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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/P46/032

## Note

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

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# 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 a Critical Expert Overview to provide information from a Phase 4 retrospective observational study (CBC134ADE03T DECORE) sponsored by Novartis. DECORE was conducted in Germany from 2010 to 2012 and included 2 paediatric patients. The purpose of this study was to collect real world data about patients who received Cubicin. The CSR for DECORE is provided with this submission.

The overview also aims to assess the impact of these results on the existing information about the product in the Novartis Core Data Sheet and in the currently approved SmPC.

*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*

In July 2015, the MAH submitted an application for the extension of the indication in cSSTI to paediatric patients (1-17 years old). The CHMP positive opinion was received on 22 October 2015 and the EC decision is expected within 2 months of the positive opinion.

# 1. Scientific discussion

## *1.1. Clinical aspects*

### a. Clinical Study

This study was designed to collect data about the use of Cubicin in the real world. It was expected that this study will provide critical information about the administrative patterns for the use of Cubicin based on the geographical differences in pathogens and the incidences of resistance in antibiotic therapy.

The data was obtained from the German CUBICIN (Daptomycin) Outcomes Registry and Experience for the Treatment of Serious Gram-positive Infections.

**Study Objectives:**

Primary:

- To evaluate the safety and tolerability of Cubicin® in the treatment of patients suffering from gram positive infections.

Secondary:

- Documentation of acceptance and efficacy of therapy using Cubicin® in the clinical treatment of patients under everyday routine practise study

Patients were recruited for the study in multiple centres throughout the Federal Republic of Germany.

**Design and duration of the study:**

Inclusion criteria included:

- the attending physician had already decided on the treatment of Cubicin for the patient,

- the patient was treated with at least one dose of Cubicin,

- the patient had been informed about the objectives of this study and had given a written consent to participation in this study.

All occurring adverse events (AE) were registered in conventional CIOMS II line listings and periodically sent to the drug safety department of NOVARTIS for further processing.

Patients were observed over a period of ca. 30 days under therapy with Cubicin. This collective contains completed baseline-documentations of 170 patients at 24 separate sites.

**Study population**

A total of 170 patients were involved, out of which only two were paediatric patients (13yrs, 17yrs). One patient was treated for cSSTI and osteomyelitis caused by MRSA, the second patient for infection with Staphylococcus epidermidis. Cubicin treatment was completed and resulted in complete recovery of both patients.

*As this assessment relates only to paediatric subjects, no further comments are made on the rest of the study population.*

**Results**

*Efficacy*

Both paediatric subjects made a full recovery.

*Safety*

No serious adverse events or non-serious adverse events associated with Cubicin treatment were documented in either of the two patients.

### 1.2 Discussion on clinical aspects

The applicant has submitted the results on 2 paediatric subjects from a phase 4 clinical study in Germany. The results from this small number of 2 paediatric patients from study CBC134ADE03T (DECORE) appear to be consistent for efficacy and safety with those from patients obtained in previous clinical trials with Cubicin. However no firm conclusions can be made due to the extremely limited number of paediatric patients.

On the basis of this study, there is no change in the benefit-risk profile of Cubicin for the existing indications. No changes are proposed to the Basic Prescribing information.

## 2. C overall conclusion and recommendation

### Overall conclusion

The benefit/risk balance remains unchanged and positive in the approved indications at present.

The data provided in this submission do not raise any safety or efficacy concerns for daptomycin in the paediatric population.

Based on these results the applicant proposes no amendments to the Basic Prescribing Information.

No further action is considered necessary.