EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Doribax

(Doripenem)

Procedure No. EMEA/H/000891/P46/025

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

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

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1. INTRODUCTION

On 2010-09-24 the MAH submitted a completed paediatric study for Doribax, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Doribax and that there is no consequential regulatory action.

2. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study

Doripenem was provided as single-use type 1 clear glass vials containing 500-mg (on an anhydrous basis) of sterile doripenem powder. (Study drug Batch/Lot number: B100619/CF7037, Expiration Date: November 2010; B116086/CF8035, Expiration Date: October 2011). The powder is fine, and white to slightly yellowish in appearance. Doripenem vials were stored at a controlled room temperature (15°C to 30°C or 59°F to 86°F). Doripenem powder was constituted with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and was shaken to form a suspension. The constituted doripenem was further diluted in 0.9% sodium chloride injection (normal saline). There was no need to develop a paediatric specific formulation since the existing 500 mg vial drug product was adequate to deliver an appropriate paediatric dose.

Clinical aspects

1. Introduction

The MAH submitted a final report for:

DORI-PED-1001 *An Open-Label Study to Evaluate the Single-Dose Pharmacokinetics and Safety of Doripenem in Pediatric Subjects 6 to 17 Years of age, Inclusive, With Cystic Fibrosis*

2. Clinical study

- **Methods**

- Objectives

The primary objective of this study was to assess the pharmacokinetics of doripenem after a single 30-mg/kg doripenem 4-hour IV infusion administered to paediatric subjects 6 to 17 years of age, inclusive, with CF. Safety and tolerability was also assessed.

- Study design

This was a multicenter, open-label, single-dose, PK study in children with CF who were receiving treatment with another non-study antibiotic for an infection, colonization, or prophylaxis in a hospital or supervised outpatient clinic setting. Doripenem was not being used in this study to treat infection and did not replace the subject's prescribed antibiotic(s).

- Study population /Sample size

Male and female paediatric subjects 6 to 17 years of age, inclusive, with a documented diagnosis of CF were included in the study.

Assuming inter-subject variability of 35% in AUC and Cmax (based on previous data in adults) a sample size of 10 subjects in each of the age groups (≥6 to <12 years and ≥12 to <18 years) was determined to be sufficient to estimate the mean AUCs and Cmax for that age group within 78% and 128%, respectively, of their true values with 95% confidence.

- Treatments

Doripenem was administered as a single 30-mg/kg (approximately equivalent to a 2-g/70 kg dose in adult subjects) 4-hour IV infusion. For subjects ≥33.4 kg, a total dose of 1000-mg doripenem was administered. The maximum dose, on a mg/kg basis, for any subject did not exceed 1000 mg.

- Outcomes/endpoints

No formal endpoints were applied, since the objective was to study the pharmacokinetics, safety and tolerability.

Blood samples for measurement of doripenem and doripenem-M1 concentrations were collected during the infusion and up to 5 hours after the end of the infusion. Conventional methods for calculation of pharmacokinetic parameters were employed. In addition, the %time above certain MIC values over 0-8 hours were calculated.

- Statistical Methods

Conventional methods were used.

➢ **Results**

- Recruitment/ Number analysed

This study was conducted from 18 May 2009 to 24 March 2010. Twenty-two subjects were enrolled, of which 20 (91%) subjects completed the study per protocol. Two subjects were withdrawn from the study; 1 due to the adverse event of infusion site extravasation (Subject 100801) and 1 due to interruption in study drug infusion for more than 10 minutes (Subject 100206).

- Baseline data

All subjects enrolled in this study were white and non-hispanic or Latino with a median age of 12 years (range: 6 to 17 years) and mean BMI of 17.5 kg/m2. Fifty-nine percent of subjects were male and 41% were female. Details are given in Table 1.

Table 1. Demographics and baseline characteristics.

(Study DORI-PED-1001: Safety Analysis Set)

	≥6 to <12 Years (N=10)	≥12 to <18 Years (N=12)	Total (N=22)
Age (Years)			
Mean (SD)	7.5 (1.35)	15.1 (1.98)	11.6 (4.22)
Median	7.0	16.0	12.0
Range	(6;10)	(12;17)	(6;17)
Sex, n (%)			
Female	6 (60)	3 (25)	9 (41)
Male	4 (40)	9 (75)	13 (59)
Race, n (%)			
White	10 (100)	12 (100)	22 (100)
Ethnicity, n (%)			
Not Hispanic or Latino	10 (100)	12 (100)	22 (100)
Baseline Weight (kg)			
Mean (SD)	23.4 (3.45)	49.5 (9.33)	37.7 (15.08)
Median	23.4	52.6	36.1
Range	(20;32)	(33;65)	(20;65)
Baseline Height (cm)			
Mean (SD)	120.9 (8.58)	161.9 (12.32)	143.3 (23.42)
Median	120.0	157.9	143.7
Range	(110;141)	(142;177)	(110;177)
Baseline BMI (kg/m^2)			
Mean (SD)	16.0 (1.20)	18.8 (2.25)	17.5 (2.30)
Median	16.2	18.4	17.3
Range	(14;18)	(15;23)	(14;23)

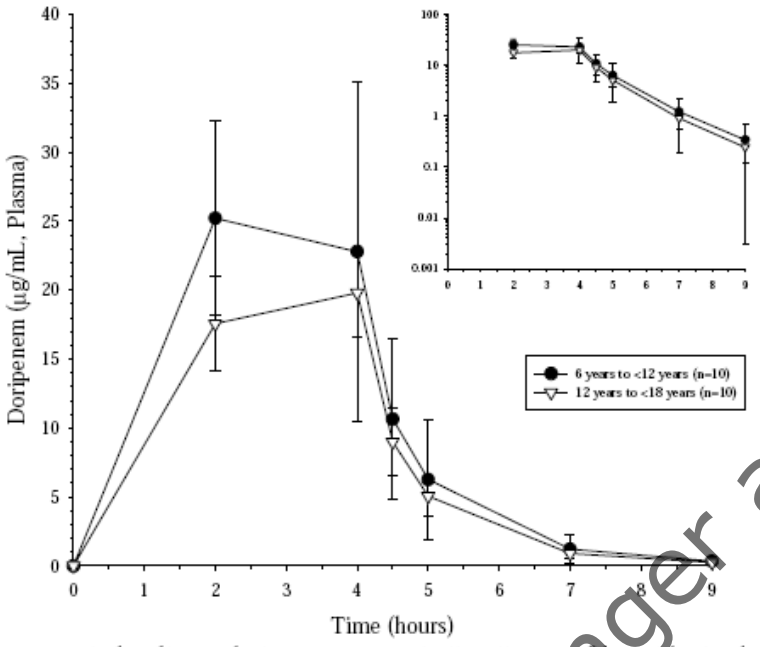
Key: BMI: body mass index; SD:standard deviation

- Pharmacokinetic and pharmacodynamic results

The mean plasma concentrations *versus* time profiles are presented in Figure 1 and Figure 2. The pharmacokinetic parameters for doripenem are found in Table 2 together with data from a previous study in adult CF subjects who received 1000 mg (DORI-NOS-1009 2009). The relationship between BMI-corrected clearances an age is shown in

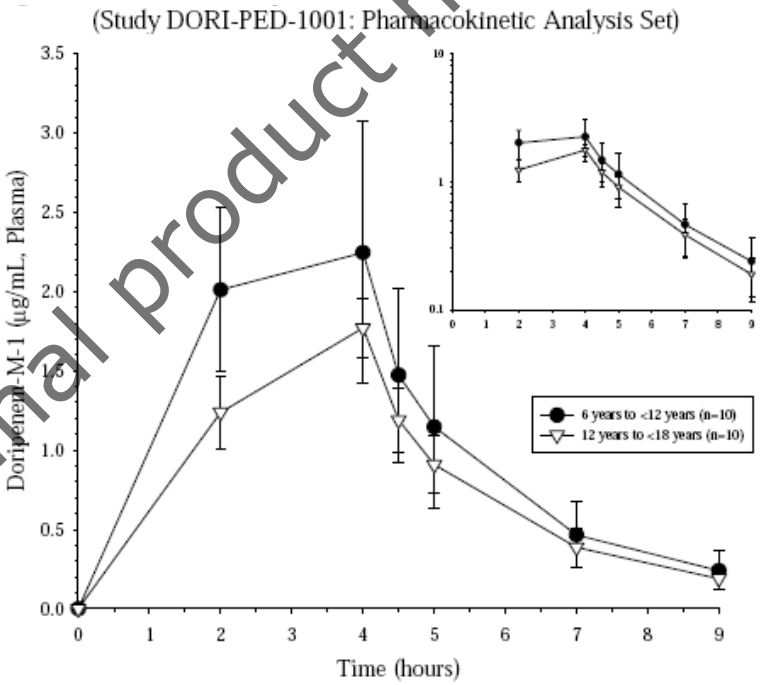
Figure **3**. The median (range) percent time above the MIC over 0-8 hours for doripenem are presented in Table 3.

Figure 1. Mean plasma concentration of doripenem *versus* time presented with standard error bars. Closed symbols 6 years to < 12 years, open symbols 12 years and above.



Note: Inlay plot represents log-linear doripenem concentration-time profile, with standard error bars, and over the entire 9 hour sampling period.

Figure 2. Mean plasma concentration of doripenem-M1 *versus* time presented with standard error bars. Closed symbols 6 years to < 12 years, open symbols 12 years and above.



Note: Inlay plot represents log-linear doripenem concentration-time profile, with standard error bars, and over the entire 9 hour sampling period.

Table 2. Pharmacokinetic parameters of doripenem per age group as mean(SD).
(Study DORI-PED-1001: Pharmacokinetic Analysis Set)

PK Parameter		6 yr to <12 yr 30 mg/kg	12 yr to <18 yr 30 mg/kg[b]	18 yr to <45 yr[c] 1000 mg
n		9	10	9
C_{max}	(µg/mL)	29.0 (9.13)	19.9 (3.05)	20.0 (5.62)
t_{max}	(h)[a]	3.98 (2.00-4.18)	3.98 (2.00-4.00)	4.00 (3.00-4.02)
t_{last}	(h)[a]	9.00 (7.10-9.00)	9.00 (8.98-9.28)	8.00 (8.00-12.00)
AUC_{last}	(µg•h/mL)	95.6 (31.2)	72.7 (11.8)	79.7 (24.9)
AUC_{∞}	(µg•h/mL)	96.1 (31.7)	73.0 (11.8)	80.3 (24.9)
$t_{½}$	(h)	0.874 (0.159)	0.881 (0.0897)	1.00 (0.270)
Vd_{ss}	(L)	8.79 (3.11)	18.0 (4.04)	12.6 (3.29)
Vd_{ss}/BW	(L/kg)	0.377 (0.133)	0.374 (0.0465)	0.228 (0.0777)
Vd_{ss}/BMI	($L/kg/m^2$)	0.545 (0.166)	0.979 (0.208)	0.605 (0.205)
CL	(L/h)	8.06 (3.08)	14.0 (2.27)	13.5 (3.78)
CL/BW	(mL/min/kg)	5.84 (2.42)	4.92 (0.672)	4.04 (1.24)
CL/BMI	($mL/min/kg/m^2$)	8.39 (2.81)	12.7 (2.12)	10.8 (3.53)
CL_{CR}	($mL/min/1.73m^2$)	151 (36.1)	160 (51.7)	117 (23.5)

[a] Median (range)

[b] 9 subjects received the maximum dose allowed by the protocol (1000 mg).

[c] Cross reference CSR DORINOS1009 2009.

BW - Body Weight

Figure 3. Doripenem plasma clearance corrected for BMI *versus* age.

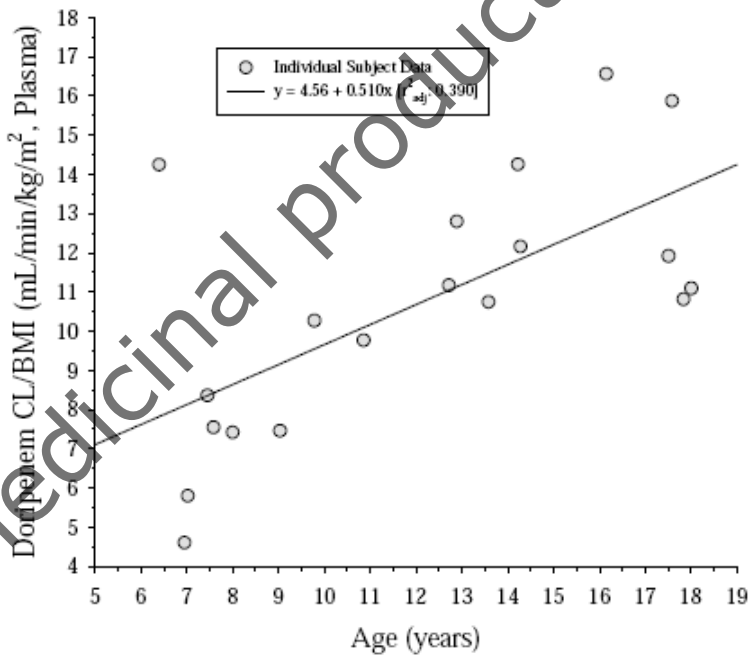


Table 3. Median (range) % time above MIC per age group.

(Study DORI-PED-1001: Pharmacokinetic Analysis Set)

	0-8h[b]	
	6 yr to <12 yr	12 yr to <18 yr
MIC	30 mg/kg	30 mg/kg[a]
n	9	10
2 µg/mL	78.2 (57.9-98.4)	77.7 (69.2-82.8)
4 µg/mL	65.0 (47.7-84.1)	62.6 (55.1-71.4)
8 µg/mL	50.4 (36.3-73.6)	46.7 (38.3-52.0)
16 µg/mL	35.7 (0.0-52.8)	29.4 (1.23-38.3)

[a] 9 subjects received the maximum dose allowed by the protocol (1000 mg).

[b] Doripenem concentration at 8h calculated as the average of the doripenem concentrations at 7h and 9h.

- **Safety results**

Twenty-two subjects were enrolled in Study DORIPED1001, of which 20 (91%) subjects completed the study per protocol. Two subjects were withdrawn from the study, one due to the adverse event of infusion site extravasation, and one due to interruption in study drug infusion for more than 10 minutes.

There were no deaths or serious adverse events (SAEs) reported in the study.

Thirteen (59.1%) of 22 subjects reported at least one adverse event in this study. All treatment-emerging adverse events (TEAE) reported in this study were mild in severity. The most common adverse events were reported in the SOC of general disorders and administration site conditions (22.7%), gastrointestinal disorders (13.6%), investigations (13.6%), and skin and subcutaneous tissue disorders (13.6%). Adverse events reported during the study at an incidence rate of 5% or greater were alanine transferase (ALT) increased, hyperhidrosis, hypokalaemia, and cough; each of these events was reported for two subjects. Seven (31.8%) subjects had one or more TEAEs that were considered by the investigator to be possibly or probably related to the study drug. They included infusion site erythema, infusion site irritation, increased ALT, increased bilirubin, elevated creatinine, hypokalaemia, vomiting, diarrhoea, and nausea. Increased ALT and hypokalaemia were reported by two subjects each; all other events were reported by one subject each. Phlebitis, hepatic enzyme increased, nausea and diarrhoea are already identified as adverse drug reactions associated with doripenem and are captured in the EU SmPC for Doribax. The two cases of hypokalaemia were confounded by concomitant therapies, and the subject with elevated creatinine never had values above the upper limit of normal (ULN) reported during the study. Too few adverse events were reported to identify trends with respect to age groups and frequency of adverse events. No consistent pattern in changes from baseline was observed across haematology, serum chemistry, or urinalysis analytes. No clinically meaningful changes in mean vital signs parameters were reported in the study.

3. Discussion on clinical aspects

The study was conducted to help determine the appropriate doripenem dosing regimens for the CF population and the obtained results will be useful for choosing the doses for future (not yet planned) larger pivotal studies in the paediatric population. Doripenem systemic exposure, as measured by AUC of doripenem, as well the estimated primary pharmacokinetic parameters (clearance and volume of distribution) were in agreement with those estimated for paediatric subjects within the same age ranges without CF administered a 500-mg equivalent doripenem single-dose (DORI-NOS-1009 2009).

The following table details the studies included in the clinical development so far and, accordingly, at present no further studies are planned.

Study title	Study number	Date of completion	Date of submission of final study report
An Open-Label, Single-Ascending-Dose, Single-Sequence, Pharmacokinetic Study of Doripenem in Adult Subjects With Cystic Fibrosis	DORI-NOS-1009	6 August 2008	N/A, this study only includes adult patients
An Open-Label Study to Evaluate the Single-Dose Pharmacokinetics and Safety of Doripenem in Pediatric Subjects 6 to 17 Years of Age, Inclusive, With Cystic Fibrosis	DORIPED1001	24 March 2010	Current submission

The present study included paediatric patients with cystic fibrosis, i.e. a different patient population compared to the currently targeted population, according to the approved indications. Reported adverse reactions considered to be at least possibly related to doripenem administration were all of mild severity and in line with currently listed events. Based on the limited database in the current study, no new safety issues were identified in this study.

3. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submitted paediatric study does not influence the benefit risk for Doribax and there is no need for regulatory action.

- **Recommendation**

☒ **Fulfilled - No further action required**

4. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable