EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cubicin

DAPTOMYCIN

Procedure no: EMEA/H/C/000637/P46/030.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Rapporteur's assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended.

Cubicin

International non-proprietary name: Daptomycin

Procedure no.: EMA/H/C/0637/P46

Marketing authorisation holder (MAH): Novartis Europharm Ltd,UK

Rapporteur:	Dr Greg Markey
Deadline for Rapporteur's AR:	24 March 2015
Deadline for CHMP member's comments:	8 April 2015
Date of the Rapporteur's final report:	13 April 2015

Administrative information

Invented name of the medicinal product:	Cubicin
INN (or common name) of the active substance(s):	Daptomycin
MAH:	Novartis Europharm Ltd,UK
Currently approved Indication(s)	Cubicin is indicated for the treatment of: • Complicated skin and skin structure infections • Staphylococcus aureus bloodstream infections (bacteremia)
Pharmaceutical form(s) and strength(s):	350 mg and 500 mg powder for solution for infusion or injection
Rapporteur's contact person: Name of the Assessor:	Name: Graham Searle Tel: 0044 203 080 7709 Email: graham.searle@mhra.gsi.gov.uk Name: Dr S Bhat
Product PTL:	**Name:** Tel: Email:

1. Introduction

The present paediatric data is submitted by the MAH in accordance with article 46 of Regulation EC No 1901/2006.

The applicant has submitted the final clinical study report of a recently completed phase IV retrospective observational study (CBC134A2403; EUCORESM) sponsored by Novartis. This study was conducted in 18 countries and enrolled 6,075 patients, including 81 paediatric patients. The purpose of this study was to collect real-world data on the use and clinical outcomes for patients who received Cubicin.

This study was not designed for studying the paediatric population specifically. Cubicin is not approvedfor use in the paediatric population, however some guidelines recommend its use for managing MRSA bacteremia, infective IE, acute hematogenous osteomyelitis, and septic arthritis in pediatric patients.

The applicant had previously submitted a Critical Expert Overview to review the available paediatric results from this study, which was assessed in Dec 2014. No new safety concerns have arisen during this study.

About the product

Daptomycin is a cyclic lipopeptide natural product that is active against Gram positive bacteria only. The mechanism of action involves binding to bacterial membranes of both growing and stationary phase cells causing depolarisation and leading to a rapid inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

Daptomycin pharmacokinetics are generally linear and time-independent at doses of 4 to 12 mg/kg administered as a single daily dose by 30-minute intravenous infusion for up to 14 days in healthy volunteers. Steady state concentrations are achieved by the third daily dose. Daptomycin is eliminated primarily by the kidney.

Cubicin was first authorised via the centralised route in 2006.

Approved indication(s) and posology

Indication

Cubicin is indicated for the treatment of the following infections in adults:
- Complicated skin and soft-tissue infections (cSSTI).
- Right-sided infective endocarditis (RIE) due to Staphylococcus aureus.
- Staphylococcus aureus bacteraemia (SAB) when associated with RIE or with cSSTI.

Posology

Adults

- cSSTI without concurrent *Staphylococcus aureus* bacteraemia: Cubicin 4 mg/kg is administered once every 24 hours for 7-14 days or until the infection is resolved
- cSSTI with concurrent *Staphylococcus aureus* bacteraemia: Cubicin 6 mg/kg is administered once every 24 hours. The duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient.

- Known or suspected right-sided infective endocarditis due to *Staphylococcus aureus*: Cubicin 6 mg/kg is administered once every 24 hours. The duration of therapy should be in accordance with available official recommendations. .

In patients with renal impairment, dose adjustment is needed.

Paediatric population

The safety and efficacy of Cubicin in children and adolescents aged below 18 years has not been established. Currently available data are described in section 5.2 of the SPC but no recommendation on posology are made.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that this study is a stand-alone study.

EUCORE was a non-interventional, multicenter, retrospective, patient registry designed to collect real-world outcome data on patients who had received at least one dose of daptomycin for the treatment of a serious Gram-positive bacterial infection.

Annual database locks occurred from 2008 to 2014. Data collected until September 15 of each year (2008 and 2009) or until July 31 (2010 to 2012) were included in these analyses as well as in the final study analysis (2014). These data originated from patients who had completed daptomycin treatment at least 1 month before the end of the collection period and thus had been followed up for 30 days.

The study was designed to allow all sites at which patients had been treated with daptomycin and all countries in which Novartis is the MAH for Cubicin to participate. The study was not restricted to adult patients, thus it was open for the collection of data from paediatric patients as well.

Rapporteurs comments:

The dosages used with in this study for the paediatric patients have not been mentioned. It is assumed the dosage used were the same as those used in the three PK studies conducted previously in paediatric patients and submitted to EMA:

DAP-PEDS-05-01 (2007): An evaluation of the pharmacokinetics of a single dose of daptomycin (4 mg/kg) in paediatric patients aged two to seventeen years.

DAP-PEDS-07-02: An evaluation of the pharmacokinetic profile and safety of a single dose of daptomycin (8 and 10 mg/kg) in paediatric subjects aged two to six years.

DAP-PEDS-09-01: An evaluation of the pharmacokinetic profile and safety of a single dose of daptomycin (4 and 6 mg/kg) in paediatric subjects aged three months to twenty four months.

As the final report is expected very shortly (Jan 2015), the applicant should provide full details of the dosages used, in that report.

The Rapporteur will await the submission of these data.

1.2. Clinical aspects

Study population

A total of 81 paediatric patients were included in this registry study. The majority of paediatric patients were male (65.4%), adolescents (56.8%) and Caucasian (92.5%).

Table 2-1 Patient disposition and analysis sets for paediatric patients (All patients)

	n (%)
Entered EUCORE	81 (100)
Completed Cubicin (daptomycin) therapy	49 (60.5)
Switched therapy	27 (33.3)
Discontinued due to an adverse event	4 (4.9)
Other	1 (1.2)
Entered safety population	81 (100)
Entered efficacy population	81 (100)

Demographics

Baseline age range, n (%)	0 to <1 years	2 (2.5)
	1 to <2 years	3 (3.7)
	2 to <7 years	10 (12.3)
	7 to <12 years	20 (24.7)
	12 to <18 years	46 (56.8)
Sex, n (%)	Male	53 (65.4)
	Female	28 (34.6)

The most common primary infections were bacteraemia (19.8%) and cSSTI (18.5%), followed by osteomyelitis (13.6%), endocarditis (12.3%) and foreign body/prosthetic infection (12.3%). The main reason for switching treatment from a previous antibiotic to daptomycin was failure of the previous antibiotic treatment. Staphylococcus aureus was the most common primary pathogen (23.8% methicillin-resistant, 66.7% methicillin-susceptible and 9.5% methicillin susceptibility unknown).

Table 2-3 Baseline infection - type of primary infection for paediatric patients (Safety population)

	N=81 n (%)
Bacteraemia	16 (19.8)
Complicated skin and soft tissue infection (cSSTI)	15 (18.5)
Osteomyelitis	11 (13.6)
Endocarditis	10 (12.3)
Foreign body / Prosthetic infection	10 (12.3)
Uncomplicated skin and soft tissue infection (uSSTI)	8 (9.9)
Urinary tract infection / pyelonephritis	3 (3.7)
Septic arthritis	3 (3.7)
NOS (not otherwise specified)	3 (3.7)
Surgical antibiotic prophylaxis	2 (2.5)

Efficacy data

Overall clinical success rates were similar in patients treated with daptomycin either as first line (93.7%) or second line (92.0%) treatment. The clinical success rate (cured plus improved) was 100%

for endocarditis, osteomyelitis and uSSTI; 94.4% for bacteraemia; 76.9% for cSSTI; and 89.5% for other infections.

Table 2-4 Clinical outcome by infection type for paediatric patients (Efficacy population)

	N=81 n (%)
Endocarditis	
Total	11 (100)
Cured	7 (63.6)
Improved	4 (36.4)
Osteomyelitis	
Total	13 (100)
Cured	4 (30.8)
Improved	9 (69.2)
Bacteraemia	
Total	18 (100)
Cured	13 (72.2)
Improved	4 (22.2)
Non-evaluable	1 (5.6)
Other	
Total	19 (100)
Cured	9 (47.4)
Improved	8 (42.1)
Non-evaluable	2 (10.5)
Complicated skin and soft tissue infection	
Total	13 (100)
Cured	2 (15.4)
Improved	8 (61.5)
Non-evaluable	3 (23.1)
Uncomplicated skin and soft tissue infection	
Total	7 (100)
Cured	7 (100)

Patients with more than one infection type were assigned to the most severe infection according to the hierarchy:
Endocarditis > osteomyelitis > bacteraemia > other (foreign body, septic arthritis, pyleonephritis/UTI, necrotizing infections, necrotizing fasciitis, surgical/non-surgical antibiotic prophylaxis, metastatic abscess, NOS) > complicated skin and soft tissue infection > uncomplicated skin and soft tissue infection
Osteomyelitis category contains PJI

Safety data

Patient exposure (Pediatric patients)

A total of 81 pediatric patients received at least 1 dose of daptomycin therapy, and the median dose of daptomycin was 6.0 mg/kg (range 4.0-18.5 mg/kg). The most frequently prescribed initial dose was 6 mg/kg (45.7%). An initial dose of 4 mg/kg was administered in 18.5% of patients. Other initial doses given to the remaining 35.8% of patients included ≥8 mg/kg to ≤10 mg/kg (13.6%), >6 mg/kg to <8 mg/kg (11.1%) and >10 mg/kg (6.2%).

Table. Initial dose for pediatric patients (Safety population) N=81n (%)

		N=81 n (%)
Initial dose	4 mg/kg	15 (18.5)
	6 mg/kg	37 (45.7)
	Other	29 (35.8)
	<4 mg/kg	0 (0.0)
	>4 mg/kg and ≤5 mg/kg	1 (1.2)
	>5 mg/kg and <6 mg/kg	3 (3.7)
	>6 mg/kg and <8 mg/kg	9 (11.1)
	≥8 mg/kg and ≤10 mg/kg	11 (13.6)
	>10 mg/kg	5 (6.2)
Initial dose (mg/kg)	n	81
	Mean	6.6
	SD	2.66
	Median	6.0
	Min - Max	4.0 - 18.5

Median duration of therapy was 12.5 days (1-47 days).

Safety assessments consisted of all AEs, serious adverse events (SAEs), with their severity and relationship to study drug, and regular assessments of physical condition, vital signs, weight, and laboratory parameters. Safety analysis included all patients given at least 1 dose of the study drug.

Six (7.4%) out of 81 paediatric patients reported adverse events (rash (2), tachycardia (1), anaphylactic reaction (1), hypersensitivity (1), increased blood creatine phosphokinase (1), osteosarcoma (1), acute renal failure (1), dyspnoea (1), and pulmonary haemorrhage (1). Four patients had an increase in CPK levels but none of these patients reported myopathy related AEs. Three patients had SAEs that led to pemanent disontinuation of study drug (anaphylactic reaction, pulmonary haemorrhage and death, acute renal failure). One patient died but the death was considered not related to daptomycin.

Rapporteurs comments:

Although Cubicin is not approved for use in children, some off-label use is taking place. The doses used vary but the most common is 6mg/kg (as recommended in the IDSA guideline,2011). No new adverse events of concern were identified and the safety data from the paediatric patients in this study were consistent with the known safety profile of daptomycin.

1.2.1. Discussion on clinical aspects

The applicant had previously submitted only a clinical overview to provide an update. The full study report has been provided now.

There were no new or unexpected safety findings from the 81 paediatric patients enrolled in study CBC134A2403 (EUCORE). Both safety and efficacy results are consistent with those from adult patients obtained in this and previous clinical trials and with data from the literature.

On the basis of the paediatric results of study CBC134A2403, there is no change in the benefit-risk profile of Cubicin for the existing indications. The clinical safety and efficacy findings remain consistent with the information in the Novartis Core Data Sheet and prescribing information for Cubicin. Therefore, no SmPC changes are needed based on the results of this study at present.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The benefit/risk balance remains positive in the approved indications at present and no further regulatory action is proposed at this stage relating to the (off-label) use in the paediatric population.