SCHEDULING STATUS S4

PROPRIETARY NAME (and dosage form)

DRYMRED 500 (Lyophilized powder for IV infusion)

COMPOSITION

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

Excipients: Sodium hydroxide

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 20.1 Antibiotic and antibiotic combinations

PHARMACOLOGICAL ACTION

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).

Pharmacokinetic properties:

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, nfrefrigo 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:

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 CLcr < 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 **"DOSAGE AND DIRECTIONS FOR USE"**.

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/m^2) and 6 extremely obese (BMI ≥ 40 kg/m^2) 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 $AUC_{0-\infty}$ increased approximately 58 % in elderly subjects compared with young healthy subjects. There were no differences in C_{max}. Refer to **"DOSAGE AND DIRECTIONS FOR USE"**.

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 **"DOSAGE AND DIRECTIONS FOR USE"**.

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 (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 **DRYMRED 500** in patients with left-sided infective endocarditis and in patients with artificial 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 **"WARNINGS AND SPECIAL PRECAUTIONS"**).

CONTRA-INDICATIONS

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

WARNINGS AND SPECIAL PRECAUTIONS

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.

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 **"SIDE-EFFECTS"**). 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 **"DOSAGE AND DIRECTIONS FOR USE"**), including those on haemodialysis or CAPD, and patients taking other medications 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. **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 **"SIDE-EFFECTS"**).

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.

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 **"DOSAGE AND DIRECTIONS FOR USE"** and **"Pharmacokinetic properties [special populations]"**). 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 **"Pharmacokinetic properties [special populations]"**).

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/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.

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.

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.

INTERACTIONS

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). However, some cases of marked rises in CPK levels and cases of rhabdomyolysis occurred in 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 **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 **"WARNINGS AND SPECIAL PRECAUTIONS"**).

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 **"DOSAGE AND DIRECTIONS FOR USE: Compatible intravenous solutions"**).

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 indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnasal development. **DRYMRED 500** should not be used during pregnancy.

Breast-feeding:

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.

DOSAGE AND DIRECTIONS FOR USE

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.

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 **"Pharmacokinetic properties [Special populations]"** and **"WARNINGS AND SPECIAL PRECAUTIONS"**).

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 "Pharmacokinetics"
	< 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 **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"Pharmacokinetic properties [Special populations]"**).

(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, **DRYMRED 500** should be administered following the completion of

dialysis on dialysis days (see **"Pharmacokinetic properties [Special populations]"**).

(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 **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/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 **DRYMRED 500** in patients under the age of 18 have not been established.

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:

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 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**.

SIDE-EFFECTS

Infections and infestations:

Frequent:

Candida infections, fungal infections, fungaemia, oral candidiasis, osteomyelitis, urinary tract infections, urinary tract infections fungal, vaginal candidiasis

Frequency not known:

Clostridium difficile-associated diarrhoea (CDAD)

Blood and the lymphatic system disorders:

Frequent:

Anaemia

Less frequent:

Eosinophilia, leukocytosis, lymphadenopathy, thrombocytopenia, thrombocytosis, thrombocythaemia

Immune system disorders:

Frequency not known:

Anaphylaxis, hypersensitivity reactions (including pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, pulmonary eosinophilia, angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), vesicobullous rash with mucous membrane involvement and sensation of oropharyngeal swelling), infusion reactions (including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste)

Metabolism and nutrition disorders:

Less frequent:

Decreased appetite, hyperglycaemia, hypokalaemia, hypomagnesaemia, electrolyte imbalance

Psychiatric disorders:

Frequent:

Anxiety, insomnia

Less frequent:

Hallucination, mental status change

Nervous system disorders:

Frequent:

Headache, dizziness

Less frequent:

Dyskinesia, paraesthesia, taste disorder, tremor

Frequency not known:

Peripheral neuropathy

Eye disorders:

Less frequent:

Eye irritation, blurred vision

Ear and labyrinth disorders:

Less frequent:

Tinnitus, vertigo

Cardiac disorders:

Less frequent:

Atrial fibrillation, atrial flutter, cardiac arrest, supraventricular tachycardia, exstrasystole

Vascular disorders:

Frequent:

Hypertension, hypotension

Less frequent:

Flushing

Respiratory, thoracic and mediastinal disorders

Less frequent:

Cough, dyspnoea

Frequency not known:

Eosinophilic pneumonia (see **"WARNINGS AND SPECIAL PRECAUTIONS"**)

Gastrointestinal disorders:

Frequent:

Diarrhoea, nausea, vomiting

Less frequent:

Abdominal distension, abdominal pain, constipation, dry mouth, dyspepsia, epigastric discomfort, flatulence, gingival pain, oral hypoaesthesia, loose stools, stomatitis, glossitis

Hepato-biliary disorders:

Frequent:

Abnormal liver function tests

Less frequent:

Jaundice

Skin and subcutaneous tissue disorders:

Less frequent:

Eczema, heat rash, pruritus, pruritus generalised, rash (excluding vesicular), rash vesicular, urticarial

Frequency not known:

Acute generalised exanthematous pustulosis

Musculoskeletal, connective tissue and bone disorders:

Less frequent:

Arthralgia, back pain, limb pain, muscle cramps, muscle weakness, myalgia, myositis

Frequency not known:

Rhabdomyolysis

Renal and urinary disorders:

Less frequent:

Proteinuria, renal failure acute, renal impairment, including renal failure and renal insufficiency

Reproductive system and breast disorders:

Less frequent:

Vaginitis

General disorders and administration site conditions:

Frequent:

Injection site reactions (including infusion site reaction, injection site bruising, injection site burning, injection site inflammation, injection site irritation, injection site oedema, injection site pain, injection site phlebitis, injection site pruritus and injection site thrombosis)

Less frequent:

Asthenia, chest pain, discomfort (not otherwise specified), oedema, fatigue, jitteriness, pyrexia, rigors, weakness, pain

Investigations:

Frequent:

Increased alanine aminotransferase, increased blood creatine phosphokinase

Less frequent:

Increased aspartate aminotransferase, increased blood alkaline phosphatase, increased blood bicarbonate, increased blood phosphorus, increased International Normalised Ratio (INR), increased lactate dehydrogenase (LDH), prolonged prothrombin time, increased myoglobin, increased serum creatinine

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdose may be exaggerated.

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).

IDENTIFICATION

A pale yellow to light brown lyophilized cake or powder.

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

PRESENTATION

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.

STORAGE INSTRUCTIONS

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.

REGISTRATION NUMBER

51/20.1/0734

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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