Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Daptomycin

Proprietary Product Name: Cubicin

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

November 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au> .

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{ss}	Area under the curve at steady state
BIP	Baseline infecting pathogen
BLQ	Below the limit of quantitation
CE	Clinically evaluable
CI	Confidence interval
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
C_{trough}	Plasma concentration just before dosing
CoNS	Coagulase-negative Staphylococci
CPK	Creatine phosphokinase
CSR	Clinical study report
cSSSI	Complicated skin and skin structure infection
Cubist	Cubist Pharmaceuticals LLC (formally know an Cubist Pharmaceuticals, Inc), an indirect, wholly-owned subsidiary of Merck Sharp & Dohme Corp
DLP	Data lock point
DMC	Data monitoring committee
eCRF	Electronic case report form
EOIV	End of IV therapy

Abbreviation	Meaning
EOT	End of therapy
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
IDSA	Infectious Disease Society of America
IE	Infective endocarditis
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MIC_{90}	Minimum inhibitory concentration required to inhibit growth of 90% of specific organisms
MITT	Modified intent-to-treat
MRSA	Methicillin resistant *Staphylococcus aureus*
MSSA	Methicillin sensitive *Staphylococcus aureus*
n	Number of participants
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
q24h	Every 24 hours
RIE	Right-sided infective endocarditis
RMP	Risk management plan
SAB	*Staphylococcus aureus* bacteraemia
SAE	Serious adverse event
SD	Standard deviation

Abbreviation	Meaning
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA query
SOC	Standard of care
TEAE	Treatment emergent adverse event
TOC	Test of cure
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
V_{ss}	Volume of distribution at steady-state

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	19 January 2019
Date of entry onto ARTG:	25 January 2019
ARTG numbers:	143586, 143574
, *Black Triangle Scheme*	No
Active ingredient:	Daptomycin
Product name:	Cubicin
Sponsor's name and address:	Merck Sharp & Dohme (Australia) Pty Ltd North Ryde Post Business Centre, North Ryde BC, NSW, 1670
Dose form:	Powder for injection (IV)
Strengths:	350 mg; 500 mg
Container:	Vial
Pack size:	1 vial (single pack)
Approved therapeutic use:	*Staphylococcus aureus Bloodstream Infections (Bacteraemia)* *Cubicin is indicated in paediatric patients (1 to 17 years of age) with Staphylococcus aureus bacteraemia not due to pneumonia, caused by daptomycin-susceptible isolates. Empiric treatment should be reviewed based on the results of susceptibility testing. Prescribing should be in accordance with nationally or locally-endorsed guidelines for the treatment of Staphylococcus aureus bacteraemia.*
Route of administration:	Intravenous (IV) injection
Dosage:	Dosage is relative to age and bodyweight, given as an IV infusion over 60 minutes once every 24 hours for 14 days. See the Product Information (PI) for further details

Product background

This AusPAR describes the application by Merck Sharp & Dohme (Australia) Pty Ltd (the sponsor) to register Cubicin daptomycin 350 mg and 500 mg powder for injection vial for the following indication:

> *Cubicin is also indicated in paediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates.*

Cubicin, daptomycin is a cyclic lipopeptide antibacterial agent, derived from the fermentation of *Streptomyces roseosporus*. It exhibits concentration dependent bactericidal activity against aerobic Gram positive organisms with in vitro activity encompassing most clinically relevant Gram-positive bacteria including isolates resistant to methicillin, vancomycin and linezolid. It binds to bacterial membranes and causes a rapid depolarization of membrane potential resulting in inhibition of protein, DNA and RNA synthesis and bacterial cell death. The mechanism of action is distinct from that of any other antibiotic.

This application is to extend the indication for the use of Cubicin to include paediatric patients, 1 to 17 years of age, with *Staphylococcus aureus* (*S. aureus*) bacteraemia (SAB) caused by methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) isolates.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 8 December 2008.

The approved indications at the time of the submission were as follows:

> *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.*
>
> *Daptomycin is not indicated for the treatment of pneumonia.*
>
> ***Adult patients (18 years of age and over)***
>
> - ***Complicated Skin and Skin Structure Infections***
>
> *Cubicin is indicated for the treatment of adults (18 years of age and over) with complicated skin and skin structure infections (cSSSI) who require parenteral therapy and who have intolerance to alternative agents (especially penicillin allergy) or who have failed on other therapy, and when caused by organisms known to be susceptible to daptomycin.*
>
> - ***Staphylococcus aureus Bloodstream Infections (Bacteraemia)***
>
> *Cubicin is indicated in adults (18 years of age and over) for Staphylococcus aureus bloodstream infections (bacteraemia), including right-sided native valve infective endocarditis (RIE), caused by methicillin-susceptible and methicillin-resistant isolates. The efficacy of daptomycin in patients with prosthetic heart valves or in left-sided endocarditis due to Staphylococcus aureus has not been demonstrated. In the setting of Staphylococcus aureus bacteraemia (SAB), if a focus of infection is diagnosed as left-sided endocarditis after Cubicin therapy has been initiated, then consideration should be given to instituting alternative antibacterial therapy (see Section 4.4 Special Warnings and Precautions For Use).*

Paediatric patients (1 to 17 years of age)

Daptomycin is not indicated for treatment of patients less than 1 year of age (see Section 4.4 Special Warnings and Precautions for Use, Paediatric use).

Daptomycin has not been studied in treatment of infective endocarditis in children (see Section 5.1 Pharmacodynamic Properties, Clinical trials and Section 4.4 Special Warnings and Precautions for use).

- ***Complicated Skin and Skin Structure Infections***

Cubicin is indicated for the treatment of patients aged 1 to 17 years with complicated skin and skin structure infections (cSSSI) who require parenteral therapy and who have intolerance to alternative agents (especially penicillin allergy) or who have failed on other therapy, and when caused by organisms known to be susceptible to daptomycin.

International status

At the time the TGA considered this application; a similar application had been approved or was under consideration in the countries or regions described below.

United States

Submitted on 1 March 2017; approved on 1 September 2017, indicated for:

> *Cubicin is indicated for the treatment of pediatric patients (1 to 17 years of age) with Staphylococcus aureus bloodstream infections (bacteremia).*

European Union

Via the European Union (EU) under the EU centralised procedure; submitted on 16 December 2016, approved on 16 November 2017; indicated for:

> *Adult and paediatric (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 paediatric patients, use in bacteraemia should be associated with cSSTI.*

Canada

Submitted on 23 March 2018; still under review.

New Zealand

Submitted on 11 December 2017, gazetted 12 July 2018; indicated for:

> *Paediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant.*

Singapore

Submitted on 6 October 2017; approved on 17 August 2018; indicated for:

> *Adult (≥ 18 years of age) and paediatric (1 to 17 years of age) patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria:*
>
> *Staphylococcus aureus (including methicillin-resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae subsp. equisimilis, and Enterococcus faecalis (vancomycin susceptible isolates only).*
>
> *Paediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteremia) caused by methicillin-susceptible and methicillin-resistant isolates.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

II. Registration time line

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2017-04652-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2018
First round evaluation completed	2 July 2018
Sponsor provides responses on questions raised in first round evaluation	31 August 2018
Second round evaluation completed	18 October 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	30 October 2018
Sponsor's pre-Advisory Committee response	19 November 2018
Advisory Committee meeting	6 December 2018
Registration decision (Outcome)	19 January 2019
Completion of administrative activities and registration on ARTG	25 January2019
Number of working days from submission dossier acceptance to registration decision*	200

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

The sponsor has submitted an application extend the indication for the use of Cubicin (daptomycin) to include paediatric patients, 1 to 17 years of age, with *S. aureus* bacteraemia (SAB) caused by MSSA and isolates.

Drug class

Daptomycin, a cyclic lipopeptide antibacterial agent, is derived from the fermentation of *Streptomyces roseosporus*. It exhibits concentration dependent bactericidal activity against aerobic Gram positive organisms with in vitro activity encompassing most clinically relevant Gram-positive bacteria including isolates resistant to methicillin, vancomycin and linezolid. It binds to bacterial membranes and causes a rapid depolarization of membrane potential resulting in inhibition of protein, DNA and RNA synthesis and bacterial cell death. The mechanism of action is distinct from that of any other antibiotic.

In adults, daptomycin pharmacokinetics (PK) are generally linear and time independent at doses of 4 to 12 mg/kg administered 24 hourly (q24h). Steady state trough concentrations are achieved by the third daily dose. It is reversibly bound to human plasma proteins, primarily to serum albumin in a concentration independent manner. The overall mean binding ranges from 90% to 93%. The volume of distribution at steady state (V_{ss}) in healthy adults is approximately 0.10 L/kg and is independent of dose.

In *in vitro* studies, daptomycin was not metabolised by human liver microsomes and does not inhibit or induce the activities of human cytochrome P450 isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. The site of metabolism has not been identified. It is excreted primarily by the kidney. Minor amounts of three oxidative metabolites and one unidentified compound have been detected in urine.

Surveillance studies have demonstrated a daptomycin minimum inhibitory concentration for 90% of specific organisms (MIC_{90}) of 0.5 µg/mL for both MSSA and MRSA with > 99% of MRSA isolates categorised as susceptible by the United States (US) Food and Drug Administration (FDA), the European Committee of Antimicrobial Susceptibility Testing, and Clinical and Laboratory Standards Institute breakpoints.

Information on the condition being treated

S. aureus is a leading cause of bacteraemia.[1] In Australia, the incidence of SAB per 100,000 person-years between 2006 and 2007 was 65 for the Northern Territory and 11.2 for Australia overall. The incidence of SAB in the indigenous population is 5.8 to 20 times that of nonindigenous Australians.[1] The primary focus of the infection in Central Australia was most often skin and soft tissue infection 34% versus Australia overall 20%. The commonest cause in Australia overall, and in Sydney, was line infection at 19% and 35% respectively versus 72% in Central Australia.[1]

SAB can be classified as 'complicated' or 'uncomplicated'. These designations have implications for the extent and type of diagnostic evaluation, duration of antibiotic treatment, and overall prognosis. A single centre study of 724 episodes of SAB sought to define readily available clinical characteristics that could help identify patients at risk for

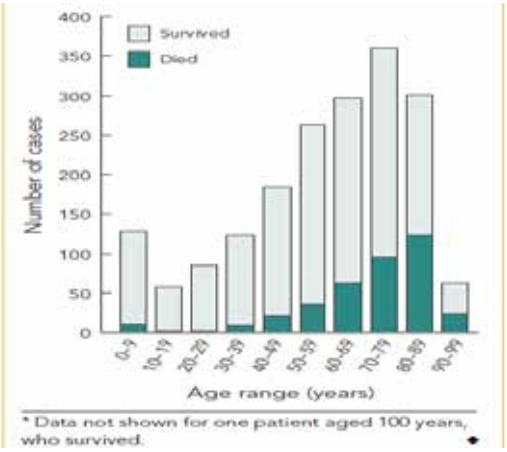
[1] Tong SYC et al. Staphylococcus aureus Infections: Epidemiology, Pathophysiology, Clinical Manifestations, and Management. *Clin Microbiol Rev.* 2015; 28: 603-661

complicated SAB which was defined for the study as infection that resulted in attributable mortality, central nervous system involvement, an embolic phenomenon, metastatic sites of infection, or recurrent infection within 12 weeks.[2] In this study, predictors of complicated SAB were community acquisition, positive follow-up blood cultures at 48 to 96 hours, persistent fever at 72 hours, and skin findings suggesting an acute systemic infection (petechiae, vasculitis, infarcts, ecchymoses, or pustules).[2] The association between positive follow-up blood cultures and persistent fever with complicated SAB and subsequently poorer outcomes has been independently validated, as recently reviewed.[3] Note, the validated association was based on a different definition of complicated SAB than that of the pivotal study (of this submission).

The primary source of infection has been found to predict 30 day mortality, with higher mortality rates for bacteraemia without a focus (22 to 48%), infective endocarditis (IE) (25 to 60%), and pulmonary infections (39 to 67%), compared to lower rates for catheter-related bacteraemia (7 to 21%), skin and soft tissue infections (15 to 17%), and urinary tract infections (UTI) (10%).[3]

Mortality rates are known to vary significantly with patient age, clinical manifestation, co-morbidities and methicillin resistance.[4] Age was found to be the strongest predictor of mortality with Australian data for 2008 shown in Figure 1.[5]

Figure 1: Cases of *S. aureus* bacteraemia and patient survival by age (from Turnidge JD et al.)[5]



A prospective cohort study utilised data from the Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis cohort for 1153 children with SAB from birth to less than 18 years in paediatric and general hospitals across Australia and New Zealand, between 1 January 2007, and 31 December 2012. In this study, 30 day mortality in 1153 Australasian children was 4.7% (50/1073 children with complete mortality data). Mortality risk groups identified were age < 1 year; Māori/Pacific Islander children; those with pneumonia, endocarditis, or sepsis syndrome or no focus; and those treated with vancomycin for methicillin-susceptible SAB. MRSA bacteremia and hospital onset infection were not associated with higher risk.[6]

[2] Fowler VG, Jr et al. 2003. Clinical identifiers of complicated Staphylococcus aureus bacteremia. *Arch Intern Med* 2003; 163: 2066–2072.
[3] van Hal SJ, et al. 2012. Predictors of mortality in Staphylococcus aureus bacteremia. *Clin Microbiol Rev* 2012; 25: 362–386.
[4] http://www.health.gov.au/internet/main/publishing.nsf/content/cda-cdi4002-pdf-cnt.htm/$FILE/cdi4002i.pdf
[5] Turnidge JD et al. Staphylococcus aureus bacteraemia: a major cause of mortality in Australia and New Zealand. *MJA* 2009; 191: 368-373
[6] McMullan, BJ et al. 2016 Epidemiology and Mortality of Staphylocuccus aureus Bacteremia in Australian and New Zealand Children. *JAMA Pediatr* 2016; 170: 979-986

Current treatment options

Treatment currently recommended in Australia for suspected SAB includes IV flucloxacillin four hourly (or cephazolin 8 hourly for type II to type IV penicillin allergy), plus vancomycin twelve hourly (or vancomycin alone for type I penicillin allergy) while awaiting cultures. For confirmed SAB, flucloxacillin is continued and vancomycin ceased if the organism is methicillin sensitive, vancomycin in continued and flucloxacillin is ceased if the organism is methicillin resistant.[7]

Sponsor's rationale

Few antibiotics with activity against MRSA are currently available, and fewer still have had their safety and efficacy evaluated in paediatric patients. Clinical studies and post marketing pharmacovigilance have demonstrated a well-characterised safety profile for daptomycin in adults. To date, the safety of daptomycin in the paediatric population appears to be comparable to that observed in adults.

Contents of the clinical dossier

The dossier included the following:

- Clinical study report (CSR) for Study DAP-PEDBAC-11-02
- Population pharmacokinetic (PK) modelling and simulation reports
- Post-marketing experience and literature.

The submission also included the following: A Clinical Overview, Summary of Clinical Pharmacology studies, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Clinical Safety, Literature References, and Synopses of Individual studies.

Paediatric data

The revised indication and dosage recommendations are based on Study DAP-PEDBAC-11-02 evaluating the safety, efficacy and PK of daptomycin versus standard of care (SOC) antibiotics in treatment of SAB in children aged 1 to 17 years. Additional support includes:

- Population PK modelling report MERC-PGS-121 describing the assessment of daptomycin steady-state pharmacokinetics for paediatric patients in Study DAP-PEDBAC-11-02.
- A population PK modelling and simulation report providing PK parameters for each paediatric SAB patients in Study DAP-PEDBAC-11-02.
- A modelling and simulation report on the comparative analysis of daptomycin exposure in paediatric and adult patients with SAB and an evaluation of exposure-creatinine phosphokinase (CPK) relationship in paediatric patients with SAB or complicated skin and skin structure infection (cSSSI).
- Analysis of cases in the global safety database and summary tabulations provided in periodic safety update reports (PSUR) from the international birthdate of 12 September 2003 to 11 September 2016.
- Results of a literature search identifying published articles and unpublished manuscripts in the Merck library management system as of 12 September 2016 describing safety information relevant to the use of daptomycin in paediatric patients.

[7] http://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/WATAG/Staph-Aureus-Bacteraemia-guideline.pdf

Pharmacokinetics

Introduction

Based on animal models, it is assumed that mean steady state systemic exposure area under the curve (AUC) is the principle PK/pharmacodynamic (PD) driver. The mean and standard deviation (SD) PK parameters for daptomycin at steady state in adults following IV administration of daptomycin over a 30 minute period at 6 mg/kg q24h to healthy young adults showed that AUC was 632 µg*h/mL (SD = 78), the maximum plasma concentration (C_{max}) was 93.9 µg/mL (SD = 6.0) and the mean volume of distribution was 0.101 L/kg (SD = 0.007). Daptomycin PK was generally linear and time-independent at daptomycin doses of 4 to 12 mg/kg q24h administered for up to 14 days. Steady-state trough concentrations were achieved by the third daily dose. Clearance and volume of distribution in children are higher than in adults, and vary by age. To produce exposures equivalent to those in adults, higher doses are required in children, as shown in Table 2.

Table 2: Pharmacokinetic results across studies in children versus adults (by dose, mean age and infusion time)

	Children					Adults	
Parameter	4 mg/kg[a] 2 to 6 yr 0.5 hr	8 mg/kg[b] 2.1-6.5 yr 1.0 hr	10 mg/kg[b] 3.0-6.2 yr 1.0 hr	4 mg/kg[a] 7 to 11 yr 0.5 hr	4 mg/kg[a] 12 to 17 yr 0.5 hr	4 mg/kg[c] 32.7 yr 0.5 hr	6 mg/kg[c] 31.8 yr 0.5 hr
C_{max}, µg/mL	39.1	68.4	79.2	45.8	50.6	57.8	93.9
AUC_{inf}, µg*hr/mL	204	429	550	280	385	494	632
$t_{1/2}$, hr	5.1	5.4	5.7	5.3	7.8	8.1	7.9
CL, mL/hr/kg	21.5	19.5	19.1	16.5	10.7	8.3	9.1
V_{ss}, L/kg	0.14	0.14	0.14	0.11	0.11	0.096	0.101
AUC/dose	51	54	55	70	96	124	105

a. Study DAP-PEDS-05-01
b. Study DAP-PEDS-07-02
c. Study DAP-00-02
*Note: All subjects were dosed by infusion.

Studies providing pharmacokinetic data

The revised indication and dosage recommendations are based on Study DAP-PEDBAC-11-02 evaluating the PK of daptomycin versus SOC antibiotics in treatment of SAB in children aged 1 to 17 years.

Additional support includes:

- Population PK modelling report MERC-PGS-121 describing the assessment of daptomycin steady-state PK for paediatric patients in Study DAP-PEDBAC-11-02
- A population PK modelling and simulation report providing PK parameters for each paediatric SAB patients in Study DAP-PEDBAG-11-02
- A modelling and simulation report on the comparative analysis of daptomycin exposure in paediatric and adult patients with SAB and an evaluation of exposure-CPK relationship in paediatric patients with SAB or cSSSI.

Study DAP-PEDBAC-11-02 PK

DAP-PEDBAC-11-02 was a Phase IV, partially blinded, multicentre, multinational study assessing safety and efficacy of IV daptomycin versus SOC in treatment SAB in patients aged 1 to 17 years. A total of 55 patients were randomised to daptomycin treatment at

doses proposed for registration. Fifty-one (51) daptomycin-treated patients each provided ≥ 1 sample for PK analysis and were included in the exposure response population.

Pharmacodynamics

Studies providing pharmacodynamic data

Resistance

Development of daptomycin-resistance during therapy has been identified but is considered rare. The mechanisms of resistance appear diverse. Non-susceptible strains often exhibit single nucleotide polymorphisms in the multi-peptide resistance factor gene (mprF) and the yycFG genes in the yycFGHI operon, loci are known to be involved in key cell membrane function. Daptomycin-resistant strains demonstrate other changes in the cell membrane physiology including resistance to cell membrane depolarisation, increased permeability and reduced surface binding of daptomycin. Modifications of the cell wall may also contribute to resistance, including enhanced expression of the dlt operon and progressive cell wall thickening.

A longitudinal analysis has assessed in vitro antimicrobial activity of daptomycin against Gram-positive bacterial strains from paediatric and adult patients in 2012 (US) and 2014 (US and EU).

US data (2012)

Isolate sources included skin and skin structures (1,808; 34.0%), bloodstream (853; 16.0%), pneumonia in hospitalised patients (751; 14.1%) and others (1,907; 35.9%).

In total 3,747 *S. aureus* isolates were tested, of which 47.3% were MRSA. The majority of isolates had a daptomycin minimum inhibitory concentration (MIC) of ≤ 0.25 µg/mL (75.0%) and MIC ≤ 0.5 µg/mL (98.9%). Specific to SAB, 492 *S. aureus* isolates for all age groups combined were tested; 44% were MRSA. The majority had a daptomycin MIC of ≤ 0.25 µg/mL (72.5%) and 97.2% were inhibited at daptomycin MIC ≤ 0.5 µg/mL.

Daptomycin MIC values were similar among SAB MRSA isolates (67.6% and 97.7% inhibited at ≤ 0.25 µg/mL and ≤ 0.5 µg/mL, respectively) compared to SAB MSSA (76.3 and 96.8% inhibited at ≤ 0.25 µg/mL and ≤ 0.5 µg/mL, respectively). Daptomycin MIC_{50} and MIC_{90} values;[8] for SAB isolates were 0.25 and0.5 µg/mL for both MRSA and MSSA. Daptomycin MIC frequency distribution for SAB *S. aureus* isolates from patients ≤ 17 years old (n = 63; 12.8%) were similar to distribution in adults.

US and EU data (2014)

Isolate sources included skin and skin structures (3,708; 43.0%), bacteraemia (2,363; 27.4%), pneumonia in hospitalised patients (1,378; 16.0%) and others (1,183; 13.7%). In total, 5,374 *S. aureus* strains (3,441 US, 1,933 EU) were tested; 38.4% were MRSA. The majority had a daptomycin MIC of ≤ 0.25 µg/mL (81.6%) and 99.4% were inhibited at a daptomycin MIC of ≤ 0.5 µg/mL. For the US and EU, MIC_{50}/MIC_{90} values were 0.25/0.5 µg/mL.

Specific to SAB, 1,075 *S. aureus* isolates were tested. The majority had a daptomycin MIC of ≤ 0.25 µg/mL (81.7%) and MIC ≤ 0.5 µg/mL (99.2%) with identical MIC50/90 values of 0.25/0.5 µg/mL in US and EU irrespective of MRSA or MSSA status. For patients < 17 years

[8] MIC_{50} = minimum inhibitory concentration required to require the inhibition of growth of 50% of specific organisms; MIC_{90} = minimum inhibitory concentration required to require the inhibition of growth of 90% of specific organisms

of age (n=174; 130 US, 44 EU), daptomycin MIC frequency distributions for SAB *S. aureus* isolates were no different from the population overall.

Six (0.11%) *S. aureus* strains were-non-susceptible: 5 MRSA strains with daptomycin MIC of 2 µg/mL and 1 MSSA strain with MIC of 4 µg/mL. Five were from USA (4 cities in 4 states). Longitudinal analysis of the US results also showed no change in daptomycin MIC_{50}/MIC_{90} values between 2012 and 2014.

Efficacy

Studies providing efficacy data

Pivotal Study DAP-PEDBAC-11-02 was a Phase IV, open label (evaluator-blinded), comparative, multicentre, multinational study assessing safety and efficacy of IV daptomycin versus SOC antibiotics in the treatment of patients aged 1 to 17 years with SAB, conducted between March 2013 and January 2016 in North America, Europe, Central/South America, and Australia/Asia with 25 sites enrolling participants.

Clinical efficacy was a secondary outcome, and was based on the blinded investigators' clinical assessment of signs and symptoms at the end of intravenous therapy (EOIV) Visit or end of oral therapy for those who received oral study drug and at test of cure (TOC)/Safety Visit. Cure represented resolution of clinically significant signs and symptoms associated with admission infection (that is, return to pre-infection Baseline). No further antibiotic therapy required for the primary infection.

Improvement was defined as partial resolution of clinical signs or symptoms of infection such that no further antibiotic therapy was required for the primary infection. For patients switched from IV study drug to oral study drug, 'Improved' at the EOIV Visit was defined as the partial resolution of clinical signs or symptoms of infection such that no further IV antibiotic therapy was required for the primary infection.

Microbiological efficacy was divided into microbiological success or failure. Success involved all baseline infecting pathogens being eradicated with no source of infection present within 7 days from start of effective IV antibiotics for uncomplicated bacteraemia, and 10 days for complicated bacteraemia; or when source of infection was not removed and no superinfecting Gram-positive pathogen(s) were isolated on-therapy, at end of therapy (EOT), and TOC.

Overall outcome was based on microbiological and clinical outcome at the TOC/Safety Visit.

Evaluator's conclusions on efficacy

The results support efficacy of daptomycin treatment in the studied age group. There are qualifications.[9]

Safety

Studies providing safety data

Pivotal Study DAP-PEDBAC-11-02 was a Phase IV study as described under Section: *Efficacy*, above. The primary objective was to assess the safety of IV daptomycin

[9] See Section: Clinical Questions and Second Round Evaluation for details of questions and issues raised regarding efficacy in the first round clinical evaluation.

versus SOC antibiotics in treatment of paediatric patients between 1 and 17 years of age with bacteraemia.

Patient exposure

Population

The safety population includes all 81 participants (daptomycin 55; comparator 26).

Extent of exposure

Comparator drugs administered were: vancomycin 15 (57.7%), cefazolin 6 (23.1%), semi-synthetic penicillins 5 (19.2%) (oxacillin 4 (15.4%), flucloxacillin 1 (3.8%)), and linezolid 1 (3.8%). One participant was switched from vancomycin to linezolid after five days.

The mean (median) duration of IV treatment was: daptomycin 12.2 (11.0) days versus comparator 12.3 (11.5) days. The total median duration of IV plus oral treatment was: daptomycin 20 days (range 1 to 141 days) versus comparator 18 days (range: 2 to 58 days).

Forty-eight (59.3%) participants converted to oral study drug: daptomycin 32 (58.2%) versus comparator 16 (61.5%). The mean (median) treatment duration of oral treatment was daptomycin 22.7 days (15.0 days) versus comparator 17.7 days (16.0 days).

Amoxicillin/clavulanate and cephalexin were the most commonly administered oral antibiotics, each administered to 10 daptomycin participants (18.2%) and administered respectively to 7 (26.9%) and 6 (23.1%) of the comparator participants.

Mean duration of IV treatment was 13.1 days for daptomycin versus 11.7 days for comparator in the 1 to 6 years old group, 10.8 days versus 14.1 days for the 7 to 11 year old group, 12.7 days versus 10.9 day for the 12 to 17 years old group.

The mean duration of IV and IV + oral therapy was greater in participants with complicated versus uncomplicated bacteraemia: IV complicated 14.2 days versus uncomplicated 11.5 days; IV + oral: complicated 30.5 days versus uncomplicated 22.2 days: Eight participants with complicated bacteraemia received treatment beyond 42 days; 7 of whom had osteomyelitis. One participant with uncomplicated bacteraemia as assessed by the site was treated for a total of 141 days impacting the mean durations of treatment for uncomplicated bacteraemia; however, the investigator considered it complicated due to the presence of osteomyelitis.

The mean durations of oral treatment in the daptomycin group versus comparator respectively were: 1 to 6 year old group 23.8 days versus 13.5 days; 7 to 11 age group 23.0 days versus 25.4 days; 12 to 17 year olds 21.1 days versus 16.0 days.

Table 3: Study DAP-PEDBAC-11-02; Summary of duration of treatment (safety population)

	All Ages		
	Daptomycin (N=55)	Comparator (N=26)	Overall (N=81)
Duration of treatment with IV study drug (days) [a]			
N	55	26	81
Mean (SD)	12.2 (7.94)	12.3 (7.30)	12.3 (7.69)
Median	11.0	11.5	11.0
Min, Max	1, 44	2, 31	1, 44
Duration of oral treatment (days) [b]	32	16	48
Mean (SD)	22.7 (23.08)	17.7 (9.03)	21.0 (19.57)
Median	15.0	16.0	15.0
Min, Max	5, 125	6, 33	5, 125
Number of IV+Oral Dosing Days[a]			
N	55	26	81
Mean (SD)	25.3 (22.98)	22.6 (14.92)	24.5 (20.67)
Median	20.0	18.0	18.0
Range	1, 141	2, 58	1, 141
Duration of Total Study Drug (IV and IV+Oral) [a]			
Received study medication for <3 days	3 (5.5%)	2 (7.7%)	5(6.2%)
Received study medication for 3-7 days	6 (10.9%)	1 (3.8%)	7 (8.6%)
Received study medication for > 1 week to 2 weeks	6 (10.9%)	6 (23.1%)	12 (14.8%)
Received study medication for > 2 to 3 weeks	15 (27.3%)	7 (26.9%)	22 (27.2%)
Received study medication for > 3 to 4 weeks	11 (20.0%)	2 (7.7%)	13 (16.0%)
Received study medication for > 4 to 5 weeks	2 (3.6%)	1 (3.8%)	3 (3.7%)
Received study medication for > 5 to 6 weeks	4 (7.3%)	5 (19.2%)	9 (11.1%)
Received study medication for > 6 weeks	8 (14.5%)	2 (7.7%)	10 (12.3%)

DAP: daptomycin; IV: intravenous; Min: minimum; Max: maximum; SD: standard deviation
a. All subjects are included whether or not they received oral treatment.
b. Only subjects who received oral treatment are summarized. Percentages are based on the number of subjects who received oral treatment.

Safety issues with the potential for major regulatory impact

Clinically relevant treatment emergent adverse events

There were no reports of drug hypersensitivity, eosinophilic pneumonia, dysregulation of in vivo coagulation, serious hepatotoxicity, or bone marrow toxicity among the adverse events reported in the daptomycin group.

Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Queries (SMQ) of peripheral neuropathy; and rhabdomyolysis/myopathy identified 5 (9.1%) daptomycin-treated and 1 (3.8%) comparator treated patients.

The most commonly reported SMQ term, lood creatine phosphokinase (CPK) increased, was reported for 4 (7.3%) daptomycin-treated patients with 2 cases considered treatment related. The other adverse events (AEs) identified were: daptomycin: muscular weakness (1) and acute renal failure (1) versus comparator myositis (1). The daptomycin-treated patient with renal failure was also had blood CPK increased. None of these events was considered a serious adverse event (SAE) and only 1 of these events (mild, non-serious blood CPK increased in a subject 2 years of age) led to study drug discontinuation. The events were considered consistent with the prior treatment experience in adults.

Clinical laboratory results

No new safety signals were apparent from the review of clinical chemistry or haematology laboratory results. Elevations abnormal liver function tests are expected events for daptomycin and are listed in the current product information.

Creatine phosphokinase

Post-Baseline increased CPK x 1 to 2.5 upper limit of normal (ULN) were recorded for daptomycin 13 (24.1%) versus comparator 5 (19.2%). Sustained CPK elevations (2 consecutive post-Baseline CPK values above ULN), were recorded for daptomycin

14.5% versus comparator 11.5%. CPK > x 2.5 ULN were reported for 2 daptomycin participants versus comparator 0.

Treatment emergent adverse events (TEAE) of increased CPK were reported for 4 daptomycin treated patients, one each in the 1 to 6 year group and 7 to 11 year group and two in the 12 to 17 year group. No patients in the comparator arm had TEAE of increased CPK. For two patients, AEs of blood CPK increased were deemed unrelated to study drug had defined aetiologies (ankle arthrotomy and hip arthrotomy). One participant discontinued daptomycin due to raised CPK.

The fourth patient, 11 years of age, experienced an AE of blood CPK increased on Day 8 of IV daptomycin therapy. The CPK at the time 222 U/L was within normal limits (reference range 38 to 324 U/L) but was elevated from baseline level of 29 U/L. The AE was deemed mild in severity and related to study drug but was a non-serious event and study drug was not withdrawn. The CPK value at the EOIV Visit (study Day 15) was 357 U/L. No post-IV therapy value was recorded; however, the event was considered resolved on Study Day 57 (justification not supplied). This child also experienced an AE of renal failure on Day 11 of IV daptomycin, deemed mild in severity and unrelated to study drug. This was treated with hydration and daptomycin was continued. The event was considered resolved on study Day 54.

Liver function tests

Seven daptomycin-treated patients had elevations in alanine aminotransferase (ALT), (reference range 3 to 35 U/L) and aspartate aminotransferase (AST), (reference range 15 to 46 U/L) compared to 1 comparator-treated patient. Four in the daptomycin arm and the 1 in the comparator arm, were < 5 x ULN. No participant with an AST or ALT > 5 x ULN discontinued treatment due to the elevation in liver transaminases. Two daptomycin treated patients had ALT or AST levels > 5 to ≤ 10 x ULN, and 1 had ALT or AST levels > 10 x ULN. Each of these patients had elevated levels at Baseline.

A daptomycin treated patient had elevated baseline ALT (200 U/L) of unknown aetiology. The peak values of ALT on Day 1 (211 U/L) and the AST (286 U/L were flagged as > 5 x ULN. The patient discontinued after 2 days following withdrawal of parental consent.

A daptomycin treated patient had baseline ALT (270 U/L) and AST (181 U/L) that remained elevated throughout the study, with peak values for ALT (287 U/L) and AST (213 U/L) occurring post-IV therapy and at the EOIV Visit, respectively. This patient had an ongoing history of hepatomegaly and elevated alkaline phosphatase associated with enteral feeding due to short bowel syndrome and cholestasis due to total parental nutrition.

A daptomycin treated patient had baseline ALT (689 U/L) and AST (490 U/L) of unknown aetiology. Peak values occurred at baseline and began to recover during treatment nearing normal limits by the post IV therapy Visit.

Physical examination

At Baseline, physical examination was considered normal in 38 (69.1%) participants in the daptomycin arm and 14 (53.8%) in the comparator arm. By the EOIV Visit, the numbers of physical examinations considered normal were: daptomycin 51 (92.7%) versus comparator 23 (88.5%). At the TOC/Safety Visit, the numbers with physical examinations recorded as normal were: daptomycin 53 (96.4%) versus comparator 20 (76.9%). No safety signal was revealed by neurological examination.

It is considered unusual that over half to two thirds of participants with bacteraemia requiring IV treatment would have normal physical examinations.[10]

[10] See Section: Clinical questions (below) for further details

Motor developmental assessment

At Baseline and Late Follow-up Visit, a questionnaire was used to evaluate motor development of 30 children (daptomycin 20 versus comparator 10) aged < 7 years. The proportion of participants able to perform the activity remained the same or increased at the Late Follow-up Visit compared to the Screening/Baseline Visit for the majority of the motor development activities in both treatment groups. Overall, findings in motor development skills were concluded to be consistent with patient medical conditions including location of the infection or underlying conditions impacting motor function, and there was no clear evidence for peripheral neuropathy.

The questionnaire was said to be modified from the guidance from the American Academy of Pediatrics; (http://brightfutures.aap.org/tool_and_resource_kit.html). The link did not lead directly to a recognisable source. The questionnaire was based on parents assessments at Baseline which may be subject to recall bias. It was not entirely clear from the protocol, but it appears likely that the questionnaire was also filled using parents' assessments at final check and not supported by Investigator's observations. It is unlikely that the study questionnaire is a validated tool and its usefulness is questioned.[10]

Post marketing data

Periodic safety update report: 12 September 2016 to 11 September 2017[11]

Calculated cumulative exposure to daptomycin from worldwide marketing experience is summarised in Table 4. Cumulative exposure from completed clinical trials is summarised in Table 5.

Table 4: Cumulative exposure from worldwide marketing experience to 11 September 2017

	Exposure (number of patients exposed) from 11-Sep-2015 to 11-SEP-2016	Interval Exposure (number of patients exposed) 12-SEP-2016 to 11-SEP-2017	Total Exposure (number of patients exposed from IBD to 11-SEP-2017
Cumulative exposure	530,207	667,608	3,794,774

Limitation: The dosage could differ based on the conditions of the patient like weight and renal function, etc., so the data should be interpreted with caution.

[11] This PSUR was the subject of a series of questions; see Section: Clinical questions (below) for further details.

Table 5: Cumulative exposure to daptomycin from completed clinical trials

	Number of subjects
Age Group (year)	
<18	385
19 to 65	1480
66 to 75	669
Missing	7
Total	2541

Gender	Number of subjects
Female	1139
Male	1402
Total	2541

Racial/Ethnic Group	Number of subjects
Asian	106
Black	447
Caucasian	1659
Other	289
Unknown	40
Total	2541

Note: Data from completed trials as of 11-SEP-2017

The following were noted:

1. Study DAP-PEDOST-11-03 was a Phase III, multicentre, randomised, double-blinded, study evaluating efficacy, safety and pharmacokinetics of daptomycin versus active comparator in treatment of paediatric participants age 1 to < 18 years with acute haematogenous osteomyelitis (AHO) due to Gram-positive organisms. Patients were randomised (1:1) to receive IV daptomycin once daily (7, 9 or 12 mg/kg depending on age group) or IV active comparator. The primary objective was to demonstrate the non-inferiority of IV daptomycin compared with vancomycin or nafcillin or β-lactam equivalent in paediatric subjects with AHO with respect to improvement in the general categories of pain, inflammation, and limb function on or before study Day 5 in the modified intent-to-treat (MITT) population. As of 11 September 2017, 149 participants were enrolled and 146 received at least one dose of study medication. The trial failed to achieve the primary objective.
2. Based on assessment of cases, a causal association between daptomycin therapy and the AEs thrombocytopaenia and platelet count decreased may exist. Therefore, the market authorisation holder will add these Preferred Terms to the '*Adverse Reactions, Post-Marketing Experience*' sections of the Company Core Data Sheet as 'uncommon' events.
3. A 5 year-long *in vitro* surveillance study to check drug susceptibility changes of clinically isolated MRSA to 'Cubicin' IV 350 mg (daptomycin) and other selected antimicrobial agents in Japan has concluded. The study 'Cubicin' Drug Susceptibility Survey (Survey Number: PNM11B048) was conducted between 2012 and 2017. Three hundred strains of MRSA per year, for a total of 1500 strains over 5 years were identified from blood or skin-related tissues and antimicrobial susceptibility tests were performed according to the Clinical and Laboratory Standards Institute standard method. MIC_{90} of daptomycin was 0.5 µg/mL against all blood-derived MRSA (100 strains/year) and skin related tissue-derived MRSA (200 strains/year) isolated from 2012 to 2016. MRSA susceptibility to daptomycin was unchanged over the 5 year surveillance period. Compared to other antimicrobial agents (vancomycin,

teicoplanin, linezolid, arbekacin tested, daptomycin had the lowest geometric means of MIC.

4. Lin YT, Tsai JC, Yamamoto T, Chen HJ, Hung WC, Hsueh PR, Teng LJ Emergence of a small colony variant of vancomycin-intermediate *S aureus* in a patient with septic arthritis during long-term treatment with daptomycin J Antimicrob Chemother 71(7) :1807-14, 2016.
5. Small colony variants (SCVs) of *S aureus* are associated with persistent and drug-resistant infections. The first reported instance of emergence of SCVs was in a 73 year old patient with vancomycin-intermediate *S. aureus* (VISA) infection during long-term treatment of septic arthritis with daptomycin. Daptomycin-resistant SCVs of VISA evolved in a stepwise manner and the mutation of fabF was considered likely responsible for the physical and ultrastructural characteristics and daptomycin resistance.

Table 6 includes a summary of identified and potential risks and missing information. The cumulative reviews of cases of the safety concerns were consistent with previous analysis for this identified risk apart from the important potential risk, bone marrow toxicity: thrombocytopenia and platelet count decreased.

Table 6: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Severe skeletal muscle toxicity • Reduced susceptibility to ddaptomycin in Staphylococcus aureus • Peripheral neuropathy • Severe hypersensitivity reactions (including pulmonary eosinophilia and severe cutaneous reactions, including acute generalised exanthematous pustulosis • Eosinophilic pneumonia (including organising pneumonia
Important potential risks	• Bone marrow toxicity • Severe hepatotoxicity • Dysregulation of *in vivo* coagulation
Missing information	• Patients with hepatic impairment • Pregnant/ lactating women

Periodic safety update report: 12 September 2014 to 11 September 2015[11]

There were no new resistance data available from this period. The following points were noted:

1. Ototoxic effect of daptomycin applied to the guinea pig middle ear.[12]

   Twenty-three male Hartley guinea pigs were divided into three groups to receive daptomycin (50 mg/ml), gentamicin (50 mg/ml, positive control), or saline solution

[12] Oshima, H et al 2014 Ototoxic effect of daptomycin applied to the guinea pig middle ear. *Acta otolaryngologica* 2014; 134: 679-683.

(negative control). Pre-treatment auditory brainstem responses (ABRs) were obtained. Topical solutions of 0.1 mL were applied through the tube into the middle ear twice a day for 7 days. Post-treatment ABRs were obtained 7 days after the last treatment. Hair cell loss was investigated with whole-mount cochlear surface preparations. The saline-treated (negative control) group showed no deterioration of ABR threshold. The daptomycin-treated group showed mild deterioration and the gentamicin-treated group showed severe deterioration in ABR threshold. Hair cells were preserved in the daptomycin and saline-treated groups but severely damaged in the gentamicin group.

Market authorisation holder note: Peripheral neuropathy is an identified risk with daptomycin, and neurosensory hearing changes may be one presentation of this risk. Continued monitoring of post-marketing experience for clinical correlation is ongoing.

Evaluator's conclusions on safety

Examination of safety does not uncover any obvious safety signal. Numbers are relatively small and severity of the underlying condition is such as to preclude determination of occurrence of uncommon or rare events related to treatment with daptomycin. Of most particular concern is the lack of any data on children 1 to < 2 years of age while proposing a higher dose than has previously been approved for children of that age.

First round benefit-risk assessment

Indication

It is recommended that the indication is extended to include paediatric patients aged 1 to 17 with MSSA and MRSA bacteraemia. This is in accordance with the FDA approved indication rather than the EU indication which specifies that bacteraemia should be associated with cSSTI.

In the proposed *Indications* section of the PI, the placement of paediatric indication for bacteraemia in proximity to that of adults could be read as implying that the paediatric indication includes right sided bacterial endocarditis. Endocarditis was an exclusion criterion in pivotal Study DAP-PEDBAC-11-02 and no patient in the study had endocarditis. It is recommended that the indications are separated under Adult and Paediatric headings rather than cSSSI and bacteraemia headings as proposed.

The existing paediatric cSSSI indication comes with qualification that use is limited to patients who have intolerance to alternative agents or have failed other therapy. For consistency, it is recommended that this is carried through to the SAB indication in view of the potential risks, in particular to the youngest patients recommended the highest per kg dose.

The following revision or similar is advised:

> ***Indications***
>
> *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).*
>
> ***Adult patients (≥ 18 years of age)***
>
> *Consideration should be given to official, local guidance on the appropriate use of antibacterial agents.*
>
> *Daptomycin is not indicated for the treatment of pneumonia.*

Complicated Skin and Skin Structure Infections

Cubicin is indicated for the treatment of adults with complicated skin and skin structure infections (cSSSI) who require parenteral therapy and who have intolerance to alternative agents (especially penicillin allergy) or who have failed on other therapy, and when caused by organisms known to be susceptible to daptomycin.

Staphylococcus aureus Bloodstream Infections (Bacteraemia)

Cubicin is-indicated in adults for Staphylococcus aureus bloodstream infections (bacteraemia), including right-sided native valve infective endocarditis (RIE), caused by methicillin-susceptible and methicillin-resistant isolates

The efficacy of daptomycin in patients with prosthetic heart valves or in left-sided endocarditis due to Staphylococcus aureus has not been demonstrated. In the setting of Staphylococcus aureus bacteraemia (SAB), if a focus of infection is diagnosed as left-sided endocarditis after Cubicin therapy has been initiated, then consideration should be given to instituting alternative antibacterial therapy (see Precautions).

Paediatric patients (1 to 17 years of age)

Daptomycin is not indicated for treatment of patients less than one year of age. (See Precautions: Use in children)

Daptomycin is not indicated for the treatment of pneumonia. Daptomycin has not been studied in treatment of empyema, septic embolus to the lung, right and left sided endocarditis or meningitis. (See Clinical Trials and Precautions)

Consideration should be given to local guidelines on the appropriate use of antibacterial agents.

Complicated Skin and Skin Structure Infections

Cubicin is indicated for the treatment of patients aged 1 to 17 years with complicated skin and skin structure infections (cSSSI) who require parenteral therapy and who have intolerance to alternative agents (especially penicillin allergy) or who have failed on other therapy, and when caused by organisms known to be susceptible to daptomycin.

Staphylococcus aureus Bloodstream Infections (Bacteraemia)

Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy, and when caused by orgasms know to be susceptible to daptomycin.

Dosage and administration

There is no objection to the recommended age and weight based doses.

The proposed duration of treatment is '*Up to 42 days*' which is in accordance with the US PI. The EU Summary of Product Characteristics (SmPC) includes the following:

> 'Minimum duration of Cubicin for paediatric SAB should be in accordance with the perceived risk of complications in the individual patient. The duration of Cubicin may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient. In the paediatric SAB study, the mean duration of IV Cubicin was 12 days, with a range of 1 to 44 days. The duration of therapy should be in accordance with available official recommendations.'

Argument for the proposed duration of treatment could not be located in the dossier, the reference specified in the justification.

The protocol specified durations of treatment were based on definitions of uncomplicated and complicated bacteraemia as shown in Table 7. In passing, it is noted that the summary of the study in the Clinical Trials section does not mention these definitions or how they may have impacted the study. The protocol specified allowable maximum duration of treatment of 42 days was limited to participants aged ≥ 12 years with complicated bacteraemia.

Table 7: Study DAP-PEDBAC-11-02 Protocol specified duration of treatment

Duration of therapy post randomization:

Age (years)	Uncomplicated bacteremia[a]	Complicated bacteremia[a,b]
≥ 12	Max: 28 days Min: 5 days	Max: 42 days Min: 7 days
1 to 11	Max: 28 days Min: 5 days	Max: 28 days[c] Min: 7 days

a Some of this therapy could have been administered at home as per local practice. Switch to oral therapy was discouraged, but was acceptable, if allowed by study site's practice standard.

b Subjects with complicated bacteremia with osteomyelitis and positive blood cultures may have received a shorter duration of IV therapy (less than 7 days) after discussion with the Sponsor designated Medical Monitor.

c Children under 12 years of age who were classified as having complicated bacteremia after IV treatment was started and who responded to treatment by Day 28 but who required additional IV treatment may have continued on IV daptomycin or SOC if benefit outweighed the potential safety risk.

The longest duration of treatment with IV daptomycin in the study was 44 days for a 2 year old female patient with MRSA bacteraemia complicated by osteomyelitis and septic arthritis, conditions for which treatment approval has not yet been specifically granted. This duration was an outlier; only 4 other participants recorded durations in the vicinity of 28 days and only one of these exceeded this by one day. Treatment of one 2 year old child for 44 days affords no reassurance of safety of protracted treatment in the wider patient population. Of particular concern would be prolonged treatment of infants as young as 12 months.

It is recommended that 28 days is specified as the upper limit of treatment and that the recommendation comes with footnotes that:

- Local treatment guidelines should be consulted
- Duration is in accordance with the perceived risk of complications
- The mean (median) duration of treatment in Study DAP-PEDBAC-11-02 was 12 (11) days.

Clinical questions and second round evaluation

There are 9 responses to questions or comments on the clinical evaluation report after the first round of evaluation, presented below.

Question/comment 1

Study DAP-PEDBAC-11-02 pharmacokinetics

In the sponsor's post-first round response, the sponsor divided the first evaluator's comment into 3 issues.

Issue 1

The line listing of results includes multiple examples of trough levels < 3 µg/mL: age 2 to 6 years (47.4%), 7 to 11 years (21.0%) and 13 to 17 4 years (30.8%). It is assumed that 3 µg/mL was the lower limit of quantification (LLOQ). The only method of handing of missing data (in general) located in the protocol did not specify that it was relevant to PK

results, that is, samples with bioanalytical values below the limit of quantification were treated as missing for summary statistics, but were included in lowest quartile for exposure response analysis. It is noted that the plasma concentration just before dosing (C_{trough}) minimums shown in a specified table [not included in this AusPAR] are above 3 µg/mL which suggests that the handling of missing data described above may have been used; however, this reporting is considered to misrepresent the findings.

Sponsor's response

The reviewer is correct that the lower limit of quantitation of the bioanalytical assay for daptomycin was 3 µg/mL. This information is provided in the bioanalytical report for the paediatric bacteraemia study (Study DAP-PEDBAC-11-02.

The bioanalytical report (Ref. 5.3.1.4: 04JC7N) is included with this response [not included in this AusPAR]. Data handling for summary statistics of peak and trough concentrations was described in the statistical analysis plan (a section of the clinical study report) and footnoted in a table in the CSR (this table was part of the Table 6 of the agency's clinical evaluation report). For the convenience of the reviewer, the text of the footnote is reproduced below:

Included trough concentrations were those collected 22 to 26 hours following the end of previous IV infusion. Peak samples were these collected within 15 minutes after end of infusion. One peak sample was excluded due to collected after a 118 minutes infusion. Concentrations below the LLOQ were not included.

The data handling procedure for the summary of daptomycin concentration data in this study was consistent with that described in the PK analysis plan for the Phase IV study in paediatric patients with CSSSi (Study DAP-PEDS 07-03) (Submission PM-2015-03531-1-2, TGA approved 16 December 2016) to maintain continuity in the paediatric development program.

As described in the Study DAP-PEDBAC-11-02 CSR, two exposure response analyses were conducted: (1) Peak and trough levels summarised by age groups were reviewed with summaries of AEs; and (2) the correlation between exposure (peak and trough) and CPK levels was assessed graphically. Peak and trough daptomycin concentrations by age groups were summarised as outlined above. In the graphical analysis, trough concentrations below LLOQ were imputed as half LLOQ, as indicated in the footnotes for 3 figures of the Study DAP-PEDBAC-11-02 CSR. This imputation is a commonly used and acceptable approach to retain information related to samples below LLOQ in the analysis. In summary, a consistent approach was taken in the handling of samples with concentrations below LLOQ in the PK analysis and the exposure-response analyses such that the PK data, and for the purposes of the exposure-response assessment, can be interpreted similarly. Thus the sponsor does not consider the reporting to misrepresent the findings.

Issue 2

Based on the method of assessment and reporting it was not possible to determine whether trough levels < 3 µg/mL fell below the *S. aureus* MIC and if so, for how long. AUC results would be of particular interest but could not be located in the CSR. As very young children have higher clearance than adults, increasing the frequency of a smaller weight based dose rather than increasing the dose and the duration of administration could have been an alternative method of administration.

Sponsor's response

The daptomycin PK/PD parameter best correlated with antibacterial efficacy has been shown to be the ratio of AUC and the pathogen's MIC (AUC/MIC) in animal infection models, and not the time of daptomycin concentration above MIC. Therefore, AUC, but not C_{trough}, is the PK parameter of interest, and, as discussed below, AUC matching was the

determinant of dosing in paediatric patients, and would provide efficacy and safety similar to that established in adults. Daptomycin AUC in paediatric bacteraemia patients in Study DAP-PEDBAC-11-02 was estimated using a population PK modelling approach; this was described is a separate report, not in the Study DAP-PEDBAC-11-02 clinical study report.

Daptomycin dose selection for paediatric bacteraemia patients was based on matching AUC attained in adult bacteraemia patients receiving the recommended 6 mg/kg dose, at which the safety/efficacy profiles have been established. Daptomycin PK in paediatric bacteraemia patients were assessed using a previously developed paediatric population PK model, and were summarised in the paediatric bacteraemia dossier. The results of the PK assessment showed that the AUC distributions in paediatric bacteraemia patients in Study DAP-PEDBAC-11-02 at the evaluated dosing regimens were comparable to the AUC distribution in adult bacteraemia patients receiving the 6 mg/kg dose. These results support the appropriateness of the recommended paediatric dosing regimens.

Increasing the dosing frequency at a lower weight-based dose is not considered to be an appropriate alternative for daptomycin administration in young paediatric patients, as in a preclinical study in dogs, both incidence and severity of musculoskeletal toxicity associated with daptomycin administration increased with dosing frequency while maintaining the same total daily dose (toxicology report submitted with the adult complicated skin and skin structure infection dossier). The observation in the preclinical study was consistent with clinical data, which showed that once daily 8 mg/kg daptomycin was well tolerated in healthy adults (Study DAP-00-02 submitted with the adult complicated skin and skin structure infection dossier), whereas musculoskeletal toxicity was observed in healthy adult subjects at twice daily 4 mg/kg (Study B8B-MC-AVAP submitted with the adult complicated skin and skin structure infection dossier), despite lower daily serum daptomycin AUC at 4 mg/kg twice daily in Study B8B-MC-AVAP compared to plasma daptomycin AUC at 8 mg/kg once daily in Study DAP-00-02.

Issue 3

The listing also suggests that there may have been problems at one site, probably in Ukraine. At this site:

- The only child tested aged< 7 years had both pre-dose and post-dose levels < 3 μg/mL at an unscheduled visit. No participant of any age at any other site had post-dose level < 3 μg/mL.
- The only child tested aged between 7 and 11 years had a post-dose result < 3 μg/mL.
- At age 12 to 17 years, 4 participants were tested, one had pre- and –post-dose results < 3 μg/mL, 1 more had post-dose level < 3 μg/mL, and 2 more had pre-dose levels < 3 μg/mL. One of the patients with pre-dose level < 3 μg/mL had post-dose level 5.59 μg/mL which was considerably lower than participants at other centres recorded. One participant with post-dose level < 3 μg/mL had pre-dose level 24 μg/mL. Even if pre- and post-dose samples were swapped, 24 μg/mL is low compared to post-dose levels of participants at other centres. At other centres only one participant in this age group had a pre-dose level < 3 μg/mL.

According to the CSR all participants' results were included in the analysis. Using results from this site would have resulted in lowering of mean concentration results and the mean results were above the predicted levels as were shown. The results from this site are considered potentially unreliable and the sponsor's opinion is required. In addition, if PK results from this site were unreliable as they appear, were there indications that efficacy and safety results from this site were also questionable. Was the site visited or audited?

Sponsor's response

The sponsor acknowledges that the evaluator is seeking additional information about the site for the Study DAP-PEDBAC-11-02 trial. It is important to note that

Cubist Pharmaceuticals was the sponsor of this trial for the majority of the time that the Study DAP-PEDBAC-11-02 trial was conducted from March 2013 to October 2015. On 21 January2015, Cubist was acquired by Merck & Co., Inc., Kenilworth, NJ, USA [that is, the sponsor].

Based on the review of available documents, the sponsor has provided additional information on the site as described below and believes that the PK, efficacy, and safety data from this site were appropriately included in the overall analysis of trial data as described in the Study DAP-PEDBAC-11-02 CSR.

Monitoring visits for the site: A total of 14 monitoring visits for the site were performed by [information redacted] Cubist's contract research organization (CRO).

The first Site Monitoring Visit occurred on 8 December2014 and the eighth Site Monitoring Visit coincided with the dates of the Good Clinical Practice (GCP) site audit (see below). Following the site audit, 6 additional Site Monitoring Visits were performed prior to the Site Close-Out Visit (see below).

Audit Visit for the site: On 20 and 21 April 2015, [information redacted] performed a routine GCP audit of the site for Cubist. During the audit, the following significant findings were directed to the site:

- protocol compliance (critical);
- blinding of study personnel (critical);
- management of investigational products and administration (major);
- Ethics Committee document submissions (major);
- personnel-delegation log (major); and
- discrepancies between source documentation and electronic case report form (eCRF) (major).

In addition, the following significant findings were directed to Cubist's clinical research organisation:

- inadequate monitoring (critical); and
- principal investigator access to eCRF (major).

The following significant findings were made to the sponsor:

- Inadequate Informed Consent Form and assent forms (critical); and
- documentation of process for required unblinding (major).

Due to the significant findings identified, the audit conclusions recommended that immediate actions be taken to ensure compliance with International Conference on Harmonisation (ICH) GCP, regulatory requirements, and sponsor business needs. Thereafter, the issues identified were discussed and addressed at Site Monitoring Visits #9 (14 to 15 May 2015), #10 (27 May 2015), #11 (18 to 19 June 2015), #12 (30 June 2015), #13 (25 to 26 August 2015), and #14 (13 to 15 October 2015) as well as the site close-out visit (4 May 2016).

Based on the review of available documents, while there was significant GCP noncompliance at this site, the sponsor does not believe that the identified issues resulted in potential PK, efficacy, and safety data integrity concerns for the Study DAP-PEDBAC-11-02 trial.

PK data from the site: For the Study DAP-PEDBAC-11-02 trial, the daptomycin concentrations measured from available PK samples are shown in a listing of the CSR. Of the 6 subjects randomised to the daptomycin group at the site, daptomycin concentrations

in pre- and post-dose samples were measured in 4 subjects [subject identifiers redacted], only from a post dose sample in 1 subject [redacted], and only from a pre-dose sample in 1 subject [redacted]. Of the 10 daptomycin concentrations measured for these 6 subjects, 8 were < 3 μg/mL, that is, less than quantifiable levels. For subject [redacted], there is no obvious explanation for the pre- and post- dose daptomycin concentrations of 24 μg/mL and < 3 μg/mL, respectively.

Among the audit findings noted for this site with respect to protocol compliance, it was noted that for subjects receiving daptomycin (that is, 6 out of 7 subjects randomised at the site at the time of the audit report), three additional injections of saline water were administered per day in order to maintain the blind of the investigator, as explained by the study site at the time of audit visit. At the Site Monitoring Visit #8, the sub-investigator reported that such normal saline injections were not part of the blinding plan and not considered as part of blinding or protocol procedures but for 'detoxification' of trial subjects due to 'heavy concomitant therapy given per local routine practice.' The site agreed to stop using normal saline injections for blinding purposes in the future and that any normal saline injections given were recorded as concomitant medication. In the absence of information regarding: (1) the normal saline volume that was injected; (2) sites of normal saline injection and its relative location to the site of daptomycin IV administration; and (3) timing of normal saline injection with regard to the daptomycin IV administration, it is not possible to establish a causal relationship between such saline injections and the daptomycin concentration measurements obtained from these subjects.

Among the audit findings noted for this site with respect to the management of investigational products and administration, it was noted that there was no documentation to confirm who performed the preparation of the investigational product and who administered it to the subject. At the Site Monitoring Visit #10, it was clarified that none of the investigators and sub-investigators had access to the investigational products and the comparator, pharmacy file, and shipment documents or knew of the dosage forms of daptomycin and vancomycin provided to the site or how to reconstitute and dilute these drugs for infusion; only the unblinded study coordinator received the investigational products/comparator and oral antibiotic shipments and calculated the doses of investigational product to be administered. Following subsequent Site Monitoring Visits, it was noted that the documentation of investigational product administration were updated and resolved.

Among the audit findings noted with respect to discrepancies between source documents and entries in the eCRF, it was noted that daptomycin dose recorded in the CRF was the calculated dose and not the actual dose received by the subject (applicable for all entries). Per Version 3.0 of the CRF guidelines and the eCRF version in effect at the site, the site was supposed to enter the 'scheduled dose' and if the scheduled dose was partially or not given, the site would document it in the eCRF. In addition, in the Site Monitoring Visit report #12, it was identified that the difference between the administered dose and the scheduled dose recorded on the eCRF was minimal (for example, < 0.1 mL of study drug solution) and the site was following the protocol and CRF guidelines. Later versions of the CRF guidelines and CRF versions stated that the 'prepared dose' instead of the 'scheduled dose' should be recorded.

Based on the available information, including the Monitoring and Close-Out Visit reports, the sponsor does not believe that these audit findings unduly influenced the PK sampling and daptomycin level measurements at this site.

While the sponsor acknowledges that the majority of daptomycin PK samples collected from subjects enrolled at the site had low daptomycin concentrations (including less than quantifiable levels), such data were considered valid since there was no evidence from available documents to suggest that there were systematic issues with PK sample collection and processing at the site or with the bioanalytical assaying of PK samples to

support the exclusion of daptomycin concentration data from the site in the PK analysis. Monitoring visit reports documented that PK samples were collected per the study protocol and stored in the freezer appropriately with a completed temperature log and no temperature excursions. Moreover, since daptomycin concentrations below the quantitation limit were considered as missing data and programmatically excluded from the overall PK analysis, the PK samples that were included from the site would not have affected the PK summary statistics (including daptomycin peak and trough levels) as reported in the Study DAP-PEDBAC-11-02 CSR. In addition, given the overall size of the study population, the relatively small number of daptomycin-treated subjects in each of the 3 age cohorts, and the age cohort-specific daptomycin doses and clearance rates, collectively make it difficult to draw any clinically meaningful conclusions from the relative proportion of subjects with daptomycin levels below the level of quantitation across study sites. Lastly, please refer to the sponsor's response to agency comment #2 for additional details and information on PK assessment using a population PK modelling approach for this trial.

Efficacy and safety data from the site: Among other findings at this site as described in the audit report, the following were noted (please see below regarding the sponsor's assessments of these findings):

- Protocol Compliance and Personnel: (1) unblinded investigators were not defined for this site and all investigators were considered blinded to the treatment; and (2) the delegation log was inaccurate; no investigators were defined as the 'blinded evaluator' although all investigators were considered as such according to the blinding plan as explained during the audit by the study team;
- Blinding: the blinding of the study personnel could not be confirmed as the treatment arm could be deduced from the medical information available for review by the blinded investigators;
- Protocol compliance: the bicarbonate laboratory tests were not performed for any subjects at all required visits. The study team explained that the local laboratory could not perform this test.
- Inadequate submission of documents to the Ethics Committee: (1) safety information was not provided in a timely manner to the Ethics Committee; and (2) protocol deviations identified during the course of routine monitoring activities were not reported to the ethics committee for notification and the protocol deviation log in the investigator's site file was not populated with these deviations.

In response to the evaluator's comments, the sponsor has provided a summary of the efficacy and safety data for the 8 subjects enrolled at the site (see table below).

Table 8: Efficacy and safety data for subjects enrolled at a clinical research site (Study DAP-PEDBAC-11-02)

Subject ID (treatment group, age cohort)	Categorization in ITT/CE Study Populations	Protocol Deviations	Blinded Evaluator's Assessment of Clinical Outcome at the EOIV Visit	Blinded Evaluator's Assessment of Clinical Outcome at the EOOT Visit	Blinded Evaluator's Assessment of Clinical Outcome at the TOC Visit	Subject Level Microbiological Outcome at the TOC visit	AEs	SAEs
[redacted] (Daptomycin, 1-6 years)	Yes/No	Minor x 6	Improvement	Cure	Cure	Success	1	0
[redacted] (Comparator, 1-6 years)	Yes/No	Major x 4 Minor x 7	Improvement	Cure	Cure	Failure	3	0
[redacted] (Daptomycin, 7-11 years)	Yes/Yes	Minor x 2	Improvement	Cure	Cure	Success	0	0
[redacted] (Comparator, 7-11 years)	Yes/No	Major x 5 Minor x 5	Improvement	Cure	Cure	Failure	1	0
[redacted] (Daptomycin, 12-17 years)	Yes/Yes	Major x 1 Minor x 6	Improvement	Cure	Cure	Success	0	0
[redacted] (Daptomycin, 12-17 years)	Yes/No	Major x 3 Minor x 5	Improvement	Cure	Cure	Failure	0	0
[redacted] (Daptomycin, 12-17 years)	Yes/Yes	Major x 1 Minor x 8	Improvement	Cure	Cure	Failure	0	0
[redacted] (Daptomycin, 12-17 years)	Yes/Yes	Minor x 5	Improvement	Cure	Cure	Failure	0	0

ITT: Intent-to-Treat; CE: Clinically Evaluable; EOIV: End-of-IV; EOOT: End-of-Oral Treatment; TOC: Test-of-Cure; AE: adverse event; SAE: serious adverse event. Sources: DAP-PEDBAC-11-02 CSR Listings 16.2.3, 16.2.2.3, 16.2.6.2, 16.2.6.6., 16.2.6.10, and 16.2.7.1.

While all 8 subjects met the criteria for inclusion in the intent-to-treat (ITT) population, 4 subjects (daptomycin: 4; comparator: 0) met the criteria for inclusion in the clinically evaluable (CE) population and 4 subjects (daptomycin: 2; comparator: 2) were excluded from the CE population due to receipt of prior antibiotics for > 72 hours (daptomycin: subjects [redacted] and [redacted]; comparator: subject [redacted]) or treatment duration not per the clinical evaluability plan (comparator: subject [redacted]; Study DAP-PEDBAC-11-02 CSR).

None of the 8 subjects experienced an unblinding event (i.e., the blinded evaluator became unblinded to treatment group; Study DAP-PEDBAC-11-02 CSR). Following the audit visit, the site blinding plan was updated (version 4.0; 27 April 2015) with the site principal investigator designated as an unblinded physician and one of the sub-investigators designated as the blinded evaluator. The blinding of investigators was confirmed and the blinding plan was reviewed at Site Monitoring Visits.

Of the 8 subjects, 5 subjects (daptomycin: 3; comparator: 2) had 1 or more major protocol deviation (MPD) reported and all 8 subjects had 1 or more minor protocol deviations reported. The following subjects experienced 1 or more MPDs:

- Subject [redacted] (comparator; 4 MPDs): motor development skills questionnaire at screening not assessed for developmental skills immediately prior to bacteraemia as required by protocol; Day 3 haematology, chemistry, and creatine phosphokinase (CPK) not performed (each missing laboratory assessment listed as 1 MPD).
- Subject [redacted] (comparator; 5 MPDs): study assessment x 3 (not otherwise specified) not performed due to technical reasons (temporary absence of reagents; each missing study assessment listed as 1 MPD); all laboratory tests (haematology, chemistry, and CPK) not performed (based on available information, the Sponsor believes that this MPD is likely referring to the laboratory tests scheduled at the EOIV visit); total duration of treatment (38 days) exceeded the protocol specified acceptable maximum duration of treatment of 28 days (for uncomplicated bacteraemia).

- Subject [redacted] (daptomycin; 1 MPD): post-IV study assessment not performed; haematology, chemistry, and CPK assessments not complete.
- Subject [redacted] (daptomycin; 3 MPDs): Day 7 haematology, chemistry, and CPK assessments not performed (based on available information, each of the 3 missing assessments was listed as 1 MPD).
- Subject [redacted] (daptomycin; 1 MPD): informed consent signed outside of protocol window.

All 8 subjects were categorised as clinical improvement at the EOIV visit and as clinical cure at the End of Oral Therapy and TOC visits. At the subject level, 3 subjects (daptomycin: 3; comparator: 0) were categorised as microbiological success and 5 subjects (daptomycin: 3; comparator: 2) were categorised as microbiological failure at the TOC visit.

Of the 8 subjects, 3 (daptomycin: 1; comparator: 2) had 1 or more AEs reported and none had 1 or more SAEs reported during the trial:

- Subject [redacted] experienced an AE (Preferred Term) of vomiting (onset Day 3, resolved Day 3, not related to study medication, moderate intensity, not serious, and no action taken with study medication).
- Subject [redacted] experienced the following AEs:
  - Pneumonia (onset on Day 4, resolved on Day 6, not related to study medication, mild intensity, not serious, and no action taken with study medication);
  - Nausea (onset on Day 6, resolved on Day 6, not related to study medication, mild intensity, not serious, and no action taken with study medication); and
  - Body temperature increased (onset on Day 13, resolved on Day 13, not related to study medication, mild intensity, not serious, and no action taken with study medication.
- Subject [redacted] experienced an AE of lung abscess (onset on Day 6, resolved on Day 20, not related to study medication, moderate intensity, not serious, and no action taken with study medication).

Based on the data summarised above and as described below, it is the sponsor's opinion that the efficacy and safety data from Site 246 are reliable and should be included in the overall efficacy and safety data analyses for the DAP-PEDBAC-11-02 trial:

- Given the criteria for inclusion of subjects in the CE population (n=52 subjects total; daptomycin: 40; comparator: 12), it is not unexpected that half of the subjects randomised at this site were excluded from the CE population but included in the ITT population (n = 82 subjects: daptomycin: 55; comparator: 27).
- Of the major protocol deviations reported among the 5 subjects, missing laboratory assessments were categorised as MPDs for 4 subjects. Since the missing laboratory results for these 3 subjects did not occur at the identical protocol-specified study visit (for example, Day 3), such missing data likely did not substantially affect the safety analysis for the trial. Based on the nature of the other non-laboratory test MPDs reported among these 5 subjects, it is unlikely that such MPDs had an overall impact on the efficacy analysis for the trial. Lastly, a systematic analysis of MPDs reported during the conduct of the DAP-PEDBAC-11-02 trial did not reveal any impact of MPDs on the overall safety or efficacy conclusions; please refer to sponsor's response to agency comments #4(a) and Appendix 1 [not included in this AusPAR].
- None of the 8 subjects experienced an unblinding event (Study DAP-PEDBAC-11-02 CSR).

- Since none of the 8 subjects was categorised as clinically non-evaluable at the TOC visit, the efficacy data from this site did not contribute to the observed numerical difference in the proportion of non-evaluable subjects across treatment groups (daptomycin: 2.0%; comparator: 9.1%). For additional details, please refer to the sponsor's response to agency comment #4(b) [not included in this AusPAR].
- The sponsor believes that the absence of the bicarbonate laboratory test results did not impact the overall laboratory safety analyses since there was no other required chemistry laboratory tests at the site that were lacking/missing at the time of the audit report. Moreover, the bicarbonate test results were not part of the key chemistry laboratory parameters (alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, or creatine phosphokinase (CPK)) that were programmatically analysed (Study DAP-PEDBAC-11-02 CSR).
- There is no available information to suggest that safety events from subjects enrolled at Site 246 were unreliable. The inclusion of safety data from all subjects who were treated with any dose of IV study medication (daptomycin or comparator; Safety Population) as specified in the protocol and the Statistical Analysis Plan (SAP), in the safety analysis ensures that the analysis accurately reflects the reported AEs and potential safety signals seen in the DAP-PEDBAC-11-02 trial.

Evaluator's response

Issue 1

It was confirmed that results < LLOQ were excluded from analyses.

It is accepted that young children are likely to have increased clearance of daptomycin and thus it is likely that C_{trough} results < LLOQ from reliable study sites were valid. Results < LLOQ from reliable sites should not be excluded from summary analysis of measured results or from the population PK analysis. It would be more appropriate to use some method of imputation for example, half LLOQ.

Despite the sponsor's assertion to the contrary, all PK results from the questioned site are considered unreliable. They do not make sense. The results from this site should all be excluded from summary analysis of measured results and from the population PK modelling.

AUCs were not reported for individuals with measured results. This was considered a deficiency in reporting by the first round evaluator and has not been remedied in the sponsor's post-first round response. The reason not to provide AUCs based on measured results is questioned; modelled AUCs were all that were provided. It would be reassuring to know that the AUCs calculated from measured values were in line with the modelled AUC results.

Issue 2

The first round evaluator accepted that AUC have been concluded to correlate best with antibacterial efficacy. Despite this, it is not impossible that C_{trough} levels < LLOQ would influence efficacy and also the potential for development of resistance of the infecting organism. The length of time the C_{trough} is below the LLOQ is not considered irrelevant, just undocumented.

The argument against more frequent lower weight based dose for very young children is not resolved by referencing results in adults or dogs. The issue could have been addressed in modelling. However, as there has been no modelling of this approach, it is not intended to pursue this further.

Issue 3

If the sequence is correctly understood, there were 5 Site Monitoring Visits before the Audit Visit in April 20/21 2015 at which the catalogue of problems was recorded. What happened at earlier visits is not reported in the post-first round response, but it is considered unlikely that problems would suddenly first appear at the time of the sixth audit. What was found at later visits is also not recorded in any detail.

The number of participants enrolled at the questioned site prior to the April audit could not be located. For the study overall, the first participant was enrolled in the study on 6 March 2013, The Last participant was enrolled on 3 October 2015.

The only participant from this site reported in the Listing of Protocol Deviations (ITT Population), Participant [redacted], had informed consent signed out of protocol window (considered major). There was no indication in the lists of participants excluded from study populations that this major protocol deviation resulted in exclusion from analyses. The only exclusions from any study populations were from the CE population as follows:

- Daptomycin: Subject [redacted] received prior antibiotics for > 72 hr
- Daptomycin: Subject [redacted] received prior antibiotics for > 72 hr
- Comparator: Subject [redacted] received prior antibiotics for > 72 hr
- Comparator: Subject [redacted] CE treatment duration not per clinical evaluability plan
  - Per the clinical evaluability plan for uncomplicated bacteraemia a minimum of 4 days and maximum of 28 days. For complicated bacteraemia a minimum of 6 days and a maximum of 28 days for ages 1 to 11. Complicated under 12 responding by 28 days but requiring additional IV treatment can continue. Those with osteomyelitis may go beyond maximum (or minimum only after discussion with medical monitor)

The practice of 'detoxification' identified at Audit Visit 8 (date unspecified) indicates that non-compliance with the protocol continued beyond April 2015.

Updating and resolving documentation of investigational product administration suggests that the corrective measures were applied retrospectively, quite late in the study. Discrepancies between source documents and eCRF in relation to the exact doses administered do not inspire confidence.

Lack of reporting to the ethics committee in accordance with the protocol requirements is considered concerning.

The critical issue of blinding was uncovered at Audit 6. The study commenced enrolments in 2013. Without information on when the participants entered the study in relation to the April 2015 audit it is difficult to accept that none of the 8 participants experienced an unblinding event. The post-first round response that blinding was not an issue and the decision not to exclude any participant from analysis populations for reasons relating to blinding, is not accepted.

Discordance between the clinical outcomes and microbiological outcomes at TOC visit for 5 of the 8 participants is noted (table included in sponsor's relevant response, above). The proportions reporting AEs and SAEs are relatively low compared to the overall study population. However, it is conceded that these may be chance observations.

Inability to measure bicarbonate, in isolation, is not considered likely to impact the efficacy results of the study; however, the ability to measure bicarbonate is considered a basic requirement for adequate management of serious infection and inability to do so at the questioned site is of concern.

In conclusion, it appears that the site did not comply with appropriate ethical and good clinical practice standards despite overall assurances to the contrary in the CSR.

It is difficult to agree that the identified issues at this site did not result in potential data integrity concerns. Unreliable PK results were the flag that all was not well at the site. It is harder to be sure of safety and efficacy data integrity but these are also likely to be problematic based on the litany of documented failures.

It is agreed that all available safety data should be included in analyses. It is hard to specifically pinpoint reasons why individual efficacy results should be excluded.

Modelling

According to the footnote of Table 7 [not included in this AusPAR] the analysis excluded 5 patients with concentrations below the limit of quantitation (BLQ), or unexpected low concentration. As seen in Table 9, it seems likely that the five patients mentioned in Table 7 were from Site 246. The table footnote stated that the individual PK parameters for the five participants were derived based on population PK parameters and their individual demographic characteristics. The meaning of this footnote is unclear and requires explanation.

The handling of data BLQ for analysis in Study DAP-PEDBAC-11-02 and population PK modelling appears likely to have differed. According to Report 04hxdz, plasma concentrations of daptomycin BLQ of the assay were set to missing and were excluded from Bayesian evaluation. Two concentrations corresponding to peak samples for patient [redacted] (a 7 to 11 year-old) and patient [redacted] (12 to 17 year-old) were markedly lower (< 10 µg/mL) than the median peak value and they were excluded from Bayesian evaluation. No other substitutions were made to account for the aberrant data points. Based on this method of data handling and information in Table 9, it would seem logical that 18 values should have been excluded.

Table 9: Exclusion list of concentration samples

Subject ID	Time Point	Collection Time	Collection Date	Daptomycin Concentration (µg/mL)	Dose Group	Age Group	Comment
[redacted]	Trough	17:59	11/24/2013	<3.00	9 mg/kg	7 - 11 years	BLQ
[redacted]	Trough	11:55	11/17/2014	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]	Trough	16:07	4/15/2014	<3.00	9 mg/kg	7 - 11 years	BLQ
[redacted]	Trough	12:53	11/17/2014	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]	Trough	14:30	1/16/2015	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]	Peak	21:03	12/7/2013	5.3	9 mg/kg	7 - 11 years	Suspected concentration
[redacted]	Trough	13:01	4/6/2013	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]	Trough	13:00	9/4/2015	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]	Trough	13:40	10/18/2014	<3.00	9 mg/kg	7 - 11 years	BLQ
[redacted]	Trough	13:30	5/10/2015	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]	Trough	16:02	9/28/2015	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]	Trough	10:00	11/17/2014	<3.00	7 mg/kg	12 - 17 years	BLQ
[redacted]*	Trough	12:30	11/30/2014	<3.00	7 mg/kg	12 - 17 years	BLQ
[redacted]*	Peak	15:05	11/30/2014	<3.00	7 mg/kg	12 - 17 years	BLQ
[redacted]	Peak	20:00	1/16/2015	<3.00	7 mg/kg	12 - 17 years	BLQ
[redacted]*	Trough	14:25	1/25/2015	<3.00	7 mg/kg	12 - 17 years	BLQ
[redacted]*	Peak	15:00	1/25/2015	5.59	7 mg/kg	12 - 17 years	Suspected concentration
[redacted]*	Trough	15:00	3/2/2015	<3.00	7 mg/kg	12 - 17 years	BLQ
[redacted]*	Peak	14:20	2/8/2015	<3.00	9 mg/kg	7 - 11 years	BLQ
[redacted]*	Trough	11:20	2/13/2015	<3.00	12 mg/kg	1 - 6 years	BLQ
[redacted]*	Peak	13:57	2/13/2015	<3.00	12 mg/kg	1 - 6 years	BLQ

BLQ: Below limit of quantification

* Subjects collected only BLQ or unexpected low peak samples. Their individual PK parameters were derived based on population PK parameters and their individual demographic characteristics.

Note: Subject identifiers have been redacted (column 1)

Sponsor's response

All paediatric subjects with bacteraemia in Study DAP-PEDBAC-11-02 who provided at least one PK sample were included in the analysis to generate individual Bayesian PK parameter estimates (MERC-PCS-121, [Ref. 5.3.3.5: 04HXDZ]).

As summarised in the paediatric bacteraemia dossier, the paediatric population PK model previously developed to support the paediatric complicated skin and skin structure

infection application was used to assess daptomycin PK in paediatric bacteraemia patients using a Bayesian approach without re-estimating the model parameters. Therefore, the concentration data from paediatric bacteraemia patients in Study DAP-PEDBAC-11-02 did not influence the development of the paediatric population PK model.

The adequacy of the model in describing the concentration data from paediatric bacteraemia patients was demonstrated, as described in the paediatric bacteraemia dossier.

To derive individual Bayesian PK parameters for each patient contributing to PK sample collection in Study DAP-PEDBAC-11-02, the previously developed paediatric population PK model was fitted to the plasma daptomycin concentrations from each individual.

As outlined in an appendix of the modelling report (MERC-PCS-121, (Ref. 5.3.3.5: 04HXDZ)), also reproduced as a table in the clinical evaluation report, overall, two peak samples with measureable concentrations were excluded in the analysis, as the concentration values were much lower than the population mean for peak samples, and an additional 19 samples were treated as missing as the concentrations were below the limit of quantitation (4 peak samples and 15 trough samples). Therefore, the total number of samples not used for the Bayesian analysis was 21, rather than the 18 described by the reviewer. These resulted in a total of 5 subjects who provided at least one PK sample with no daptomycin concentrations for the fitting. For these 5 subjects, individual estimates of Bayesian PK parameters were derived based on individual demographic data that are covariates of daptomycin PK in the population PK model. Summary statistics of model-derived PK parameters in paediatric bacteraemia patients were provided in (a table of the clinical evaluation report). The sponsor notes that a consistent approach was used to handle BLQ PK samples in the summary statistics reported in the clinical study report and in the population PK analysis; they were treated as missing in both cases. Please see the sponsor's response above for a discussion regarding the PK samples from the questioned site.

Evaluator's response

It is not accepted that treating results < LLOQ as missing is the ideal way of doing summary of population PK analyses. In view of the more rapid clearance reported in very young children, such results were likely to be valid and valid results should not be treated as missing.

As stated in response to the sponsor's post-first round response to the first part of Question 1, all PK results from the questioned site are considered unreliable based in the lack of sense that they made, and supported by the multiple issues with GCP at the site recorded at site Visit 6.

Question/comment 2

> *Regarding first round comment on CPK versus PK:*
>
> *The statistical assessment is reassuring; however, it is unclear why a linear relationship should be found in adults and not in children. Clinical relevance will ultimately be determined clinically.*

Sponsor's response

The sponsor notes that, in the adult analysis, the slope of the linear correlation between the log-transformed CPK and steady-state daptomycin AUC was 0.000606. Although the slope in the adult analysis was statistically significant (that is, not zero), the shallow slope suggests a negligible positive correlation between the increase in CPK at the recommended clinical doses and daptomycin AUC. As described in the population PK modelling report, this is further demonstrated that at the 97.5th percentile of steady-state

daptomycin AUC observed in the clinical studies, the mean predicted CPK increase was 2-fold to 3-fold below the upper limit of normal (appendix of the Study DAP-IE-01-02 CSR, submitted in the original registration dossier, Application No. 2007-1852-2).

Consistent with the observation with the adult analysis, a very shallow, positive slope (0.000241) was estimated, suggesting negligible/minimal correlation between the log transformed CPK normalised to the upper limit of normal for the local laboratory, and the steady-state daptomycin AUC. However, the slope was not statistically different from zero; this may be related to the smaller sample size in the paediatric compared to the adult analysis. In any case, the mean predicted CPK increase at the 97.5th percentile of the steady-state daptomycin AUC observed in the paediatric clinical studies was approximately 40% of the upper limit of normal. This result also supports that at the recommended paediatric dosing regimens, CPK increase is not expected to be clinically meaningful.

Evaluator's response

The response is accepted.

Question/comment 3

Regarding the overall success rate in the total mMITT population at the TOC/Safety visit:

> *The results support efficacy of daptomycin treatment in the studied age group. There are qualifications. The issues are denoted below:*

Issue 1

Clinical improvement could be subject to observer interpretation. Assessment of clinical efficacy was the responsibility of each study site's blinded investigator and there were instances of unblinding which could have influenced clinical assessment. From the reporting, it was difficult to assess the impact on results for individual participants.

Sponsor's response

The sponsor believes that the potential risk of clinical assessments being subjected to observer interpretation was mitigated by the use of the blinded evaluator (see below).

A double-blind design for the Study DAP-PEDBAC-11-02 trial was not feasible since the recommended comparators (vancomycin, clindamycin, first generation cephalosporins, or semi-synthetic penicillins) were typically administered more frequently than once daily while daptomycin was administered once daily. Therefore, at each site, the principal investigator was not blinded to study treatment while a treatment-blinded investigator (hereafter referred to as blinded evaluator) assessed all safety and efficacy endpoints in order to minimise bias that may be associated with subjective assessments. The blinded evaluator as well as the sponsor's medical and microbiological team members remained blinded throughout the trial period.

Of the 3 subjects in whom the blinded evaluator became unblinded to study group (Study DAP-PEDBAC-11-02 CSR), 2 subjects (both in the comparator group; subject [redacted] and subject [redacted]) were categorised as experiencing a major protocol deviation (MPD; Study DAP-PEDBAC-11-02 CSR) due to unblinding and were included in the mMITT population but excluded from the CE population. A detailed review of the MPDs reported during the conduct of the DAP-PEDBAC-11-02 trial did not reveal any impact of MPDs on the overall safety or efficacy conclusions.

Issue 2

The 95% confidence interval (CI) for the treatment difference included zero and the interval was wide reflecting the small numbers analysed which particularly relevant in the comparator group and particularly for age group sub analyses. Results for a small number

of participants in the comparator group could make quite a big difference to percentages. The assessment of overall success was likely to have been influenced by the relatively large proportion of the comparator group with non-evaluable response though absolute numbers were small.

Sponsor's response

In the mMITT population of the Study DAP-PEDBAC-11-02 trial, the proportion of subjects categorised as clinical success (satisfactory response) at the Test-of-Cure (TOC)/Safety Visit was 88.2% in the daptomycin group and 77.3% in the comparator group (Study DAP-PEDBAC-11- 02 CSR). While the sponsor acknowledges that the differences between the 2 treatment groups appear to be related to the higher proportion of non-evaluable subjects in the comparator group (9.1%) as compared to the daptomycin group (2.0%), the 95% confidence interval (CI) for the treatment difference for clinical success includes 0, which indicates that the difference in percentages was within chance (Study DAP-PEDBAC-11-02 CSR). Moreover, the clinical success rates were generally similar across age groups and within treatment arms in the CE and MITT analysis populations at the TOC/Safety Visit and in each of the three (mMITT, MITT, and CE) populations, the clinical success rates at EOIV and EOT were generally comparable between the daptomycin and comparator treatment arms (Study DAP-PEDBAC-11-02 CSR). Lastly, no significant difference was found in the time to clearance of the *S. aureus* bacteraemia between daptomycin and comparator-treated subjects in the mMITT population, with median times to clearance of 2.5 and 2.0 days in the daptomycin and comparator groups, respectively (Study DAP-PEDBAC-11-02 CSR). Based on these efficacy results, the sponsor concludes that daptomycin was as effective as comparator in the treatment of *S. aureus* bacteraemia in the Study DAP-PEDBAC-11-02 trial.

Issue 3

In view of numbers, it was not possible to totally balance factors that might complicate treatment. There were more patients in the daptomycin than the comparator group with osteomyelitis at baseline. There was a perceived discrepancy in IV catheter removal during the study with potential to bias results in favour of daptomycin and this could have been influenced by non-blinded investigators. The following were calculated

- Catheters were in place at baseline in 12/55 (21.8%) of daptomycin participants: 7/12 (58.3%) had the catheter removed before the first dose or during study dosing.
- Catheters were in place in 5/27 (18.5%) of comparator participants; 1/5 (20%) had the catheter removed during the study dosing.
- Catheter placement continuing throughout the study was reported for 2/12 (16.7%) of daptomycin participants, and 3/5 (60%) of comparator patients.

Sponsor's response

The sponsor has performed post-hoc analyses of the following study population subgroups:

- Subjects (including those with medical history or adverse event (AE) of osteomyelitis; see below) in the Study DAP-PEDBAC-11-02 trial who received longer than the protocol-specified maximum duration of study drug of 42 days (Study DAP-PEDBAC-11-02 Protocol version 3.0).
  - In the context of a small subgroup population of 10 subjects who received study drug treatment for > 42 days and of whom 7 had medical history of osteomyelitis and 1 with an AE of osteomyelitis, the overall clinical outcome for these 10 subjects at the EOIV, EOT, and TOC visits was similar to those of the overall trial population. Moreover, the tolerability of study medication in these 10 subjects was similar to that of the overall trial population.

- Subjects with catheter at Baseline:
  - Based on the analyses of the limited number of subjects in whom baseline catheters were removed; the Applicant believes that there is no clinically relevant impact of the differences in the proportion of subjects in the daptomycin versus comparator groups who had the catheter removed on the DAP-PEDBAC-11-02 trial results.

Each of the two *post-hoc* analyses are described below.

- Subjects who received > 42 days of study treatment:
  - In this trial, a total of 10 subjects (daptomycin: 8; comparator: 2) received treatment beyond 42 days (DAP-PEDBAC-11-02 CSR; table reproduced in this response, shown below).
  - These 10 subjects were further categorised as follows:
    - § Age group: 1 to 6 years old: daptomycin: 3 subjects; comparator: 0 subjects; 7 to 11 years old: daptomycin: 2; comparator: 2; and 12-17 years old: daptomycin: 3; comparator: 0.
  - Type of bacteraemia: 8 subjects had complicated bacteraemia (daptomycin; 6; comparator: 2) and 2 subjects had uncomplicated bacteraemia (daptomycin: 2; comparator: 0).
- Medical history of osteomyelitis: present in 7 subjects (daptomycin: 6; comparator: 1) The sponsor notes that the presence of osteomyelitis at baseline was not controlled by randomisation.
- Adverse event (AE) of osteomyelitis: reported in 1 subject (without medical history of osteomyelitis) in the comparator group.

Of these 10 subjects, 1 (subject [redacted]) with uncomplicated bacteraemia was treated for a total of 141 days. As described in the Study DAP-PEDBAC-11-02 CSR, the site classified this subject's case as uncomplicated bacteraemia; however, after data-base lock, the investigator stated the subject should have been classified as complicated bacteraemia due to the presence of osteomyelitis. Per the investigator, the subject continued on treatment for 141 days as prophylaxis to prevent the recurrence of osteomyelitis.

Table 10: Listing of subjects with treatment > 42 Days (safety population)

Age Group	Treatment	Subject	Number of Treatment Days	Complicated/ Uncomplicated bacteremia	Osteomyelitis as Medical History*	Osteomyelitis as AE?
1 - 6 YEARS	Daptomycin		59	COMPLICATED	Y	
			43	COMPLICATED	Y	
			141	UNCOMPLICATED	Y	
7 - 11 YEARS	Daptomycin		43	COMPLICATED	Y	
			66	UNCOMPLICATED		
	Comparator		45	COMPLICATED	Y	
			58	COMPLICATED		Y
12 - 17 YEARS	Daptomycin		45	COMPLICATED	Y	
			82	COMPLICATED		
			54	COMPLICATED	Y	

Note: Subject identifiers have been redacted from table (column 3)

Clinical response of 10 subjects who received > 42 days of study drug treatment; the clinical response of 10 subjects in whom study treatment was continued beyond 42 days is shown in the following table and summarised below.

- At the End of IV therapy (EOIV) visit, all 10 subjects were classified as clinical improvement.

- At the End of Therapy (EOT) visit, 5 subjects (daptomycin: 4; comparator: 1) were classified as clinical cure, 3 subjects (daptomycin: 3; comparator: 0) were classified as clinical improvement, 1 subject in the daptomycin group was classified as not evaluable, and 1 subject in the comparator group was classified as clinical failure.
- At the Test of Cure (TOC) visit, 7 subjects (daptomycin: 6; comparator: 1) were classified as clinical cure, 1 subject in the daptomycin group was classified as clinical improvement, and 2 subjects (daptomycin: 1; comparator: 1) were classified as clinical failure.

In the context of a small subgroup population of 10 subjects who received study drug treatment for > 42 days and of whom 7 had medical history of osteomyelitis and 1 with an AE of osteomyelitis, the overall clinical outcome for these 10 subjects at the EOIV, EOT, and TOC visits was similar to those of the overall trial population.

Table 11: Clinical response for subjects receiving treatment beyond 42 days (safety population)

Treatment Group	Age Group	Subject ID	Clinical Outcome at EOIV	Clinical Outcome at EOT	Clinical Outcome at TOC
Comparator	7 - 11 YEARS		IMPROVEMENT	CURE	CURE
			IMPROVEMENT	FAILURE	FAILURE
Daptomycin	1 - 6 YEARS		IMPROVEMENT	CURE	CURE
			IMPROVEMENT	CURE	CURE
			IMPROVEMENT	IMPROVEMENT	IMPROVEMENT
	12 - 17 YEARS		IMPROVEMENT	CURE	CURE
			IMPROVEMENT	NOT EVALUABLE	FAILURE
			IMPROVEMENT	IMPROVEMENT	CURE
	7 - 11 YEARS		IMPROVEMENT	IMPROVEMENT	CURE
			IMPROVEMENT	CURE	CURE

EOIV: end of IV; EOT: end of treatment (IV+Oral); TOC: test-of-cure; IV: intravenous

Note: Subject identifiers have been redacted from table above (column 3)

Adverse events reported in 10 subjects who received > 42 days of study drug treatment: The adverse events (AEs) reported in each of the 10 subjects in whom study treatment was continued beyond 42 days are shown in a table [not reproduced in this AusPAR]. Of the 10 subjects, 8 (daptomycin: 6; comparator: 2) reported 1 or more AEs. Except for 1 AE of severe intensity (worsening of osteomyelitis of right iliac bone in subject [redacted]; all other AEs were mild or moderate in intensity.

There were 2 subjects with 1 or more serious AEs (SAEs). In the daptomycin group, subject [redacted] experienced an SAE of thrombosis of left saphenous vein (moderate intensity, not related to study drug, onset on study Day 5, dose of study drug not changed, resolved on study Day 50). In the comparator group, subject [redacted] experienced an SAE of osteomyelitis of the right iliac bone (moderate intensity, not related to study drug, onset on study Day 14, dose of study drug not changed, resolved on study Day 57) and then experienced an SAE of worsening of osteomyelitis of right iliac bone (severe intensity, not related to study drug, onset on study Day 57, study drug withdrawn, resolved on study Day 100).

There was 1 subject with treatment-related AE. In the daptomycin group, subject [redacted] experienced an AE of diarrhoea (mild intensity, related to study drug, not serious, onset on study Day 9, dose of study drug not changed, resolved on study Day 10).

In the context of the small subgroup population of 10 subjects who received study drug treatment for > 42 days, the tolerability of study medication in these 10 subjects was similar to that of the overall trial population.

Participants with catheter at Baseline: The 17 subjects in Study DAP-PEDBAC-11-02 who had a catheter at baseline were shown in the CSR listing. For each of the 17 (daptomycin: 12; comparator: 5) subjects, the corresponding treatment group, age cohort, status of catheter removal (Yes or No), and clinical outcome at the EOIV, EOT, and TOC visits are shown in a supplied table [not included here].

Of the 17 subjects, 12 (daptomycin: 10; comparator: 2) had the catheter removed and 5 (daptomycin: 2; comparator: 3) did not have the catheter removed.

In the daptomycin group, the following 3 subjects were categorised as clinical failure at the TOC visit:

- Subject [redacted]: complicated bacteraemia; SAE of recurrent *S. aureus* bacteraemia (onset Day 28; resolved Day 37, severe, not related to study medication, action taken with study medication not applicable); microbiological success and overall failure at TOC.
- Subject [redacted]: uncomplicated bacteraemia; SAE of bacteraemia (onset Day 27, resolved on Day 41, moderate intensity, not related to study medication, action taken with study medication not applicable); microbiological failure and overall failure at TOC.
- Subject [redacted]: uncomplicated bacteraemia; Discontinued from study due to an AE of increased creatine kinase levels (onset Day 3, resolved on Day 8, mild intensity, related to study medication, and medication withdrawn); microbiological success and overall failure at TOC.

In the comparator group, the following subject was categorised as not evaluable at the TOC visit:

- Subject [redacted]: was not assigned a bacteraemia classification due to withdrawal from study drug prior to the Day 5-7 bacteraemia assessments. Experienced SAE of aspiration pneumonia (onset Day 1, resolved on Day 8, moderate intensity; not related to study drug; dose not changed or withdrawn), not included in MITT population due to the subject having vancomycin-resistant Enterococcus spp. (VRE) infection at baseline and thus categorised as not evaluable at the EOIV, EOT, and TOC visits.

Based on the above analyses of the limited number of subjects in whom baseline catheters were removed; the sponsor believes that there is no clinically relevant impact of the differences in the proportion of subjects in the daptomycin versus comparator groups who had the catheter removed on the Study DAP-PEDBAC-11-02 trial results. In the daptomycin group, clinical cure at TOC was achieved by 7 out of 10 (70%) of subjects who had the baseline catheter removed. However, the Sponsor notes that of the 3 subjects that did not achieve clinical cure at TOC, 2 had recurrent bacteraemia despite the removal of the catheter, and 1 had an AE (increased creatine kinase levels) that was deemed related to study medication and for which the subject was discontinued from the study. In the comparator group, only 1 subject had the catheter removed and who was deemed not evaluable due to the VRE infection at Baseline.

Table 12: Summary of subjects with baseline catheter (safety population)

Treatment Group	Catheter removed (n)	Clinical Outcome at EOIV (n)	Clinical Outcome at EOT (n)	Clinical Outcome at TOC (n)
Comparator	Yes (2)	Cure (1); not evaluable (1)	Cure (1); not evaluable (1)	Cure (1); not evaluable (1)
	No (3)	Cure (2); not evaluable (1)	Cure (2); not evaluable (1)	Cure (3)
Daptomycin	Yes (10)	Cure (8); improvement (1); failure (1)	Cure (8); improvement (1); failure (1)	Cure (7); failure (3)
	No (2)	Cure(1); improvement (1)	Cure (2)	Cure (2)

Evaluator's response

It is agreed that a double-blind design was unfeasible; however, maintenance of blinding in the absence of a double-blind design is challenging.

The CSR listing of protocol deviations (ITT population) was consulted and no patient at Site 246 was documented as having a protocol deviation relating to blinding. Despite assurances, it is considered possible that blinding at one site, which enrolled 8 patients (9.9% of the total study population) may have been compromised. As the study neared the end of the period of enrolment, Audit Visit 6 (April 2015) uncovered critical failures of blinding and failures of GCP in a number of areas. Reassurance that the critical blinding issue reported just months before the last participant in the study overall, was resolved is not accepted unreservedly (see the response to Question/comment 1, with subsequent evaluator response above).

The following first round evaluator's points relating to possible biases are considered valid:

- The assessment of overall success was likely to have been influenced by the relatively large proportion of the comparator group with non-evaluable response is considered valid. (Issue 2)
- Small study populations with unbalanced numbers could potentially result in disproportions in factors, such as baseline osteomyelitis diagnosis, or decisions to remove catheters (foreign bodies) that may ultimately bias results.
- Discussion of participants treated for > 42 days and discussion of safety are felt to be tangential to the first round evaluator's points.

Question/comment 4

Evaluator's comment regarding physical examination findings in Study DAP-PEDBAC-11-02:

> *It is considered unusual that over half to two thirds of participants with bacteraemia requiring IV treatment would have normal physical examinations.*

Sponsor's response

The sponsor acknowledges that the description of the physical examination findings in the Study DAP-PEDBAC-11-02 CSR contains inadvertent errors. The correct information is shown below and based on the data in a table of the Study DAP-PEDBAC- 11-02 CSR.

Of the subjects in the safety study population, significant abnormalities were noted during the focused physical examination at baseline in 38 out of 55 (69.1%) subjects in the daptomycin group and 14 out of 26 (53.8%) subjects in the comparator group. During Day 1 to Week 6 of the study, the proportion of subjects with significantly abnormal findings in focused physical exams progressively decreased in both treatment groups, as expected for clinical response to study medication. Of the 55 subjects in the daptomycin

group, 1 out of 55 (1.8%) subjects at the EOIV) and TOC/Safety visit had abnormal focused examination findings. Of the 26 subjects in the comparator group, 2 out of 26 (7.7%) subjects and 4 out of 26 (15.4%) subjects had significant abnormalities noted in focused physical examinations at the EOIV and TOC/Safety visits, respectively.

Evaluator's response

The response accepted.

Question/comment 5

Regarding motor development:

> *The questionnaire was said to be modified from the guidance from the American Academy of Pediatrics. (http://brightfutures.aap.org/tool_and_resource_kit.html). The link did not lead directly to a recognisable source. The questionnaire was based on parents assessments at baseline which may be subject to recall bias. It was not entirely clear from the protocol, but it appears likely that the questionnaire was also filled using parents' assessments at final check and not supported by Investigator's observations. It is unlikely that the study questionnaire is a validated tool and its usefulness is questioned.*

Sponsor's response

The American Academy of Pediatrics guidance can be accessed via a link, and thereafter via the Early Childhood Tools link or Middle Childhood Tools link on the left hand side of the home page. These links may also be directly accessed at: https://brightfutures.aap.org/materials-and-tools/tool-and-resource-kit/Pages/Early-Childhood-Tools.aspx and https://brightfutures.aap.org/materials-and-tools/tool-andresource- kit/Pages/middle-childhood-tools.aspx, respectively (accessed 1 August 2018).

As stated in the Study DAP-PEDBAC-11-02 protocol (v1.0), the principal investigator or designee at each site screened children under age 7 years for motor developmental skills using the questionnaire provided in Appendix D of the protocol. For the baseline questionnaire, parents were asked to provide information on developmental skills immediately prior to bacteraemia. Based on the comments field in a listing in the Study DAP-PEDBAC-11-02 CSR, a subset of assessments at screening or follow-up visit cite the subject's parent(s) or caregiver. Therefore, the sponsor believes that the investigator or designee obtained information from the parent(s) or the caregiver of the subject at baseline and follow-up visits. Moreover, whether the investigator's observations were also considered in follow-up assessments for this questionnaire was not programmatically collected for this study.

The sponsor acknowledges the potential for recall bias for screening visit assessments based on parents' assessment immediately prior to bacteraemia, and does not specifically state in the Study DAP-PEDBAC-11-02 CSR that the motor developmental skills questionnaire is a validated tool for this trial. However, the sponsor respectfully notes that the peripheral neurotoxicity risk in paediatric patients with bacteraemia was carefully considered during protocol drafting and conduct of the DAP-PEDBAC-11-02 trial, including specific questions discussed with the Data Monitoring Committee (DMC); (Study DAP-PEDBAC-11-02 CSR). Given the potential limitations of monitoring for monitoring nerve and muscle toxicity in children less than 2 years of age, the motor development assessment as described above as well as focused peripheral neurological examinations were included in the schedule of activities for this study. Lastly, the sponsor notes that no safety signals were apparent from review of vital signs, neurological examinations, or physical examination findings/

Evaluator's response

The link provided requires insertion of a user ID and password which were not provided.

Motor and neurological examinations are difficult in very young children especially in the recovery period after a significant illness, an illness which in some instances may have resulted in local sequelae that impair mobility such as septic arthritis or osteomyelitis.

Small numbers of participants, difficulty in delineating subtle motor and neurological abnormalities and the relatively short period of follow-up makes it impossible to exclude even common AEs relating to motor and neurological function.

Question/comment 6

Evaluator's comment regarding CPK levels:

> *No record of any event of raised CPK in the comparator arm of the SAB Study DAP-PEDBAC-11-02 could be located by the evaluator in the CSR despite the integrated summary reporting one.*

Sponsor's response

The sponsor has provided the following clarifications:

Of the adverse events (AEs) of blood creatine phosphokinase (CPK) increased that were reported in the combined safety populations of the DAP-PEDS-07-03 and DAP-PEDBAC-11-02 trials, 1 AE of severe intensity occurred in each treatment group of the DAP-PEDS-07- 03 trial.

In the DAP-PEDBAC-11-02 trial, none of the 4 AEs of blood CPK increased was of severe intensity.

Evaluator's response

The response is accepted.

Question/comment 7

Evaluator's comment regarding PSUR: 12 September 2016 to 11 September 2017:

1. *Study DAP-PEDOST-11-03 has only been briefly summarised in the PSUR and has not been submitted to the TGA for evaluation. This study may shed light on measured pharmacokinetic and safety of use of 12 mg/kg in patients 1 year of age.*
2. *'Thrombocytopenia' and 'platelet count decreased' are not included in PI.*
3. *Cubicin Drug Susceptibility Survey (Survey Number: PNM11B048) could not be located in the dossier.*
4. *The sponsor commented that daptomycin is not approved for septic arthritis. However, this patient also had bacteraemia which is an indication not qualified as excluding patients with septic arthritis.*

Sponsor's response

1. In the DAP-PEDOST-11-03 trial, although PK samples were collected, a population PK analysis was not performed to assess daptomycin PK in this paediatric patient population; only summary statistics of peak and trough concentrations were reported. Furthermore, there were limited number (n=4) of paediatric patients 1 to < 2 years of age who received daptomycin at the 12 mg/kg dose. Therefore, no new insight was gained on the PK in paediatric patients 1 to < 2 years of age receiving the 12 mg/kg dosing regimen. There were no new safety signals identified with the use of daptomycin in this study. A synopsis of the DAP-PEDOST-11-03 CSR is attached to this

response [not included here]. The CSR for the DAP-PEDOST-11-03 trial is available upon request.

2. The TGA approved the addition of 'thrombocytopenia' and 'platelet count decreased' to the Cubicin PI on 6 July 2018 (Submission No.; PM-2018-01813-1-2). These terms have been added to the Cubicin PI provided.

3. Survey Number: PNM11B048 was a post-marketing survey conducted in Japan to observe the change in susceptibility to Cubicin (daptomycin) and other selected antimicrobial agents over a 5-year period (from April 2012 to April 2017 with a final report in August 2017), among 1,500 clinical isolates of methicillin-resistant Staphylococcus aureus collected from hospitals in Japan. The Japan survey was considered not to be relevant to the evaluation of the proposed indication in Australia. Therefore, it was not included in the application dossier to support paediatric indications. The final report summary was included in the global PSUR only to provide information on the important identified risk for decreased susceptibility in *S. aureus*.

4. The sponsor clarifies that the type of infection described in the article in Question1 is not specified in the target indication for SAB in paediatric and adult patients, but it reflects real life use of the product. The case report provides another illustration of the risk for emergence of resistance in *S. aureus* infections involving bone and joint, which typically require surgical therapy to remove sequestered foci where antibiotics have limited penetration (e.g. drainage of infected joint fluid, periosteal abscesses, and removal of devitaliwed bone or cartilage). This case report described the clinical course of a 26-year-old woman with systemic lupus erythematosus and renal impairment who was diagnosed with septic arthritis associated with persistent MRSA bacteraemia and who was treated unsuccessfully first with vancomycin then daptomycin as second-line therapy. There were noted shifts in MIC for vancomycin and daptomycin during treatment. The selection of *S. aureus* with increased daptomycin and vancomycin MICs was consistent with other published reports of decreased susceptibility associated with persistent bacteraemic infections.

   The current proposed labelling does include special precautions to advise prescribers of the risk for persistent infections and for development of non-susceptible isolates, and risk minimisation measures include timely surgical intervention (that is, drainage, debridement, or removal of prosthetics) to facilitate successful treatment, which was not done in this case report. The sponsor considers the product label to adequately address the risk for decreased susceptibility in *S. aureus* bacteraemia, but ultimately treatment decisions are made by the prescriber based on individual patient risk to benefit assessments. Additional treatment experience with daptomycin in septic arthritis was described in the European Cubicin Outcomes Registry (EU-CORE) in a total of 85 patients (including 3 paediatric patients) with an overall clinical success (cure + improvement) rate of 84.7% (Gonzalez-Ruiz et al.) and in 2/3 paediatric patients (Syriopolou et al). Therefore, there are data to support the use of daptomycin when treating SAB associated with septic arthritis.

Evaluator's response

1. Any PK data available from Study DAP-PEDOST-11-03 for patients between 1 and 2 years of age would be more than is available in the pivotal study submitted in support of the extension of indication. The synopsis of this study included in the appendix of the post-first round response does not include PK data.

2. Response accepted

3. This response is not accepted. Five years' systematically collected data including 1500 isolates may have the potential to influence that decision even if it was collected in Japan in a population not directly relevant to the paediatric indication.

4. The comments are generally agreed. The last point, that there are data to support the use of daptomycin in treatment of SAB associated with septic arthritis is not conclusive.

Question/comment 8

Evaluator's comment regarding PSUR 12 September 2014 to 11 September 2015

> *Even mild hearing loss in very young children could impact language development and may not be recognised as an AE in clinical trials unless prospectively assessed.*

Sponsor's response

The sponsor acknowledges that there may be difficulty with safety assessments in very young children with respect to assessment of hearing loss. However, there has been no suggestion of a causal association of ototoxicity with systemic exposure to daptomycin in nonclinical or clinical experience. The new information on potential for adverse effects of daptomycin when applied topically was not deemed a new safety concern associated with systemic exposure to daptomycin in patients at the recommended therapeutic doses in the target indications. The article by Oshima et al., described mild but statistically significant hearing impairment in guinea pigs following topical administration. Outer hair cells were not damaged by daptomycin, in contrast to the severe damage associated with gentamicin in the control group. The topical concentrations studied in this model are many magnitudes higher than the anticipated systemic exposure at the recommended human therapeutic dose. This study did not suggest that there was a risk for ototoxicity associated with the recommended human clinical therapeutic doses of daptomycin. The MAH does not recommend any other routes of daptomycin administration than intravenous administration.

The sponsor has continued to monitor peripheral neuropathy and central nervous system disorders in postmarketing experience with daptomycin, and specifically for new reports of events in paediatric patients. There have been few reports of hearing impairment or ototoxicity in patients exposed to daptomycin over the 14 years of postmarketing experience. Review of cumulative data and individual case reports has not suggested a causal association of daptomycin with hearing impairment in adults or in paediatric patients.

Evaluator's response

There is no recommendation proposed in relation to this pre-clinical finding.

Question/comment 9

Regarding evaluator's comment on safety overall:

> *Examination of safety does not uncover any obvious safety signal. Numbers are relatively small and severity of the underlying condition is such as to preclude determination of occurrence of uncommon or rare events related to treatment with daptomycin. Of most particular concern is the lack of any data on children 1 to < 2 years of age while proposing a higher dose than has previously been approved for children of that age.*

Sponsor's response

The sponsor respectfully asserts that Cubicin should be indicated for the treatment of paediatric patients 1 to 17 years of age with Staphylococcus aureus bacteraemia (SAB). In the DAP-PEDBAC-11-02 trial of paediatric patients with SAB, the sponsor acknowledges that no patients 1 to < 2 years of age were treated with Cubicin. However, due to several factors as outlined below, the sponsor contends that:

1. the proposed Cubicin dose (12 mg/kg) in this age group would provide comparable exposures to adults and paediatric patients (2 to 17 years) in whom the efficacy and safety of Cubicin as treatment for SAB has been studied, and bridging data support an expectation of similar efficacy and safety; and
2. paediatric patients 1 to < 2 years of age with SAB should have the opportunity to derive clinical benefit from Cubicin, which is of substantial clinical relevance given the limited number of antibiotics indicated for SAB in the paediatric population.

The infant age group has been challenging to enrol in clinical trials for antimicrobial products such as Cubicin due to the limited size of the eligible patient population. However, the medical need for treatment for SAB is still unmet, though the number of patients is small.

Since the pharmacological mechanism of action of daptomycin is not age-dependent, the sponsor asserts that the efficacy, pharmacokinetic (PK), and safety data for the DAP-PEDBAC- 11-02 trial as well as the existing PK and integrated safety data for the use of Cubicin in paediatric patients, including those with complicated skin and skin structure infections (cSSSI) can be extrapolated to support the use of Cubicin in the infant paediatric population (1 to < 2 years of age) with SAB. The efficacy, safety, pharmacokinetic (PK), and exposure/safety considerations for the use of Cubicin in paediatric patients (1 to < 2 years of age) with SAB are discussed below.

Efficacy considerations: In the DAP-PEDBAC-11-02 trial, the efficacy of daptomycin and comparator study drug was similar across the age cohorts. With comparable PK exposure, there is no expectation that efficacy in patients 1 to < 2 years of age would differ from that observed across the age cohorts. The extrapolation of efficacy to paediatric patients 1 to < 2 years of age is possible because daptomycin targets external pathogens (that is, in the case of SAB, *S. aureus*), and the mechanism of action is not age dependent. Therefore, it is not expected that the response to daptomycin treatment or the daptomycin exposure-response relationship would be different across age groups.

Safety considerations: Safety data describing the safety analysis by age group from the DAP-PEDBAC-11-02 trial as well as the integrated Phase IV safety findings and integrated paediatric program safety analyses are summarised in the supplied appendix [not included here]. The overall safety conclusions from the DAP-PEDBAC-11-02 trial (including by age group analyses) as well as the integrated paediatric cSSSI and bacteraemia studies and all paediatric studies are as follows:

- In the DAP-PEDBAC-11-02 trial, daptomycin was well tolerated in paediatric subjects with SAB at treatment durations of up to 42 days. The safety profile of daptomycin was consistent across all 3 age groups (2-6 years (no subjects < 2 years of age were enrolled), 7-11 years, and 12-17 years) and comparable to standard of care in this trial. This analysis supports the Applicant's position that the use of daptomycin is well-tolerated as compared to the comparator in all 3 age groups in the DAP-PEDBAC-11-02 trial. Moreover, this analysis supports the safety profile of daptomycin at higher exposures to treat SAB as compared to the exposure required for cSSSI in the paediatric population.
- The analysis of the number of treatment-emergent adverse events (TEAEs) per 100 IV treatment person-days for all ages and age cohorts by treatment group in the DAP-PEDBAC- 11-02 trial supports the sponsor's position that the use of daptomycin is well-tolerated as compared to the comparator in all 3 age groups in the DAP-PEDBAC- 11-02 trial. This analysis also supports the safety profile of daptomycin at higher exposures to treat SAB as compared to the exposure required for cSSSI in paediatric patients.

- The 2 integrated safety analyses do not identify a new safety signal associated with a specific age group and confirm the previously identified and potential risks observed in adult studies:
  - Integrated safety data from the two Phase IV paediatric daptomycin studies (paediatric cSSSI trial (Study DAP-PEDS-07-03) and paediatric bacteraemia trial (Study DAP-PEDBAC-11-02); overall there were 30 subjects who were < 2 years of age in the daptomycin group (all from the DAP-PEDS-07-03 trial)) for which the corresponding safety data are presented in the Summary of Clinical Safety and also summarised in an appendix.
  - Integrated data from the two Phase IV studies and three Phase I; overall, there were 54 subjects (that is, an 80% increase from integrated data from the two Phase IV studies) who were < 2 years of age in the daptomycin group, including 30 subjects from the DAP-PEDS-07-3 trial and an additional 24 subjects < 2 years of age from Phase I studies.

The safety analyses as well as the PK data (see below) support the sponsor's position that there is no expectation of an age group-specific TEAE profile for paediatric patients 1 to 17 years old, such as clinically relevant differences in the frequency or severity of changes in markers for skeletal muscle toxicity (creatine phosphokinase (CPK) elevations), neurologic disorders, hypersensitivity reactions, or other safety concerns associated with daptomycin from clinical trial experience in adults. At this time, the Applicant proposes to monitor safety experience in patients 1 to < 2 years of age and treated with daptomycin by collection of spontaneously reported events as well as periodic literature searches.

PK considerations: The daptomycin PK data from the DAP-PEDBAC-11-02 trial are comparable to those obtained with the approved 6 mg/kg dose in adult SAB/RIE (right-sided infective endocarditis) patients. Such PK data are consistent with the observed efficacy profile of daptomycin to treat SAB in the paediatric population.

In order to extrapolate the efficacy from adult and older children with SAB to infants 1 to < 2 years of age with SAB based on PK, simulations have been conducted.

As the DAP-PEDBAC- 11-02 trial did not treat any paediatric SAB patients 1 to < 2 years of age, steady state AUC (AUC_{ss}) in children 1 to < 2 years receiving 60-minute IV infusion of 12 mg/kg daptomycin once daily was simulated (N=1000).

Although PK data were obtained in those ≥ 2 years of age, in order to compare exposures in patients 1 to < 2 years of age with other paediatric age groups, AUC_{ss} was also simulated for paediatric SAB patients 2 to 17 years of age receiving the age-specific, weight-based doses: 2 to 6 years, 12 mg/kg 60-minute IV infusion (N=1000), 7 to 11 years, 9 mg/kg 30 minute IV infusion (N=1000), and 12 to 17 years of age, 7 mg/kg 30 minute IV infusion (N=1000).

The 'virtual paediatric populations' used in the simulations were generated from age and body weight distributions using a generalised additive model on age normative data for male and female paediatric subjects based on the growth charts at the Centers for Disease Control and Prevention (CDC). Steady state C_{max} and minimum plasma concentration (C_{min}) for paediatric SAB patients were also simulated. For the simulation, the previously developed paediatric population PK model, which was developed with PK data from paediatric subjects 3 months to 17 years of age, was used. As described in the SAB paediatric dossier, this model was used to generate Bayesian PK estimates in paediatric patients with SAB in Study DAP-PEDBAC-11-02 based on the sparsely collected PK samples.

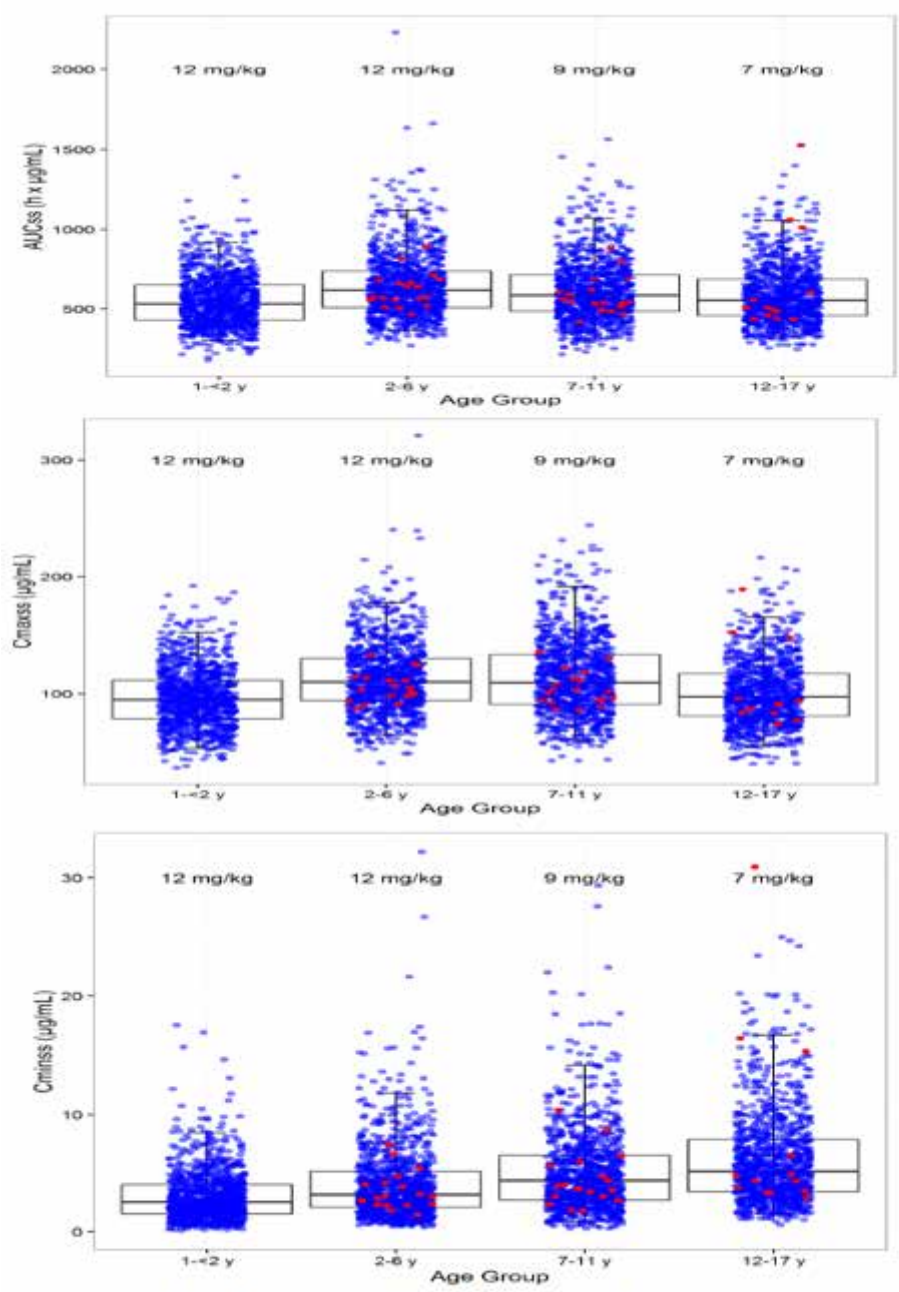
As shown in Figure 2, the simulated distributions for daptomycin steady-state exposures (AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$) in paediatric SAB patients 2 to 17 years of age receiving the age-specific, weight-based doses were consistent with those from the Bayesian PK estimates

from the DAP-PEDBAC-11-02 trial. This confirms the appropriateness and rigor of the use of the simulated data across the paediatric population, including in those whereby PK data were not obtained (that is, subjects 1 to < 2 years of age). The simulated distributions for AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$ in paediatric SAB patients 1 to < 2 years receiving a 60 minute IV infusion of 12 mg/kg daptomycin substantially overlapped with the corresponding distributions of other paediatric age groups at the recommended age-specific, weight-based doses, with no clear monotonic trends for simulated AUC_{ss} or $C_{max,ss}$ across age groups. Consistent with an increase in weight-normalised CL with decreasing age, the central tendency of the simulated $C_{min,ss}$ was slightly lower in younger paediatric patients compared to adolescents.

Table 13 provides the descriptive statistics of daptomycin AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ for paediatric SAB patients from these simulations. Although, in general, predicted exposure in those 1 to < 2 years of age may be slightly less than those in older paediatric patients, the mean (standard deviation) AUCss for paediatric SAB patients 1 to < 2 years receiving the 60-minute IV infusion of 12 mg/kg daptomycin was 551 (161) µg·hr/mL and was comparable to the AUCss of 545 (296) µg·hr/mL in adults receiving the approved 6 mg/kg dose for SAB/RIE whereby efficacy and safety has been established.

In summary, the simulation results support comparable AUCss distributions of paediatric SAB patients 1 to < 2 years receiving 60-minute IV infusion of 12 mg/kg daptomycin with that of other paediatric age groups (2 to 17 years of age) receiving the recommended age-specific, weight-based doses, and with adult SAB/RIE patients receiving the approved 6 mg/kg dose. These data support age-specific, weight-based dosing across paediatric population. The comparable AUC distributions in paediatric and adult SAB patients support similar probabilities of attaining the antibacterial AUC/MIC target among all paediatric age groups, including children 1 to < 2 years of age. Overall, given the primary role of renal excretion in the elimination of daptomycin with no metabolism identified in in vitro microsome assessments, typical ontogenic maturational factors such as those impacting drug metabolising enzymes or transporters are not expected and support PK extrapolation from patients > 2 years into those 1-< 2 years of age based upon allometric approaches.

Figure 2: Distributions of simulated steady state daptomycin AUC (AUC_{ss}), C_{max} ($C_{max,ss}$) and C_{min} ($C_{min,ss}$) (box plots and blue symbols) for paediatric SAB patients 1 to < 2 years receiving the 60-minute 12 mg/kg IV infusion are comparable to those for paediatric SAB



Box, 25th and 75th Percentiles; Line Within Box, Median; Error Bars, 2.5th and 97.5th Percentiles. Red Symbols Represent Posteriori Bayes PK Exposure Estimates for Pediatric SAB Patients with PK Data in Study DAP-PEDBAC-11-02

Table 13: Descriptive statistics of simulated steady state daptomycin AUC (AUC_{ss}), C_{max} ($C_{max,ss}$) and C_{min} ($C_{min,ss}$) in paediatric SAB patients receiving the age-specific, weight-based doses evaluated in Study DAP-PEDBAC-11-02

Age Group	Dose	Mean (SD) Median [2.5th, 97.5th Percentile]		
		$C_{min,ss}$ (µg/mL)	$C_{max,ss}$ (µg/mL)	AUC_{ss} (hr x µg/mL)
1-2 years	12 mg/kg	3.03 (2.17) 2.51 [0.510, 8.46]	96.9 (25.6) 94.9 [53.8, 153]	551 (161) 531 [301, 918]
2-6 years	12 mg/kg	4.03 (3.08) 3.14 [0.739, 11.8]	114 (29.7) 111 [65.0, 178]	647 (200) 617 [362, 1121]
7-11 years	9 mg/kg	5.05 (3.48) 4.33 [0.890, 14.1]	114 (32.3) 110 [61.7, 192]	613 (191) 585 [318, 1070]
12-17 years	7 mg/kg	6.11 (3.86) 5.12 [1.52, 16.7]	101 (28.0) 97.4 [56.1, 166]	587 (180) 553 [327, 1056]
Adults†	6 mg/kg	6.90 (3.54) 6.24 [2.42, 16.6]	108 (143) 75.2 [25.9, 370]	545 (296) 469 [258, 1060]

†Post hoc PK parameters estimated from adult patients with creatinine clearance >80 mL/min receiving 6 mg/kg dose in the Phase 3 study DAP-IE-01-02 using the final adult population PK model. N=62 for AUC and C_{max}; N=61 for C_{min}

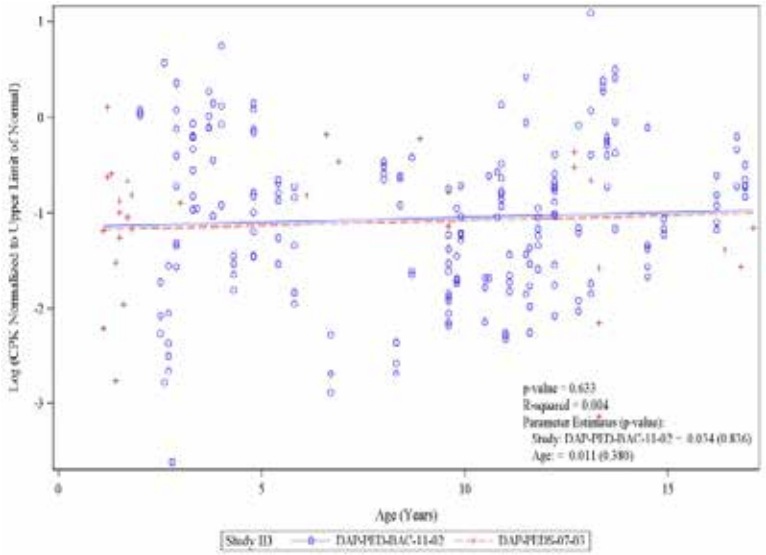
Exposure-Safety considerations: An increase in CPK is correlated with increases in daptomycin dose/exposure, and is an adverse experience of clinical interest. In the paediatric bacteraemia dossier, the Applicant included an exploratory analysis that demonstrated no clinically meaningful correlation between CPK increase and daptomycin AUC in pooled paediatric cSSSI and SAB patients in Studies DAP-PED-07-03 and DAP-PEDBAC-11-02 receiving the age-specific, weight based doses.

In consideration of the comment, as the DAP-PEDBAC-11-02 trial did not treat infant SAB patients 1 to < 2 years of age, an additional exploratory analysis was conducted to assess the relationship between natural-log transformed CPK normalised to upper limit of normal (ULN) and age in the two paediatric studies (Study DAP-PED-07-03 for cSSSI and Study DAP-PEDBAC-11-02 for SAB). As in the previously submitted exploratory PK-CPK analysis, CPK was normalised to the upper limit of normal (ULN) to reduce variability in CPK values due to the use of local laboratories, and natural-log transformation was used because normalised CPK is log-normally distributed.

As shown in Figure 3, log(CPK normalised to ULN) was not correlated to age for either paediatric patient population, with no significant difference between the two studies. This result supported that CPK from the two studies could be pooled for a single analysis, and that the lack of correlation between log(CPK normalised to ULN) and age could be extended to paediatric SAB patients 1 to < 2 years of age. For each trial, the corresponding slope of the regression line is virtually horizontal (parameter estimate of age p-value=0.380).

Together with the observations that (1) the simulated exposure distribution in paediatric SAB patients 1 to < 2 years of age receiving the 60-minute 12 mg/kg daptomycin IV infusion is not higher than that in paediatric SAB patients 2 to 6 years of age receiving the same dosing regimen, and (2) the PK-CPK analysis that demonstrated no clinically meaningful increase in CPK at the exposures achieved with the proposed paediatric SAB and the approved cSSSI doses, the CPK-age analysis supports that no clinically meaningful increase in CPK for paediatric SAB patients 1 to < 2 years at the 60 minute 12 mg/kg daptomycin IV infusion is expected.

Figure 3: Lack of a correlation between log (creatine kinase normalised to upper limit of normal) and age in paediatric patients with complex skin and skin structure infection in Study DAP-PEDS-07-03 or with bacteraemia in Study DAP-PEDS-BAC-11-02



Conclusions: As discussed above, the efficacy and safety profiles of daptomycin was consistent across all 3 age groups in the DAP-PEDBAC-11-02 trial, and integrated safety analyses of paediatric SAB and cSSSI patients did not identify a new safety signal associated with a specific age group. The PK and exposure/safety (including CPK) analyses support the sponsors position that the safety profile of paediatric SAB patients 1 to < 2 years receiving 60-minute IV infusion of 12 mg/kg daptomycin is not expected to be different from that in the other paediatric age groups receiving the proposed age-specific, weight-based SAB dosing regimens, and that doses of 12 mg/kg in paediatric patients 1 to < 2 years are expected to result in comparable PK, efficacy, and safety as those established in older paediatric patients (2 to 17 years) and adults. Based on the totality of the evidence, the Applicant respectfully asserts that the overall benefit-risk of the use of Cubicin in paediatric patients 1 to < 2 years of age remains favourable and supports the dose recommendations and an indication in paediatric patients 1 to < 2 years of age with SAB.

Evaluator's response

It is accepted that all patients should have access to effective and safe treatment for SAB. The challenge in enrolling paediatric patients in clinical trials is acknowledged.

It is considered biologically plausible that with comparable exposure, efficacy in the age group of 1 to < 2 years should be similar to that of older children and adults.

With respect to safety, it is noted that the dose recommendation for treatment of bacteraemia in the youngest patients differs from, and is higher than that approved for treatment of cSSSI: 12 mg/kg for up to 42 days vs. 10 mg/kg for up to 14 days respectively.

The requested extension of indication is for SAB bacteraemia. Table 14 is the Australasian Society for Infectious Diseases recommendation with respect to duration of treatment of SAB;[13] which specifies 7 to 14 days. The protocol specified duration of treatment for patients 1 to 11 years was 28 days.

[13] https://www.asid.net.au/documents/item/1243

Table 14: ANZPID-ASAP Guidelines for antibiotic duration and IV-oral switch in children

Staphylococcus aureus bacteraemia	7-14 days [D-IV]	No oral switch	MSSA: 7-14 days [D-IV] MRSA: 14 days [D-IV] Longer if persistent positive cultures or complications [D-expert opinion]	If associated endocarditis, refer to endocarditis guideline If associated osteomyelitis/septic arthritis, IV duration may be shortened to 4-7 days if improving quickly and uncomplicated, with remainder oral [C-III]

The first round evaluator made the assessment that the examination of safety did not uncover any obvious, new or unexpected safety signal.

With respect to population PK analysis, it is agreed that the simulated results appear reassuring. Simulations based on 'virtual paediatric populations' are considered informative but not definitive. Simulations that include few measure data points may be biased due to sampling errors, even more so, simulations based on no actual measured data points.

Indication

First round indication

The indication proposed by the sponsor is:

> *Cubicin is also indicated in paediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates.*

The first round evaluator noted the approved indication for treatment of cSSSI is limited to patients who have intolerance to alternative agents or have failed other therapy. For consistency, it was recommended that this also applies to the SAB indication.

The first round recommended indication was:

> *Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy, and when caused by orgasms know to be susceptible to daptomycin.*

Post-first round response

The sponsor has not adopted the revised text proposed by the evaluator for the paediatric SAB indication since the efficacy study was done in first line therapy, not salvage therapy.

In the post-first round response, the sponsor proposes retention of the originally proposed indication with only minor editorial change, that is:

> *Cubicin is indicated for the treatment of patients aged 1 to 17 years for S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates.*

Second round response

The response appears to imply that the paediatric indication relevant to cSSSI was based on study of salvage therapy. Study DAP-PEDS-07-03, included in the cSSSI extension of indication application PM-2015-03531-1-2, did not specify rescue treatment in the statement of objectives or in the inclusion criteria. The objectives were to assess the safety and efficacy and PK of age dependent doses of IV daptomycin administered for up to 14 days in comparison with SOC therapy in paediatric subjects aged 1 to 17 years with cSSSI caused by Gram-positive pathogens.

The pivotal SAB Study DAP-PEDBAC-11-02 included limited numbers of participants. Six of the 51 daptomycin treated patients (11.8%) were enrolled at a site which reportedly had significant difficulties with GCP. Despite the sponsor's conclusions in the post-first round response, the results generated by this site are considered unreliable.

There were no study participants aged 1 to < 2 years. Patients were treated with higher doses of daptomycin than the approved doses for cSSSI. Doses were based on population PK predictions in turn based on very limited observed data with no PK data for the age group 1 to < 2 years. Furthermore, as AUC results based on observed PK parameters have not been submitted, it is not possible to compare the observed and modelled results in the study population.

While there were no safety signals detected, safety has still to be extensively studied. For very young children, muscular and neurological safety concerns are difficult to assess clinically. The time constraint of the study limited assessment of neurological and muscular problems that may only become apparent as the time comes for developmental milestones to be passed.

It is likely that the once daily dose proposed would be attractive to practitioners, inclining them to prescribe daptomycin in the first instance; however, the current SOC treatment options have long histories of use. The recommendation remains that daptomycin should not be first line treatment.

The proposal to include (bacteraemia) '*caused by methicillin-susceptible and methicillin-resistant isolates*' is not recommended. Susceptibility to daptomycin is the more relevant consideration.

The FDA approved indication is:

> *Cubicin is a lipopeptide antibacterial indicated for the treatment of: Staphylococcus aureus bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age).*

The EU approved indication is:

> *Adult and paediatric (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 paediatric patients, use in bacteraemia should be associated with cSSTI.*

Based on the considerations outlined above and consistent with the TGA approved cSSSI indication, the recommended indication is:

> *Cubicin is indicated for the treatment of daptomycin sensitive Staphylococcus aureus bloodstream infections (bacteraemia) in paediatric patients aged 1 to 17 years with intolerance to alternative agents or who have failed on other therapy*.

Second round benefit-risk assessment

It is recommended that indication is extended to the paediatric patient population aged 1 to 17 years with SAB.

The sponsor is advised to urgently provide the required '*Assessment of Risk of Development of antimicrobial resistance'* for review by the TGA. In addition, the sponsor should indicate whether a post-approval antibiotic resistance local (Australian) surveillance program is planned/has been set up and whether its details are included in the risk management plant (RMP).

Recommended indication

The recommended indication is as follows:

> *Cubicin is indicated for the treatment of daptomycin sensitive Staphylococcus aureus bloodstream infections (bacteraemia) in paediatric patients aged 1 to 17 years with intolerance to alternative agents or who have failed on other therapy.*

Dosage and administration recommendation

Patients 12 to 17 years: 7 mg/kg once every 24 hours infused over 30 minutes.

Patients 7 to 11 years: 9 mg/kg once every 24 hours infused over 30 minutes.

Patients 1 to 6 years of age: 12 mg/kg once every 24 hours infused over 30 minutes.

- The recommended doses are for patients with normal renal function. Dose adjustment for paediatric patients with renal impairment has not been established.
- Local treatment guidelines should be consulted in determining duration of treatment. In the paediatric *S. aureus* bacteraemia Study DAP-PEDBAC-11-02 the mean (median) duration of IV daptomycin was 12 (11) days: range 1 to 44 days.
- No patient with SAB aged 1 to < 2 years was included in Study DAP-PEDBAC-11-02. Dosages are based on population PK modelling.

Table 15: Recommended dosage

Staphylococcus aureus bloodstream infections (bacteraemia)

The recommended dosage regimens based on age for paediatric patients with *S. aureus* bloodstream infections (bacteraemia) are shown in Table 13.

Table 13: Paediatric Patients (1 to 17 years of age) with *S aureus* bacteraemia

Age group	Dosage*	Duration of therapy
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	• Local treatment guidelines should be consulted in determining duration of treatment. In the paediatric S. aureus bacteraemia (SAB) study the mean duration of IV daptomycin was 12 days (median 11 days; range 1-44 days). • No patient with SAB aged 1 to < 2 years was included in paediatric SAB study. Dosages are based on population pharmacokinetic modelling.
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
1 to 6 years	12 mg/kg once every 24 hours infused over 60 minutes	

* Recommended dosage is for paediatric patients (1 to 17 years of age) with normal renal function.
Dosage adjustment for paediatric patients with renal impairment has not been established.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[14]

- The sponsor has applied to extend the indications of daptomycin (Cubicin) which is currently approved for the treatment of complicated skin and skin structure infections in adults and paediatric patients (1 year and above), and staphylococcus aureus bloodstream infections (bacteraemia) in adults. The current submission seeks to extend the bacteraemia indication to include paediatric patients (1 to 17 years of age).
- The sponsor has submitted EU-RMP version 10.1; dated 17 May 2017; data lock point (DLP) 11 September 2016, and Australian specific annex (ASA) version 1.2; dated 27 November 2017 in support of this application. The most recently evaluated EU-RMP was Version 9.1 (dated 1 October 2015; DLP 11 September 2014) and ASA Version 1.1 (dated 30 October 2015) through submission PM-2015-03531-1-2.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 16: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Severe skeletal muscle toxicity	ü[1]	–	ü	ü[2]
	Reduced susceptibility to daptomycin in *S. aureus*	ü[1]	–	ü	ü[3]
	Peripheral neuropathy	ü[1]	–	ü	–
	Severe hypersensitivity reactions (including pulmonary eosinophilia and severe cutaneous reactions)	ü[1]	–	ü	–
	Eosinophilic pneumonia	ü[1]	–	ü	–
Important	Bone marrow toxicity	ü[1]	–	ü	–

[14] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
potential risks	Severe hepatotoxicity	ü[1]	–	ü	–
	Dysregulation of in vivo coagulation	ü[1]	–	ü	ü[2]
Missing information	Patients with hepatic impairment	ü	–	ü	–
	Pregnant or lactating women	ü	–	ü	–

1) Specific adverse reaction follow-up questionnaire; 2) Dosing card for physician 3) Leaflet for laboratories

- Routine pharmacovigilance, including specific adverse reaction follow-up questionnaires have been proposed to monitor the identified safety concerns. Routine and additional risk minimisation activities have been proposed to mitigate the safety concerns as indicated in the table above. This is acceptable from the RMP perspective.
- The pharmacovigilance and risk minimisation approaches described above were previously accepted by the TGA, and remain acceptable given the similarity of the summary of safety concerns and similar population for the proposed extension of indication. This is acceptable from the RMP perspective.

Post-second round update

The sponsor has provided reasonable response to the outstanding recommendations in the second round RMP evaluation report. There are no outstanding RMP issues with this submission.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Cubicin EU-Risk Management Plan (RMP) (version 10.1, dated 17 May 2017, data lock point 11 September 2016), with Australian Specific Annex (version 1.2, dated 27 November 2017), included with submission PM-2017-04652-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Overview

Daptomycin, a cyclic lipopeptide antibacterial agent, is derived from the fermentation of Streptomyces roseosporus. It exhibits concentration-dependent bactericidal activity against aerobic Gram positive organisms with in vitro activity encompassing most

clinically relevant Gram-positive bacteria including isolates resistant to methicillin, vancomycin and linezolid. It binds to bacterial membranes and causes a rapid depolarization of membrane potential resulting in inhibition of protein, DNA and RNA synthesis and bacterial cell death. The mechanism of action is distinct from that of any other antibiotic.

Surveillance studies have demonstrated a daptomycin minimum inhibitory concentration for 90% of specific organisms (MIC_{90}) of 0.5 µg/mL for both MSSA and MRSA with > 99% of MRSA isolates categorised as susceptible by the US FDA; and the European Committee of Antimicrobial Susceptibility Testing and Clinical and Laboratory Standards Institute breakpoints.

S. aureus is a leading cause of bacteraemia. In Australia, the incidence of SAB per 100,000 person-years between 2006 and 2007 was 65 for the Northern Territory and 11.2 for Australia overall. Mortality rates are known to vary significantly with patient age, clinical manifestation, co-morbidities and methicillin resistance. Age has been found to be the strongest predictor of mortality in Australia.

A prospective cohort study utilised data from the Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis cohort for 1153 children with SAB from birth to less than 18 years in paediatric and general hospitals across Australia and New Zealand, between 1 January 2007, and 31 December 2012. In this study, 30 day mortality in 1153 Australasian children was 4.7% (50/1073 children with complete mortality data). Mortality risk groups identified were age < 1 year; Māori/Pacific children; those with pneumonia, endocarditis, or sepsis syndrome or no focus; and those treated with vancomycin for methicillin-susceptible SAB. MRSA bacteraemia and hospital-onset infection were not associated with higher risk.

Australian Therapeutic Guidelines recommend flucloaxacillin (or cephazolin/cefalotin for hypersensitivity to penicillin) and vancomycin in combination for treatment of gram-positive cocci identified by gram-stain in blood cultures whilst awaiting the results of cultures and susceptibility testing.

The sponsor's rationale for the current submission is that few antibiotics with activity against MRSA are currently available, and fewer still have had their safety and efficacy evaluated in paediatric patients. Clinical studies and post marketing pharmacovigilance have demonstrated a well-characterised safety profile for daptomycin in adults. To date, the safety of daptomycin in the paediatric population appears to be comparable to that observed in adults.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Revised indication and dosage recommendations are based on Study DAP-PEDBAC-11-02 evaluating safety, efficacy and PK of daptomycin versus SOC antibiotics in treatment of SAB in children aged 1 to 17 years. Additional support from population PK modelling, simulation exposure in paediatric and adults patients with SAB and PSUR end date September 2016.

Pharmacology

Pharmacokinetics

Based on animal models, it is assumed that mean steady state systemic exposure AUC is the principle PK/PD driver. The mean and SD PK parameters for daptomycin at steady state in adults following IV administration of daptomycin over a 30 minute period at 6 mg/kg q24h to healthy young adults showed that AUC was 632 µg*h/mL (SD = 78), 90% of whom had AUC exposures between 270 to 1151 µg*h/mL. Young children are likely to have increased clearance of daptomycin and thus it is likely that C_{trough} results will be lower. To produce exposures equivalent to those in adults, higher doses are required in children.

Study DAP-PEDBAC-11-02 was a Phase IV, partially blinded, multicentre, multinational study assessing safety and efficacy of IV daptomycin versus SOC in treatment SAB in patients aged 1 to 17 years. A total of 55 patients were randomised to daptomycin treatment at doses proposed for registration. Fifty-one (51) daptomycin-treated patients each provided ≥ 1 sample for PK analysis

A previously developed paediatric population model (CUBI-PCS-106) was based on the 3 Phase I paediatric pharmacokinetic trials (Studies DAP-PEDS-05-01, DAP-PEDS-07-02, and DAP-PEDS-09-01) and the Phase IV safety and efficacy trial in paediatric cSSSI patients (Study DAP-PEDS-07-03).

The clinical evaluation report accepted that the AUC distributions in paediatric bacteraemia patients in Study DAP-PEDBAC-11-02 at the evaluated dosing regimens were comparable to the AUC distribution in adult bacteraemia patients receiving the 6 mg/kg dose. These results support the appropriateness of the recommended paediatric dosing regimens.

Table 17: Mean (covariance (%)) of daptomycin pharmacokinetics in paediatric SAB patients from Study DAP-PEDBAC-11-02 estimated using paediatric population pharmacokinetics modelling

Parameters	Mean (CV%)		
	1 to 6 years (Dose: 12 mg/kg) N=19	7 to 11 years (Dose: 9 mg/kg) N=19	12 to 17 years (Dose: 7 mg/kg) N=13
Infusion duration (hr)	0.5	0.5	1.0
C_{max} (µg/mL)	106 (12.0)	104 (13.8)	104 (34.1)
C_{min} (µg /mL)	3.46 (46.0)	4.35 (51.4)	8.00 (102.7)
AUC_{0-24} (µg*hr /mL)	620 (17.6)	579 (20.1)	656 (51.0)
CL/WT (mL/hr/kg)	19.9 (17.1)	15.9 (17.7)	12.4 (31.3)
V_{ss}/WT (mL/kg)#	137 (9.4)	126 (7.4)	115 (14.1)
Terminal elimination half-life (hr)	5.14 (11.0)	6.01 (13.7)	7.52 (30.1)

As Study DAP-PEDBAC-11-02 did not treat any paediatric SAB patients 1 to < 2 years of age, area under the curve at steady state (AUC_{ss}) in children 1 to < 2 years receiving 60 minute IV infusion of 12 mg/kg daptomycin once daily was simulated. Simulation results support comparable AUC_{ss} distributions of paediatric SAB patients 1 to < 2 years receiving 60 minute IV infusion of 12 mg/kg daptomycin with that of other paediatric age groups (2 to 17 years of age).

Pharmacodynamics

The clinical evaluation report has discussed development of daptomycin resistance under Section: Pharmacodynamics [not included in this AusPAR]. A resistance risk assessment to address TGA guidelines has subsequently been submitted.

Efficacy

Study DAP-PEDBAC-11-02

Study DAP-PEDBAC-11-02 was a Phase IV, open label (evaluator-blinded), comparative, multicentre, multinational study assessing safety and efficacy of IV daptomycin versus SOC antibiotics in treatment of patients aged 1 to 17 years with SAB, conducted between March 2013 and January 2016 in North America, Europe, Central/South America, and Australia/Asia with twenty-five sites enrolling participants.

For study purposes, SAB was defined as uncomplicated or complicated as follows:

- Uncomplicated bacteraemia: the absence of positive cultures for *S. aureus* obtained 2 to 4 days after the initiation of study therapy; no fever after 72 hours of initiating effective therapy; no evidence of metastatic sites of infection; no evidence of endocarditis; and no implanted devices.
- Complicated bacteraemia: that occurring in patients with positive blood cultures who did not meet the above criteria for uncomplicated bacteraemia.

Males or females between the ages of 1 and 17 years were included with proven or probable SAB defined as:

- *Proven infections*: *S. aureus* identified in ≥ 1 blood culture bottle by culture methods or by rapid diagnostic test obtained within 3 days before the first dose of study medication.
- *Probable infections*: a preliminary blood culture result demonstrating Gram-positive cocci suggestive of staphylococcal infection. If the final blood culture yielded coagulase negative staphylococci (CoNS) after enrolment, only high risk patients with persistent bacteraemia documented by multiple cultures taken on separate days or from different sites yielding the same organism could continue on study therapy.

Study objectives

The primary objective was to assess the safety of IV daptomycin versus SOC antibiotics in treatment of paediatric patients 1 to 17 years of age with bacteraemia.

Clinical efficacy was a secondary objective with assessment based on the blinded investigators' clinical assessment of signs and symptoms at the EOIV or end of oral therapy for those who received oral study drug and at TOC/Safety Visit. Microbiological efficacy was a secondary objective reported as microbiological success or failure. All baseline infecting pathogens eradicated with no source of infection present within 7 days from start of effective IV antibiotics for uncomplicated bacteraemia, and within 10 days for complicated bacteraemia. Overall outcome was a success if both clinical and microbial outcomes were successful.

Treatment groups

Treatment assignment stratified by age was based on a centralised computer generated schedule in a 2:1 ratio to daptomycin or comparator. The sponsor, medical and microbiology teams were to remain blinded through the study.

Eighty-two (82) patients were randomised, 55 to daptomycin and 27 to the comparator. The majority were enrolled in the US (36) and Ukraine (25). Overall, 70 participants (86.4%) completed IV treatments. Forty-eight (58) (59.3%) converted to oral study

medication: 32 (58.2%) in the daptomycin arm and 16 (61.5%) in the comparator arm. Of these, 46 (95.8%) completed oral study treatment.

In the 1 to 6 year age group, 22 were randomised to daptomycin and 11 to comparator. 18 (81.8%) completed IV therapy in daptomycin group and 10 completed comparator IV treatment (100% of those were treated). Reasons for discontinuation included: AE, 1; persistent positive blood cultures, 1; and subject/parent/legal guardian decision, 1 participant.

In the 7 to 11 year age group, 19 were randomised to daptomycin and 9 to comparator. 17 (89.5%) completed IV in the daptomycin group and 8 (88.9%) completed comparator IV treatment. Reasons for discontinuation included: AE, 1; persistent positive blood cultures, 1; and subject/parent/legal guardian decision, 1 participant.

In the 12 to 17 year age group, 14 were randomised to daptomycin and 7 to comparator. 12 (85.7%) completed IV in the daptomycin group and 5 (71.4%) completed comparator IV treatment. Reasons for premature discontinuation of IV treatment included: 'other' (no set up of research home health care; not evaluable at Baseline) 2; AE, 1 and participant/parent/legal guardian decision, 1 participant.

The safety population included 81 participants (daptomycin 55; comparator 26).

The modified intention to treat (mITT) population included 76 participants (daptomycin 52; comparator 24). 1 comparator-treated did not receive study drug, 3 daptomycin-treated and 2 comparator-treated participants did not meet clinical criteria for infection at baseline.

The mMITT population included 73 participants (daptomycin51; comparator 22). Three (3) participants without proven SAB at baseline were excluded.

The clinical efficacy (CE) population included 52 participants (daptomycin 40; comparator 12).

Analysis populations

Participant ranged from 2 to17.6 years of age, the majority were white (75.3%). Overall there were proportionally more males (66.7%) than females although in the comparator group aged 1 to 6 years there were more females than males. Overall, 91.4% of participants had normal creatinine.

All participants in the safety population had baseline Gram-positive, aerobic blood cultures. Overall, 73 participants had proven SAB at baseline including 51 (92.7%) daptomycin-treated and 22 (84.6%) comparator treated participants. MSSA infection was detected in 80.0% of the daptomycin arm and 73.1% of the comparator arm, with MSRA infections detected in 12.7% of the daptomycin arm and 11.5% of the comparator arm.

In the safety population bacteraemia was classified as complicated in 56.6%, with a lower proportion in the daptomycin group (51.9%) than in comparator group (66.7%). The most common reasons for classification as complicated were:

- Fever after 72 hours of study therapy: daptomycin 14 (26.9%) comparator 9 (37.5%)
- Metastatic foci of infection: daptomycin11 (21.2%); comparator 8 (33.3%)
- Positive blood cultures > 4 days: daptomycin 12 (23.1%): comparator 5 (20.8%).

In the 1 to 6 years age group in safety population (daptomycin n=22, comparator n=10) microbiological enrolments was by blood culture and gram stain in 86.4% of daptomycin group and 100% in comparator group. Diagnosis was proven in 90.9% in daptomycin group and 88.9% in comparator group, and probable for other participants. MSSA infecting organisms were 77.3% in daptomycin group and 70% in comparator group. MRSA infecting organisms were 13.6% in daptomycin group and 10% in comparator

group. Coagulase-negative Staphylococci infectious organisms were 9.1% for daptomycin group and 10.1% for comparator group.

Bacteraemia classification was uncomplicated in 45.4% in daptomycin group versus 33.3% in comparator group; complicated in 45.5% in daptomycin group versus 70% in comparator group and not classified in 9% in daptomycin group versus 0% in comparator group.

Most common types of infection were:

- device (catheter) related: daptomycin 40% versus comparator 10%
- osteomyelitis: daptomycin 15% versus comparator 20%
- unknown: daptomycin 35% versus comparator 50%.
- There was one case of pneumonia in the comparator arm, none in the daptomycin arm. There were no cases of endocarditis.

In the 7 to 11 years age group in safety population (daptomycin n = 19, comparator n = 9), microbiological enrolment was by blood culture and gram stain in 68.4% of daptomycin group and 77.8% in comparator group. Diagnosis was proven in 94.4% in daptomycin group and 100% in comparator group, and probable for the other participant. MSSA infecting organisms were 77.3% in daptomycin group and 88.9% in comparator group. MRSA infecting organisms were 15.8% in daptomycin group and 11.1% in comparator group. Coagulase-negative Staphylococci were not isolated. Bacteraemia classification was uncomplicated in 57.9% in daptomycin group versus 33.3% in comparator group; complicated in 42.2 in daptomycin group versus 55.6% in comparator group and not classified in 0% in daptomycin group versus 11.1% in comparator group.

Most common types of infection were:

- device (catheter) related: daptomycin 15.8% versus comparator 37.5%
- osteomyelitis: daptomycin 21.1% versus comparator 0%
- abscess: daptomycin 10.5% versus comparator 0%
- appendiceal: daptomycin 10.5% versus comparator 0%
- unknown: daptomycin 35% versus comparator 50%.

There were no cases of pneumonia or endocarditis.

In the 12 to 17 years age group in safety population (daptomycin n=14, comparator n=7), microbiological enrolment was by blood culture and gram stain in 100% of daptomycin group and 85.7% in comparator group. Diagnosis was proven in 100% in daptomycin group and 85.7% in comparator group, and probable for other participants. MSSA infecting organisms were 92.9% in daptomycin group and 57.1% in comparator group. MRSA infecting organisms were 7.18% in daptomycin group and 14.3% in comparator group. Coagulase-negative Staphylococci were 0% in daptomycin group and 14.3% in comparator group. Bacteraemia classification was uncomplicated in 28.6% in daptomycin group versus 28.6% in comparator group; complicated in 64.3% in daptomycin group versus 57.1% in comparator group and not classified in 7.1% in daptomycin group versus 14.3% in comparator group.

Most common types of infection were:

- osteomyelitis: daptomycin 23.1% versus comparator 0%
- peritonitis: daptomycin 23.1% versus comparator 33.3%.

There were no cases of pneumonia, endocarditis or infection of prosthetic material.

All participants had at least 1 baseline comorbid condition. Ongoing or prior medical history of bacteraemia was the most common infection (daptomycin 69.1% versus comparator 61.5%), not including 8 daptomycin (14.5%) and 6 comparator (23.1%) participants with the reported specific term SAB.

Administration of prior non-study antibiotics was reported for 83.6% in daptomycin groups versus 80.8% in the comparator group.

Of the 49 daptomycin-treated participants with MIC data, the majority of Baseline *S. aureus* isolates had a daptomycin MIC ≤ 0.25 μg/mL (65.3%) and 98.0% had daptomycin MIC of ≤ 0.5 μg/mL. Of the 22 comparator-treated subjects with MIC data, the majority of Baseline *S. aureus* isolates had a daptomycin MIC ≤ 0.25 μg/mL (68.2%) and 95.5% were inhibited at a daptomycin MIC of ≤ 0.5 μg/mL

Comparator drugs included: vancomycin 15 (57.7%), cefazolin 6 (23.1%), semi-synthetic penicillins 5 (19.2%) (oxacillin 4 (15.4%), flucloxacillin 1 (3.8%)), and linezolid 1 (3.8%). One (1) patient received 5 days of IV vancomycin followed by IV linezolid.

The most commonly administered oral study drug medications in the daptomycin treatment arm were amoxicillin/clavulanate and cephalexin, with 10 participants (18.2%) receiving each drug. In the comparator treatment arm, amoxicillin/clavulanate was the most common oral antibiotic used in 7 (26.9%) participants followed by cephalexin, used in 6 (23.1%) participants.

Efficacy results

Overall microbilogical success rates at TOC/Safety Visit in the mMITT population were: daptomycin 39 of 51 (76.5%) versus comparator 17 of 22 (77.3%). Difference -0.8%; 95% CI for difference -21.8, 20.2.

Microbiological success rates at TOC/Safety Visit in the mMITT in the 1 to 6 year old group were: daptomycin 18 of 20 (90%) versus comparator 7 of 8 (87.5%) difference 2.5%. Microbiological success rates at TOC/Safety Visit in the mMITT in the 7 to 11 year old group were: daptomycin 14 of 17(82.4%) versus comparator 5 of 9 (55.6%) difference 26.8%.

Microbiological success rates at TOC/Safety Visit in the mMITT in the 12 to 17 year old group were: daptomycin 7of 14(50%) versus comparator 5 of 5 (100%) difference -50%.

Time to clearance of the *S. aureus* bacteraemia between daptomycin and comparator treated subjects in the mMITT population, with median times to clearance of 2.5 and 2.0 days in the daptomycin and comparator groups, respectively.

In the MITT population (n = 76), at the TOC/Safety Visit, microbiological success was recorded for 76.9% (40/52) of the daptomycin group versus 79.2% (19/24) of the comparator group.

In the clinical efficacy population (N = 52) at the TOC/Safety Visit, microbiological success was recorded for 87.5% (35/40) of the daptomycin group versus 100.0% (12/12) of the comparator group.

Twelve (12) daptomycin-treated participants (23.5%) had an unfavourable microbiological response, including 6 (11.8%) with microbiological failure and 6 (11.8%) who were non-evaluable. Five of the 6 daptomycin-treated patients, with true microbiological failures (1 uncomplicated and 4 complicated), had a baseline infecting pathogen (BIP) that persisted more than 7 or 10 days, respectively.

Five (5) comparator-treated participants (22.7%) had an unfavourable microbiological response; true microbiological failure occurred in 2 (9.1%) and 3 (13.6%) were non-evaluable.

True microbiological failures by age group included 3 participants (2 daptomycin and 1 comparator) aged 1 to 6 years, (1 daptomycin and 1 comparator) aged 7 to 11 years and 3 (all daptomycin treated) in the 12 to 17 year old age group.

Summary of pathogen-level microbiological outcome was presented [not included here]. Of the total 82 participants, 73 had *S. aureus* at Baseline, the majority being MSSA. In the mMITT population, successful eradication was reported for daptomycin 49/51 (96.1%) versus comparator 22 (100%).

Persistence of the BIP to the TOC/Safety visit was reported for 6 (10.9%) participants in the daptomycin group and 2 (7.7%) in the comparator group. Persistence was more common in participants with complicated bacteraemia (7 out of 8 participants); two of these (1 in each treatment arm) had metastatic foci of infection and 1 daptomycin-treated patient had a catheter present at the time of microbiological failure. Of the 17 participants with microbiological failure (microbiological persistence or non-evaluable), 8 had complicated bacteraemia due to metastatic foci of infection (5 in the daptomycin arm and 3 in the comparator arm).

The overall success rate in the total mMITT population at the TOC/Safety visit was presented in a table of the clinical evaluation report [not included here]. The overall success rate was daptomycin 72.5% versus comparator 59.1%. The difference (95% CI) was 13.5% (-10.5, 37.4).

The clinical evaluation report accepted that results support efficacy of daptomycin treatment in the studied age group.

Three issues were identified in the first round clinical evaluation report:

1. Clinical improvement could be subject to observer interpretation. Assessment of clinical efficacy was the responsibility of each study site's blinded investigator and there were instances of unblinding which could have influenced clinical assessment. From the reporting, it was difficult to assess the impact on results for individual participants.

   > *Sponsor's post-first round response*: The sponsor believes that the potential risk of clinical assessments being subjected to observer interpretation was mitigated by the use of the blinded evaluator. Of the 3 subjects in whom the blinded evaluator became unblinded to study group 2 subjects were categorised as experiencing a major protocol deviation. Detailed review did not reveal any impact of major protocol deviations on overall safety and efficacy conclusions in Study DAP-PEDBAC-11-02.

2. The 95% CI for the treatment difference included zero and the interval was wide reflecting the small numbers analysed which particularly relevant in the comparator group and particularly for age group sub analyses. Results for a small number of participants in the comparator group could make quite a big difference to percentages. The assessment of overall success was likely to have been influenced by the relatively large proportion of the comparator group with non-evaluable response though absolute numbers were small.

   > *Sponsor's post-first round response*: The sponsor acknowledges that the differences between the 2 treatment groups appear to be related to the higher proportion of non-evaluable subjects in the comparator group (9.1%) as compared to the daptomycin group (2.0%), the 95% confidence interval (CI) for the treatment difference for clinical success includes 0, which indicates that the difference in percentages was within chance. Moreover, the clinical success rates were generally similar across age groups and within treatment arms in the CE and MITT analysis populations at the TOC/Safety Visit and in each of the three (mMITT, MITT, and CE) populations. Median times to

clearance of 2.5 and 2.0 days in the daptomycin and comparator groups . The Sponsor concludes daptomycin was as effective as comparator in treatment of *S. aureus* bacteraemia in Study DAP-PEDBAC-11-02.

3. In view of numbers, it was not possible to totally balance factors that might complicate treatment. There were more patients in the daptomycin than the comparator group with osteomyelitis at baseline. There was a perceived discrepancy in IV catheter removal during the study with potential to bias results in favour of daptomycin and this could have been influenced by non-blinded investigators.

The sponsor has performed *post-hoc* analyses of the following study population subgroups:

- Subjects (including those with medical history or adverse event (AE) of osteomyelitis; in the DAP-PEDBAC-11-02 trial who received longer than the protocol-specified maximum duration of study drug of 42 days. 10 subjects who received study drug treatment for > 42 days and of whom 7 had medical history of osteomyelitis and 1 with an AE of osteomyelitis, the overall clinical outcome for these 10 subjects at the EOIV, EOT, and TOC visits was similar to those of the overall trial population. The tolerability of study medication in these 10 subjects was similar to that of the overall trial population.
- Subjects with catheter at baseline. Catheters were in place at baseline in 12/55 (21.8%) of daptomycin participants: 7/12 (58.3%) had the catheter removed before the first dose or during study dosing. Catheters were in place in 5/27 (18.5%) of comparator participants; 1/5 (20%) had the catheter removed during the study dosing. Based on the analyses of the limited number of subjects in whom baseline catheters were removed; the sponsor believes that there is no clinically relevant impact.

The second round clinical evaluation considered possible biases related to blinding are considered valid, that is, the relatively large proportion of the comparator group with non-evaluable response and small study populations with unbalanced numbers could potentially result in disproportions in factors, such as baseline osteomyelitis diagnosis, or decisions to remove catheters (foreign bodies) that may ultimately bias results.

Safety

The safety population includes all 81 participants (daptomycin 55; comparator 26).

The mean (median) duration of IV treatment was: daptomycin 12.2 (11.0) days versus comparator 12.3 (11.5) days. The total median duration of IV plus oral treatment was: daptomycin 20 days (range 1 to 141 days) versus comparator 18 days (range: 2 to 58 days). Mean duration of IV treatment was 13.1 days for daptomycis versus 11.7 days for comparator in the 1 to 6 years old group, 10.8 days versus 14.1 days for the 7 to 11 year group, 12.7 days versus 10.9 day for the 12 to 17 years old group.

Forty-eight (48; 59.3%) participants converted to oral study drug: daptomycin 32 (58.2%) versus comparator 16 (61.5%). The mean (median) treatment duration of oral treatment was daptomycin 22.7 days (15.0 days) versus comparator 17.7 days (16.0 days).

At least 1 treatment emergent adverse event (TEAE) was experienced by 56 (69.1%) patients: daptomycin 36 (65.5%) versus comparator 20 (76.9%). For daptomycin, at least 1 TEAE was reported for 68.2% of 1 to 6 year olds, 63.2% of 7 to 11 year olds, and 64.3% of 12 to 17 year olds. For comparators, at least 1 TEAE was reported for 60.0%, 100%, and 71.4% of these age groups, respectively. The most commonly reported TEAEs were diarrhoea, pyrexia and vomiting; the TEAEs considered related to study drug were reported in 8 (14.5%) daptomycin-treated and 4 (15.4%) comparator-treated participants during IV treatment.

No participant died during the study or follow-up period. Twenty participants experienced at least one serious adverse event (SAE): daptomycin 13 (23.6%), comparator 7 (26.9%). No SAEs were considered treatment related. SAEs were most commonly reported in the *Infections and Infestations* System Organ Class.

Three daptomycin-treated (5.5%) and 2 comparator-treated patients (7.7%) discontinued study drug due to a TEAE. One AE leading to withdrawal was considered treatment related (blood creatine phosphokinase (CPK) increase). The clinical evaluation report also considered AE leading to withdrawal in the two other daptomycin treated patients may have been treatment related. A 9 year was treated with daptomycin following cellulitis, myositis and abscess which was drained and subsequently osteomyelitis and bone fistula. A 15 year developed right ankle septic arthritis then a right sided deep vein thrombosis then septic emboli to lung and hospital acquired pneumonia. The clinical evaluation report (second round) considered the sponsor's response to questions and the clinical evaluator's comments as matters of opinion rather than definitive conclusion.

The most common clinical relevant TEAE was blood CPK increase, reported for 4 (7.3%) daptomycin-treated patients with 2 cases CPK > x 2.5 the ULN considered treatment related vs comparator 0. The other AEs identified were: daptomycin: muscular weakness (1) and acute renal failure (1).

At baseline and late follow-up visit, a questionnaire was used to evaluate motor development of 30 children (daptomycin 20 versus comparator 10) aged < 7 years. Findings in motor development skills were concluded to be consistent with patient medical conditions including location of the infection or underlying conditions impacting motor function, and there was no clear evidence for peripheral neuropathy. The second round clinical evaluation report comments that given the small numbers of participants, difficulty in delineating subtle motor and neurological abnormalities and the relatively short period of follow-up makes it impossible to exclude even common AEs relating to motor and neurological function.

Integrated analyses of safety results from all daptomycin-treated paediatric participants in the 5 completed studies were reported. In addition to the SAB and cSSSI studies, this included 3 Phase I studies without comparator arms with an additional 61 participants. The combined safety populations in these studies totalled 372 participants.

The 2 integrated safety analyses do not identify a new safety signal associated with a specific age group and confirm the previously identified and potential risks observed in adult studies.

Post-marketing experience

Cumulative data from international birth date of 12 September 2003 to 11 September 2016 and interval data (12 September 2015 to 11 September 2016) were analysed for daptomycin treated patients 1 to 17 years of age. No new risks or potential risks were identified.

The clinical evaluation report concluded that examination of safety does not uncover any obvious safety signal. Numbers are relatively small and severity of the underlying condition is such as to preclude determination of occurrence of uncommon or rare events related to treatment with daptomycin. There is a lack of any safety data on children 1 to < 2 years of age while proposing a higher dose than has previously been approved for children of that age.

Clinical evaluation report recommendations and summary of sponsor's response

The indication proposed by the sponsor is:

> *Cubicin is also indicated in paediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates.*

The first round clinical evaluation report noted the approved indication for treatment of cSSSI is limited to patients who have intolerance to alternative agents or have failed other therapy. For consistency, it was recommended that this also applies to the SAB indication.

The clinical evaluation report's recommended indication is:

> *Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy, and when caused by orgasms know to be susceptible to daptomycin.*

The sponsor has not adopted the revised text proposed by the evaluator for the paediatric SAB indication since the efficacy study was done in first line therapy, not salvage therapy. In terms of the requirement for daptomycin susceptibility testing the sponsor commented that resistance is extremely rare and reportable, and we believe that the delay of therapy as a result of testing will put a patient at increased risk of complications from a life threatening infection.

The sponsor did not agree with evaluator's recommendation to change the duration of therapy for paediatric SAB in the sponsor's post-first round response. The proposed treatment duration of up to 42 days is consistent with the current European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Expert Consensus Statements and the Diseases Society of America (IDSA) treatment guidelines. After the second round clinical evaluation report, the sponsor has amended the duration of therapy to state local treatment guidelines should be consulted in determining the duration of treatment. In the paediatric *S. aureus* bacteraemia (SAB) study the mean duration of IV daptomycin was 12 days (median 11 days; range 1 to 44 days). No patient with SAB aged 1 to < 2 years was included in paediatric SAB study. Dosage for this age group is confirmed using population pharmacokinetic modelling.

Antibiotic resistance data

The sponsor submitted antibiotic resistance data in response to question when the second round clinical evaluation report was sent.

Results of daptomycin surveillance programme worldwide 2005 to December 2012 and Australian and New Zealand 2008 to 2009 surveillance were included.

In worldwide surveillance A total of 164,457 gram-positive isolates were evaluated, including 97,542 *S. aureus*, 21,413 coagulase-negative staphylococci (CoNS), 29,619 enterococci, and 15,883 β-hemolytic streptococci. The prevalence of daptomycin-nonsusceptible isolates was extremely low for all species in all geographic regions. Against *S. aureus*, the daptomycin $MIC_{50/90}$ was 0.25/0.5 mg/L in all geographic regions (99.95% susceptible overall). Only 53 (49; 92.5%) had a daptomycin MIC value only 1 log^2 dilution above the published susceptible breakpoint.

In surveillance for Australia and New Zealand a total of 2,529 strains were consecutively collected from patients in eight Australian (1,826) and three New Zealand (703) medical centres in the 2008 to 2009 period. Daptomycin was highly active against MSSA and MRSA from Australia and New Zealand (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L for isolates from

both countries) and its activity was not adversely influenced by resistance to oxacillin. All *S. aureus* isolates were susceptible to daptomycin.

Current surveillance in Australia is performed by the Australian Group on Antimicrobial Resistance (AGAR) which reports on daptomycin non susceptibility in *S. aureus* in the National Alert System for Critical Antimicrobial Resistance, (CARAlert). According to the most recent quarterly CARAlert there has been no trend of increase or decrease in daptomycin non-susceptibility in *S. aureus*.

The projected quantities of use in Australia are currently approximately 2,200 patients annually. The projected pattern of use in Australia is almost solely confined to principal referral and large public acute care hospitals. The CARAlert 2017 report describes Highly reserved antibacterials accounted for a very small percentage of total Australian antibiotic use, for daptomycin (0.12%).

The potential impact of development of resistance to daptomycin is that it may become ineffective in treatment of *S. aureus* or Enterococci. By limiting use of daptomycin to those serious gram positive infections where there is intolerance to other therapies or where other therapies have already failed, the available alternative treatments may be few or non-existent. Therefore, the impact is not assessable.

The sponsor concludes that reduced susceptibility to daptomycin among *S. aureus* in paediatric patients with bacteraemia may also be appropriately managed through routine risk minimisation measures already in place for the approved indications in adults, which include:

- Highly reserved antibacterial agent status;
- Antimicrobial Stewardship programmes (AMS); and
- Educational materials (laboratory susceptibility testing guide.

Indications

Proposed indication

> *Cubicin is also indicated in paediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates.*

Currently registered indications

Cubicin is indicated for the treatment of adults and paediatric patients (1 to 17 years of age) with complicated skin and skin structure infections (cSSSI) who require parenteral therapy and who have intolerance to alternative agents (especially penicillin allergy) or who have failed on other therapy, and when caused by organisms known to be susceptible to daptomycin.

Daptomycin is also indicated in adults for Staphylococcus aureus bloodstream infections (bacteraemia), including right-sided native valve infective endocarditis (RIE), caused by methicillin-susceptible and methicillin-resistant isolates. The efficacy of daptomycin in patients with prosthetic heart valves or in left-sided endocarditis due to Staphylococcus aureus has not been demonstrated. In the setting of Staphylococcus aureus bacteraemia (SAB), if a focus of infection is diagnosed as left-sided endocarditis after Cubicin therapy has been initiated, then consideration should be given to instituting alternative antibacterial therapy (see Section 4.4 Special Warnings And Precautions For Use).

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.

Daptomycin is not indicated for the treatment of pneumonia.

Clinical evaluator's recommendation

The second round clinical evaluation report recommends the following indication:

> *Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy, and when caused by orgasms know to be susceptible to daptomycin.*

Risk-benefit analysis

Delegate's considerations

Summary of issues

The submission is referred to the Advisory Committee on Medicines (ACM) for advice on appropriate indications.

The second round clinical evaluation report recommends the following indication:

> *Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy, and when caused by orgasms know to be susceptible to daptomycin.*

The sponsor has not adopted the revised text proposed by the evaluator for the paediatric SAB indication since the efficacy study was done in first line therapy, not salvage therapy. The Sponsor does not accept a requirement for daptomycin susceptibility testing prior to initiation of treatment as resistance is are and the delay in therapy will put a patient at increased risk of complications from a life-threatening infection.

The Delegate considers that the prudent use guidelines in Australia and lack of development of susceptibility in current use support an extension of indications to the proposed age group. The sponsor's proposed indications do not reflect the importance rating of daptomycinin Australia and its restricted use in Australia. The Australian Strategic and Technical Advisory Group on AMR importance rating for daptomycin is high, P0 (not recommended for prophylactic use), T1 (infrequently used for listed indications), R4 use severely restricted (that is, not available for prescription under the Pharmaceutical Benefits Scheme (PBS), available in major hospitals but only with permission from a microbiologist or infectious diseases consultant, or in a special clinic) and with the comment '*Reserve agent for serious MRSA and VRE infections*'.

This Delegate accepts the sponsor's response that a requirement for daptomycin susceptibility testing prior to initiation of treatment as resistance is rare and the delay in therapy will put a patient at increased risk of complications from a life-threatening infection. The antibiotic resistance data submission by the sponsor however, does state that the selection of daptomycin is made through consultation between infectious disease physician and clinical microbiologist based on laboratory findings.

The second round clinical evaluation report considered possible biases related to blinding are considered valid. Double blind design was not feasible the recommended comparators (vancomycin, clindamycin, first generation cephalosporins, or semi-synthetic penicillins) are administered with a different dosage frequency to daptomycin. There was a relatively

large proportion of the comparator group with non-evaluable response. Small study populations with unbalanced numbers could potentially result in disproportions in factors. The Delegate accepts that small numbers of study participants are inherent for this indication and that study designs has acceptable controls and follow-up analysis to support the conclusions of favourable benefit to risk balance.

The SAB study population did not included participants aged < 2 years. The clinical evaluation report has accepted the extension of indications to include paediatric patients 1 to 17 years supported by PK modelling. The clinical evaluation report accepted that paediatric patients 1 to < 2 years of age with SAB should have the opportunity to derive clinical benefit from Cubicin.

Proposed action

The Delegate had no reason to say, at the time, that the application for extension of indications Cubicin should not be approved, subject to finalisation of the wording of indications.

Request for ACM advice

Question 1: Does the ACM consider the indications should be:

> *Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy?*

Response from sponsor

Sponsor's comments on proposed regulatory action

The sponsor welcomes the Delegate's proposal to approve the application for extension of indications for Cubicin for treatment of Staphylococcus bloodstream infections in patients 1 to 17 years of age, subject to finalisation of the wording of indications.

Cubicin was approved in 2008 for use in adults for Staphylococcus aureus bloodstream infections (bacteraemia), caused by methicillin-susceptible and methicillin-resistant isolates.

The sponsor proposed to extend the indication to include:

> *Cubicin is indicated for the treatment of patients aged 1 to 17 years with S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates.*

The Delegate considers that the sponsor's proposed indication/wording does not reflect importance rating of daptomycin in Australia and its restricted use in Australia. The Australian Strategic and Technical Advisory Group on AMR importance rating for daptomycin is high, P0 (not recommended for prophylactic use), T1 (infrequently used for listed indications), R4 use severely restricted (for example, not available for prescription under the Pharmaceutical Benefits Scheme (PBS), available in major hospitals but only with permission from a microbiologist or infectious diseases consultant, or in a special clinic) and with the comment '*Reserve agent for serious MRSA and VRE infections*'. Hence the Delegate has sought ACM advice whether the indication should be:

> *Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy.*

Sponsor response to the delegate's overview

The sponsor disagrees with the restriction of daptomycin use in paediatric patients with SAB infection who have intolerance to alternative agents or who have failed on other therapy as this restriction is not supported by the overall design of the registration Study DAP-PEDBAC-11-02 in paediatric patients with SAB.

The sponsor maintains that the proposed indication should be stated as:

> *Cubicin is indicated for the treatment of patients aged 1 to 17 years with S. aureus bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates.*

The sponsor's position on the proposed indication is based on the following reasons:

- Daptomycin was administered as first line therapy and not salvage therapy in the pivotal safety and efficacy study to support the extension of indication.
- Study DAP-PEDBAC-11-02 was a Phase IV open label (evaluator-blinded), comparative, multicentre, multinational study (including Australia) designed to assess and compare the safety and efficacy of daptomycin versus standard of care (SOC) in paediatric patients aged 1 to 17 years with *S. aureus* bacteraemia. All enrolled patients had either proven or suspected SAB. Treatment assignment was stratified by age and subjects were randomised to achieve a 2:1 ratio of subjects receiving daptomycin or SOC, respectively.
- There was no requirement for intolerance to alternative agents or restriction to patients who have failed other antibiotic therapy.
- Currently, limited antibacterial agents with activity against MRSA are available. Fewer still have had their safety and efficacy evaluated in paediatric patients. Clinical studies and post marketing pharmacovigilance have demonstrated a well characterised safety profile for daptomycin in adults. To date, the safety of daptomycin in the paediatric population appears to be comparable to that observed in adults.
- The Delegate's proposed indication would restrict Cubicin use in paediatric patients with SAB. Such restriction is not warranted due to the low risk of development of drug resistance and the positive public and individual health benefit.
- The risk profile for paediatric patients included in the EU Cubicin Outcome Research Experience (CORE) registry demonstrated low risk for emergence of resistance among *S. aureus* isolates and was similar to the adult experience.
- The sponsor believes that the restriction of daptomycin to 'last line' therapy only after documentation that all other available options have been eliminated may create unwarranted barriers to this potentially life-saving therapy being administered in a timely fashion to patients who may benefit from it.
- The sponsor's proposed indication is consistent with the approved indication for adults with SAB. The current usage of Cubicin in adults with SAB in Australia is managed appropriately with highly reserved antibacterial agent status, antibacterial stewardship programmes, and educational materials (Laboratory Susceptibility Testing Guide). The sponsor anticipates a similar approach in paediatric patients.

The sponsor acknowledges that there may be a difference between the indication described in the PI and the actual treatment algorithm for antimicrobial agents in the clinical setting. The treatment algorithm is based on the interpretation and implementation of such antibacterial importance ratings by the individual clinicians and their affiliated health care institutions. Such use under the Australian Antimicrobial Stewardship programme would assure appropriate use in paediatric patients in consultation with infectious disease specialists and clinical microbiologists, in a similar

pattern to adults. Antimicrobial stewardship programmes allow clinicians to make decisions based on local epidemiology and drug supply issues, which may vary greatly and thus can require prescribers to make individualised benefit-risk assessments.

Sponsor's conclusion

Based on the DAP-PEDBAC-11-02 trial design and data, as well as the current antimicrobial stewardship programmes and clinical practice in Australia, the sponsor believes that the proposed indication for the use of Cubicin for the treatment of patients aged 1 to 17 years with *S. aureus* bloodstream infections (bacteraemia) caused by methicillin-susceptible and methicillin-resistant isolates is justified.

Advisory Committee Considerations[15]

The Advisory Committee on Medicines (ACM) taking into account the submitted evidence of efficacy, safety and quality, considered Cubicin, 350 mg daptomycin or 500 mg daptomycin vials for intravenous infusion following reconstitution with 0.9% sodium chloride, to have an overall positive benefit-risk profile for the revised indication:

> *Cubicin is indicated in paediatric patients (1 to 17 years of age) with Staphylococcus aureus bacteraemia not due to pneumonia, caused by daptomycin-susceptible isolates. Empiric treatment should be reviewed based on the results of susceptibility testing. Prescribing should be in accordance with nationally or locally-endorsed guidelines for the treatment of Staphylococcus aureus bacteraemia.*

In providing this advice the ACM noted that:

- daptomycin is indicated in adults for Staphylococcus aureus bloodstream infections (bacteraemia) and is likely to be a second line therapy at this stage;
- daptomycin is widely used overseas and has been approved for Staphylococcus aureus bacteraemia by the FDA and EMA for paediatric (1 to 17 years) use;
- the pharmacokinetic data provided for daptomycin is limited to patients aged over 2 years, and acknowledged that 1 to 2 year old children tend to have a bodyweight that is 20% less than 2 year old children. It was further noted that there are important PK and PD differences in infants aged less than 2 years, which may have implications for differences in efficacy, safety and appropriate dosing, compared to those above 2 years. While noting that efficacy data specifically from the 1 to 2 year age group would have been optimal, the ACM acknowledged that extrapolation from available data from above 2 year of age may be reasonable, especially if supplemented with safety data from the 1 to 2 year old age group (see below);
- the PSUR indicates that 3.7 million patients were treated with daptomycin between the years of 2011 to2017, however neither the number of children nor their age breakdown was specified; and
- daptomycin cannot be used for pneumonia as it is inactivated by surfactant.

The ACM also advised that:

[15] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- the sponsor should be requested to provide data in the PSUR specifically for the paediatric population overall and with breakdown by paediatric age sub-groups, as recommended in the recently issued EMA Guideline on Good Pharmacovigilance Practices (GVP): Product or population specific considerations IV: Paediatric Population (8 November 2018);
- the contraindication of the agent with pneumonia be made as prominent as possible and stated in the indication to help make prescribers aware of the contraindication;
- nationally or locally endorsed treatment guidelines should be consulted; and
- initiation of treatment should not wait for susceptibility testing results.

The ACM considered that this application is for an extension of indications to include paediatric patients aged 1 to 17 years for the treatment of *Staphylococcus aureus* bloodstream infections (bacteraemia).

The ACM noted that the currently approved indications for Cubicin include: treatment of adults and paediatric patients (1 to 17 years of age) with complicated skin and skin structure infections; and in adults for treatment of SAB.

The ACM also noted that daptomycin is approved in the US and EU for the treatment of SAB in paediatric patients (1 to 17 years).

The ACM noted the pivotal study (Study DAP-PEDBAC-11-02) examined the pharmacokinetics of daptomycin in different age groups but that the trial did not treat any paediatric SAB patients that were < 2 years of age. Steady state AUC in children aged 1 to < 2 years receiving 60 minute IV infusion of 12 mg/kg daptomycin once daily was stimulated; results support comparable steady state AUC distributions with that of other paediatric age groups (2 to 17 years of age).

The ACM considered the appropriateness to extend the indication to paediatric patients < 2 years of age, given that the pivotal study only included patients > 2 years. It was acknowledged that patients in the 1 to 2 year old age group tend to have a bodyweight that is 20% less than 2 year old children but clinically very few comparable drugs are given at different doses for a 13 month old patient as compared to a 25 month old patient. The committee agreed that the likelihood of a similar trial being conducted in children aged < 2 years was remote, and that daptomycin would most likely be used in hospitals under the direction of a relevant expert.

The ACM noted that the PSUR indicated that 3.7 million patients were treated with daptomycin between the years of 2011 to 2017, however neither the number of children nor their age breakdown was specified. To supplement the limitations in data for 1 to < 2 year olds, the ACM advised that the sponsor should be requested to provide data in the PSUR specifically for the paediatric population overall and with breakdown by paediatric age sub-groups, consistent with the EMA guideline on Good Pharmacovigilance Practices (GVP).

The ACM further noted that Cubicin has been registered in both the US and EU for SAB paediatric patients aged 1 to 17 years, without supporting data for patients aged 1 to 2 years. Acknowledging the registration of Cubicin overseas, the ACM agreed that efficacy data specifically from the 1 to 2 year age group would have been optimal, but considered that extrapolation from available data from > 2 year olds would be reasonable, especially if supplemented with safety data from the 1 to 2 year old age group.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

Given that the PK and PD data presented for daptomycin was limited to patients over 2 years old, the ACM commented on the suitability of extending the indication to children aged 1 year old. The ACM advised that it would be reasonable to extend the indication

down to children 1 year old. Additionally, the ACM noted that daptomycin was registered for the treatment of Staphylococcus aureus bacteraemia by the EMA and FDA in paediatric patients aged 1 to 17 years.

The ACM recommended including a statement in the product information that prescribing be in accordance with nationally or locally-endorsed guidelines for the treatment of Staphylococcus aureus bacteraemia (similar to the precedent set by other antibiotics).

Additionally, the ACM advised that susceptibility testing for daptomycin should not be mandated prior to empiric use it may take some time to receive test results, and organisms are likely to be susceptible to daptomycin. However, susceptibility testing should be performed as soon as practicable and treatment reviewed based on the results.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Does the ACM consider the indications should be 'Cubicin is indicated for the treatment of Staphylococcus aureus bloodstream infections (S. aureus bacteraemia) in patients aged 1 to 17 years with who have intolerance to alternative agents or who have failed on other therapy'?*

The ACM supported the revised indication wording of:

> *Cubicin is indicated in paediatric patients (1 to 17 years of age) with Staphylococcus aureus bacteraemia caused by daptomycin-susceptible isolates.*

The ACM supported including in the indication that the source of the bacteraemia should not be pneumonia (for example, *Staphylococcus aureus* bacteraemia not due to pneumonia, caused by daptomycin-susceptible isolates).

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Cubicin daptomycin for the new indication of:

> *Staphylococcus aureus Bloodstream Infections (Bacteraemia)*
>
> *Cubicin is indicated in paediatric patients (1 to 17 years of age) with Staphylococcus aureus bacteraemia not due to pneumonia, caused by daptomycin-susceptible isolates. Empiric treatment should be reviewed based on the results of susceptibility testing. Prescribing should be in accordance with nationally or locally-endorsed guidelines for the treatment of Staphylococcus aureus bacteraemia.*

The full indications are now:

> *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.*
>
> *Daptomycin is not indicated for the treatment of pneumonia.*
>
> ***Adult patients (≥18 years of age)***
>
> ***Complicated Skin and Skin Structure Infections***

Cubicin is indicated for the treatment of adults (≥ 18 years of age) with complicated skin and skin structure infections (cSSSI) who require parenteral therapy and who have intolerance to alternative agents (especially penicillin allergy) or who have failed on other therapy, and when caused by organisms known to be susceptible to daptomycin.

Staphylococcus aureus Bloodstream Infections (Bacteraemia)

Cubicin is indicated in adults (≥18 years of age) for Staphylococcus aureus bloodstream infections (bacteraemia), including right-sided native valve infective endocarditis (RIE), caused by methicillin-susceptible and methicillin-resistant isolates.

The efficacy of daptomycin in patients with prosthetic heart valves or in left-sided endocarditis due to Staphylococcus aureus has not been demonstrated. In the setting of Staphylococcus aureus bacteraemia (SAB), if a focus of infection is diagnosed as left-sided endocarditis after cubicin therapy has been initiated, then consideration should be given to instituting alternative antibacterial therapy (see Section 4.4 Special Warnings and Precautions For Use).

Paediatric patients (1 to 17 years of age)

Daptomycin is not indicated for treatment of patients less than 1 year of age (see Section 4.4 Special Warnings and Precautions For Use, Paediatric use).

Daptomycin has not been studied in treatment of infective endocarditis in children (see Section 5.1 Pharmacodynamic Properties, Clinical trials and Section 4.4 Special Warnings and Precautions for use).

Complicated Skin and Skin Structure Infections

Cubicin is indicated for the treatment of patients aged 1 to 17 years with complicated skin and skin structure infections (cSSSI) who require parenteral therapy and who have intolerance to alternative agents (especially penicillin allergy) or who have failed on other therapy, and when caused by organisms known to be susceptible to daptomycin.

Staphylococcus aureus Bloodstream Infections (Bacteraemia)

Cubicin is indicated in paediatric patients (1 to 17 years of age) with Staphylococcus aureus bacteraemia not due to pneumonia, caused by daptomycin-susceptible isolates. Empiric treatment should be reviewed based on the results of susceptibility testing. Prescribing should be in accordance with nationally or locally-endorsed guidelines for the treatment of Staphylococcus aureus bacteraemia.

Specific conditions of registration applying to these goods

The Cubicin EU-Risk Management Plan (RMP) (version 10.1, dated 17 May 2017, data lock point 11 September 2016), with Australian Specific Annex (version 1.2, dated 27 November 2017), included with submission PM-2017-04652-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Cubicin approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

Therapeutic Goods Administration

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