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.

Reconstituted DRYMRED 500 should be further diluted with 0,9 % sodium chloride injection to be administered by IV infusion over a period of 30 minutes.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final IV solution. Stability studies have shown that the reconstituted solution is stable in the vial for 12 hours at room temperature, or up to 48 hours if stored under refrigeration at 2 – 8 °C. The diluted solution is stable in the infusion bag for 12 hours at room temperature, or 48 hours if stored under refrigeration.

The reconstituted/diluted solution should be used immediately after preparation.

Parenteral medicines should be inspected visually for particulate matter prior to administration.

Discard any unused portion of the infusion solution.

Compatible intravenous solutions:

DRYMRED 500 is compatible with 0,9 % sodium chloride injection and Lactated Ringer's injection.

DRYMRED 500 is not compatible with dextrose-containing diluents.

Because only limited data are available on the compatibility of DRYMRED 500 with other IV substances, additives or other medications should not be added to DRYMRED 500 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 DRYMRED 500.

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7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBER

51/20.1/0734

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

25 March 2019

10. DATE OF REVISION OF TEXT

22 January 2025