Dosage card

A guide to dosing Daptomycin Xellia

Daptomycin Xellia

- Indicated for the treatment of the following infection in adults and paediatric patients (1 to 17 years of age)
  - Complicated skin and soft tissue infections (cSSTIs)
  - Paediatric patients aged below 1 year should not be given Daptomycin Xellia

- Indicated for the treatment of the following infections in adults:
  - Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*
    - It is recommended that the decision to use daptomycin should take in to account the antibacterial susceptibility of the organism and should be based on expert advice
  - *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI

- Bactericidal activity against a broad range of Gram-positive bacteria

- In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, Daptomycin Xellia should be co-administered with appropriate antibacterial agent(s)

- Consideration should be given to official guidance on the appropriate use of antibacterials agents

Dose Adjustment in Renal Insufficiency

Indication for use	Creatinine clearance	Dose recommendation	Comments
cSSTI without *S. aureus* bacteraemia	≥30 ml/min	4 mg/kg once daily	(3)
	< 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 once daily	(3)
	< 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 trials 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 PK modelling results, are recommended for patients on haemodialysis (HD) or continuous ambulatory peritoneal dialysis. Whenever possible, Daptomycin Xellia should be administered following the completion of dialysis on dialysis days

(3) Please refer to SmPC

- Response to treatment, renal function and plasma CPK should be closely monitored in all patients with renal impairment
- Due to limited clinical experience Daptomycin Xellia should only be used in patients with any degree of renal impairment (CrCl<80ml/min) when it is considered that the expected clinical benefit outweighs the potential risk

Daptomycin Xellia Dosing in Paediatric Population (1 to 17 years of age) for cSSTI

- In paediatric patients, Daptomycin Xellia is given by intravenous (IV) infusion over a 30 or 60-minute period depending on the age of the patient (see Paediatric Patients)

Age Category	Dosage and Administration	Duration of therapy
12 to 17 years	5 mg/kg once every 24 hours infused IV over 30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once every 24 hours infused IV over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused IV over 60 minutes	
1 to <2 years	10 mg/kg once every 24 hours infused IV over 60 minutes	

- Paediatric patients below the age of one year should not be given Daptomycin Xellia due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs
- Creatine phosphokinase (CPK) levels must be measured at baseline and at regular intervals (at least weekly) during treatment
- In the paediatric population, daptomycin administered at doses of 5mg/kg (12 to 17 years), 7 mg/kg (7 to 11 years), 9mg/kg (2 to 6 years) and 10 mg/kg (1 to <2 years) for up to 14 days was safe and effective in the treatment of cSSTI caused by Gram-positive pathogens

Recommendations

- **Increases in plasma creatine phosphokinase (CPK) levels associated with muscular pains and/or weakness and cases of myositis, myoglobinaemia and rhabdomyolysis have been reported during Daptomycin Xellia therapy.In clinical studies, marked increases in plasma CPK to >5 x Upper Limit of Normal (ULN) without muscular symptoms occurred more commonly in Daptomycin treated patients (1.9%) than in those that received comparators (0.5%). Therefore it is recommended that:**
  - Concomitant administration of daptomycin and other medicinal products associated with myopathy (e.g. statins, fibrates, ciclosporin) should be avoided, unless the benefit outweighs the risk
  - CPK should be measured at baseline and at regular intervals (at least once weekly) during therapy in all patientsas described in the dosage card
  - More frequent monitoring of CPK levels (e.g. every 2-3 days at least during the first two weeks of treatment) should be carried out in patients who are at higher risk of developing myopathies:
    - Those with any degree renal insufficiency (creatinine clearance <80ml/min)
    - Patients taking other medicinal products known to be associated with myopathy
    - Any patient that develops unexplained muscle pain, tenderness, weakness or cramps should have CPK levels monitored every 2 days
- Cases of interference between Daptomycin Xellia and particular reagents (recombinant thromboplastin) used in some coagulation assays (Prothrombin Time [PT]; International Normalized Ratio [INR]) have been reported. The interference leads to false results, with an apparent prolongation of PT and elevation of INR.

- Drawing samples near the time of daptomycin Xellia trough plasma concentrations may minimise the potential for erroneous results.

- Results from the most recent study in paediatric population indicated that compared with adults, children show progressively higher daptomycin clearance and higher volume of distribution with decreasing age
    - Hence, higher doses will be required in children and will vary by age groups in order to produce exposures equivalent to those seen for efficacy in adults
- Because higher clearance of daptomycin was observed in previous single-dose paediatric PK studies and in the most recent paediatric study described above
    - Age-adjusted daptomycin doses were given once daily up to 14 days in order to achieve exposures equivalent to those documented in adult cSSTI studies
    - Dosing is age-dependent and weight-dependent
    - Both safety and efficacy results are consistent with those from adult studies and with data from the literature

Patient weight (kg)	Volume of Daptomycin Xellia 50 mg/ml solution required (ml)

Daptomycin Xellia 4 mg/kg

- **Indicated for adults patients with: cSSTIs and cSSTI with bacteraemia (see below 6 mg/kg dose)**

DOSAGE

Daptomycin Xellia 4 mg/kg administered as a once-daily 2-minute i.v. injection or 30-minute i.v. infusion

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

350mg vial - 7ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)

500mg vial - 10ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)

Volume of Daptomycin Xellia 50 mg/ml solution required:

Volume in ml = Bodyweight (kg) x 4/50

This volume may be injected intravenously over 2 minutes or diluted with 0.9% sodium chloride (typical volume 50 ml) for infusion over 30 minutes

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

Patient weight (kg)	Volume of Daptomycin Xellia 50 mg/ml solution required (ml)

Daptomycin Xellia 6 mg/kg

- **Indicated in adults patients with: RIE due to *Staphylococcus aureus***

DOSAGE

Daptomycin Xellia 6 mg/kg administered as a once-daily 2-minute i.v. injection or 30-minute i.v. infusion

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

350mg vial – 7 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)

500mg vial – 10 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)

Volume of Daptomycin Xellia 50 mg/ml solution required:

Volume in ml = Bodyweight (kg) x 6/50

This volume may be injected intravenously over 2 minutes or diluted with 0.9% sodium chloride (typical volume 50 ml) for infusion over 30 minutes

Patient weight (kg)	Volume of Daptomycin Xellia 50 mg/ml solution required (ml)
46	5.52
48	5.76
50	6.00
52	6.24
54	6.48
56	6.72
58	6.96
60	7.20
62	7.44
64	7.68
66	7.92
68	8.16
70	8.40
72	8.64
74	8.88
76	9.12
78	9.36
80	9.60
82	9.84

Please refer to the Summary of Product Characteristics (SmPC) before prescribing Daptomycin Xellia.

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via National Reporting System.

Reporting can be done by contacting Xellia at:

Xellia Pharmaceuticals ApS

Dalslandsgade 11

2300 Copenhagen S

Denmark

via e-mail: safety@xellia.com

or by contacting

Xellia Medical Information at:

Lambda Therapeutic Limited

Sage House, 319 Pinner Road

North Harrow

London, HA1 4HF

Telephone: + 44(0) 208 901 3370