DOSAGE CARD FOR PHYSICIANS

A GUIDE TO DOSING – DACI

Daci is indicated for the treatment of the following infections.
- Adult and pediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI).
- Adult patients with right-sided infective endocarditis (RIE) due to Staphylococcus aureus. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice.
Adult and pediatric (1 to 17 years of age) patients with Staphylococcus aureus bacteraemia (SAB)
In adults, use in bacteraemia should be associated with RIE or with cSSTI, while in pediatric patients, use in bacteraemia should be associated with cSSTI.
Daptomycin is active against Gram-positive bacteria only. In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, Daptomycin should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Recommendations

The following points should be noted when taking the decision to treat with Daci.

During Daptomycin therapy, an increase in plasma creatinine phosphokinase (CPK) levels associated with musculoskeletal adverse events have been reported. Therefore:

• Concomitant administration of Daptomycin and other medicinal products associated with myopathy (for example statins, fibrates and ciclosporin) should be avoided, unless the benefits of treatment outweighs the risk.
• CPK should be measured at baseline and at regular intervals (at least once weekly) in all patients during therapy.
• More frequent monitoring of CPK should be conducted, in patients who are at a higher risk of developing myopathies (those with either any degree of renal insufficiency (creatinine clearance < 80 ml/min) or those taking other medicines known to be associated with myopathy). For example, patients should be tested every 2-3 days during the first two weeks of treatment.

Cases of interference between Daptomycin and particular reagents (recombinant thromboplastin) used in some coagulation assays (prothrombin time (PT); International Normalised Ratio (INR)) have been reported. The interference can lead to false results with an apparent prolongation of PT and elevation of INR. Therefore:

• Drawing blood samples near the time of Daptomycin trough plasma concentrations may minimise this potential for erroneous results.

Results from studies in paediatric populations have indicated that compared to adults, children show progressively higher Daptomycin clearance and a higher volume of distribution with decreasing age. Therefore:

• In children , Higher doses will be required and will vary by age groups in order to achieve exposures equivalent to those seen for efficacy in adults.
• In the paediatric population Daptomycin administration at the following doses for up to 14 days was shown to be safe and effective in the treatment of cSSTI caused by Gram positive bacteria.

Age range (years)	Daci dose
12 -17	5 mg/kg
7-11	7 mg/kg
2-6	9 mg/kg
1-<2	10 mg/kg

Because higher clearance of Daptomycin has been observed in single-dose paediatric pharmacokinetic studies and other studies in paediatric patients the following should be noted:

• Age-adjusted Daptomycin doses were given once daily up to 14 days in order to achieve equivalent exposures to those documented from adult cSSTI studies.
• Dosing is both age-dependent and weight-dependent.
• The safety and efficacy results from the paediatric studies are consistent with those from the adult studies and with literature reports.

DACI 4 MG/KG

Indication – cSSTI in adult patients without Staphylococcus aureus bacteremia

Dosage - **Daci 4 mg/kg should be administered once daily either as a 2 minute iv injection or as a 30 minute iv infusion.**

Daci should be reconstituted to a 50 mg/ml solution with:
• 500 mg vial: 10 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion) Volume of Daci 50 mg/ml solution required:
• Volume in ml = bodyweight (kg) x 4/50
This volume may be injected intravenously over 2 minutes of diluted with 0.9% sodium chloride (typical volume 50 ml) and infused over 30 minutes.

Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)
46	3.68	66	5.28	86	6.88	106	8.48
48	3.84	68	5.44	88	7.04	108	8.64
50	4.00	70	5.60	90	7.20	110	8.80
52	4.16	72	5.76	92	7.36	112	8.96
54	4.32	74	5.92	94	7.52	114	9.12
56	4.48	76	6.08	96	7.68	116	9.28
58	4.64	78	6.24	98	7.84	118	9.44
60	4.80	80	6.40	100	8.00	120	9.60
62	4.96	82	6.56	102	8.16	122	9.76
64	5.12	84	6.72	104	8.32	124	9.92

DACI 6 MG/KG

Indication - RIE due to Staphylococcus aureus Staphylococcus aureus bacteraemia when associated with RIE or with cSSTI.

Dosage - **Daci 6 mg/kg should be administered once daily either as a 2 minute IV injection or as a 30 minute IV infusion**

Daci should be reconstituted to a 50 mg/ml solution with:

• 500 mg vial: 10 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion) Volume of Daci 50 mg/ml solution required:
• Volume in ml = bodyweight (kg) x 6/50
This volume may be injected intravenously over 2 minutes of diluted with 0.9% sodium chloride (typical volume 50 ml) and infused over 30 minutes.

Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)
46	5.52	66	7.92
48	5.76	68	8.16
50	6.00	70	8.40
52	6.24	72	8.64
54	6.48	74	8.88
56	6.72	76	9.12
58	9.96	78	9.36
60	7.20	80	9.60
62	7.44	82	9.84
64	7.68		

DOSING IN THE PAEDIATRIC POPULATION FOR cSSTI

Dosage – In the paediatric population Daci should be given by intravenous infusion over a 30 or 60 minute period depending upon the age of the patient.
Children under 1 year of age should not be given Daptomycin due to the potential risk of effects on muscular, neuromuscular and/or nervous system (either peripheral or central), such effects have been observed in neonatal dogs.

Age range	Dosage and administration	Duration of treatment
12 -17 years	5 mg/kg once every 24 hours infused iv over 30 minutes	Up to 14 days
7-11 years	7 mg/kg once every 24 hours infused iv over 30 minutes	
2-6 years	9 mg/kg once every 24 hours infused iv over 60 minutes	
1-<2 years	10 mg/kg once every 24 hours infused iv over 60 minutes	

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

DOSE ADJUSTMENT IN ADULTS WITH RENAL IMPAIRMENT

The response to treatment, renal function and plasma CPK should be closely monitored in all patients with renal impairment

Indication	Creatinine Clearance	Dose recommendation	Comments
cSSTI without S. aureus bacteraemia	≥ 30 ml/min	4 mg/kg every 24 hours	
	< 30 ml/min	4 mg/kg every 48 hours	1,2
RIE or cSSTI associated with S. aureus bacteraemia	≥ 30 ml/min	6 mg/kg every 24 hours	
	< 30 ml/min	6 mg/kg every 48 hours	1,2

(1) The safety and efficacy of the dose interval adjustment have not been evaluated in controlled clinical studies and the recommendation is based on pharmacokinetic studies and modelling results.
(2) The same dose adjustments, which are based on pharmacokinetic data in volunteers including pharmacokinetic modelling results, are recommended for patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible Daci should be administered following the completion of dialysis on dialysis days.

GENERAL NOTES BEFORE PRESCRIBING DACI

BEFORE PRESCRIBING DAPTMYCIN PLEASE ENSURE THAT YOU REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Reporting of suspected adverse reactions

Please continue to report suspected adverse drug reactions (ADRs) including medication errors (any errors while prescribing, preparing or administering the drug).
Please report all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
When making a report please provide us with as much information as possible, including the method of dilution, the dose administered and any side effects, medical history, concomitant medications etc.

References :
1- Daci leaflet
2- Medicines.org.uk. (2019). Cubicin (daptomycin): Important safety information to minimise the risk of myotoxicity and dysregulation of in vivo coagulation- Dosage Card for Physicians. [online] Available at: https://www.medicines.org.uk/emc/rm-m/628/Document [Accessed 27 Jun. 2019].

FOR MORE INFORMATION AND FOR ADVERSE EVENT REPORTING YOU CAN CONTACT US"

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