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/P46/024

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 2010-06-11 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 was also provided.

The objective of the study was to determine the doses to be used in subsequent studies in paediatric subjects (see p. 8).

2. SCIENTIFIC DISCUSSION

2.1. Information on the pharmaceutical formulation used in the study

Doripenem monohydrate for injection was supplied as single use type 1 clear 20 mL glass vials containing 500 mg (on an anhydrous basis) of sterile doripenem powder. The formulation does not contain any excipients. Each vial of doripenem was reconstituted with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and shaken to form a suspension. The suspension was then added to an infusion bag containing 100 mL of normal saline or 5% dextrose and was mixed to complete dissolution prior to administration as an intravenous infusion. For paediatric patients requiring a dose <500 mg, the entire vial suspension after reconstitution was added to an infusion bag containing a known measured volume of normal saline or 5% dextrose. An appropriate aliquot of the resultant solution was removed for administration of the desired paediatric dose. There was no need to develop a pediatric specific formulation since the existing 500 mg vial drug product was adequate to deliver an appropriate pediatric dose. An extension application for a new strength 250 mg vial, for the renally impaired, is currently under review (submitted 05 August 2009 – EMEA/H/C/891/X/0009) and may be appropriate for pediatric use once approved and pediatric studies are completed.

2.2. Clinical aspects

1. Introduction

Study DORI-NOS-1008 was an open-label Phase 1 study designed to assess the pharmacokinetics of doripenem and its metabolite, doripenem-M-1, in medically stable pediatric subjects 3 months to 17 years of age, inclusive, who were receiving antibiotic treatment for an infection or prophylaxis.

2. Clinical study

- **Methods**

  - Objective(s)

The primary objective of this study was to assess the pharmacokinetics in pediatric subjects 3 months to 17 years of age, inclusive. The secondary objective was to evaluate safety and tolerability after doripenem administration in this population.

  - Study design

This was an open-label, parallel-group, single-dose multicenter study. The study consisted of a pretreatment phase (screening of up to 3 days [Days -3 to -1]), a 1-day open-label treatment phase (Day 1), and a posttreatment phase (including end-of-study procedures on Day 1 after completion of all planned assessments or at the time of early-withdrawal, and a telephone follow-up contact on Day 7 to assess and record any new adverse events and to follow-up on any ongoing adverse events). The total duration of the study was approximately 10 days.

- Study population /Sample size

Fifty children were enrolled in the study stratified to 4 age-groups as follows: ≥3 months to <2 years (12 subjects), ≥2 years to <6 years (13 subjects), ≥6 years to <12 years (13 subjects), and ≥ 12 years to <18 years (12 subjects).

- Treatments

Doripenem was not administered simultaneously with the infusion of other non-study antibiotics. Subjects in the 3 oldest age groups (≥2 to <18 years of age) received 15 mg/kg doripenem (5 mg/mL infusion solution) as an intravenous (i.v.) infusion over 1 hour via an indwelling catheter. Subjects in the youngest age group (≥3 months to <2 years of age) received 10 mg/kg doripenem (5 mg/mL infusion solution) as an i.v. infusion over 1 hour via an indwelling catheter. The maximum dose for any subject was 500 mg.

- Outcomes/endpoints

No formal endpoints were applied. The objectives were to study pharmacokinetics, safety and tolerability.

- Statistical Methods

Conventional methods were used.

➢ **Results**

- Number analysed

All 50 subjects were included in the safety analysis. Forty-seven subjects completed the study and 46 subjects were included in the pharmacokinetic analysis.

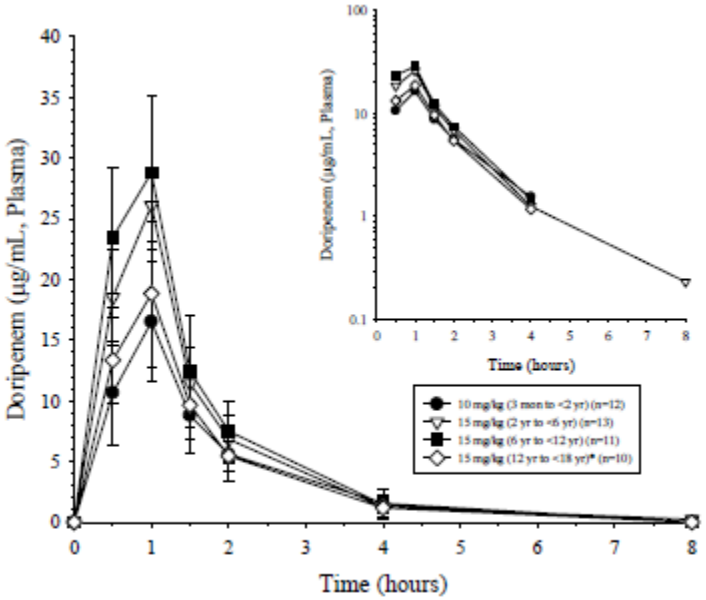
- Baseline data

	≥12 to <18 years (N=12)	≥6 to <12 years (N=13)	≥2 to <6 years (N=13)	≥3 mons to <2 years (N=12)
Race, n (%)				
N	12	13	13	12
White	11 (91.7)	7 (53.8)	9 (69.2)	7 (58.3)
Black or African American	0	3 (23.1)	2 (15.4)	5 (41.7)
American Indian or Alaskan native	0	0	1 (7.7)	0
Native Hawaiian / other pacific islander	0	1 (7.7)	0	0
Other	1 (8.3)	2 (15.4)	1 (7.7)	0
Ethnicity, n (%)				
N	12	13	13	12
Hispanic or Latino	3 (25.0)	2 (15.4)	4 (30.8)	2 (16.7)
Not Hispanic or Latino	9 (75.0)	11 (84.6)	9 (69.2)	10 (83.3)
Sex, n (%)				
N	12	13	13	12
Male	7 (58.3)	8 (61.5)	5 (38.5)	6 (50.0)
Female	5 (41.7)	5 (38.5)	8 (61.5)	6 (50.0)
Age (years)				
N	12	13	13	12
Mean (SD)	14.8 (1.04)	8.7 (2.09)	4.1 (1.31)	1.2 (0.65)
Median	15.0	8.4	4.3	1.3
Range	(12;16)	(6;12)	(2;6)	(0;2)*
Weight (kg)				
N	12	13	13	12
Mean (SD)	54.7 (5.58)	29.5 (7.50)	16.0 (3.10)	10.4 (2.67)
Median	55.1	28.0	14.9	11.3
Range	(46;65)	(20;46)	(12;22)	(6;14)
Height (cm)				
N	12	12	12	12
Mean (SD)	160.1 (13.01)	132.8 (12.95)	100.2 (12.25)	77.4 (10.61)
Median	160.0	131.0	102.5	79.0
Range	(141;190)	(115;155)	(80;117)	(62;92)
Body Mass Index (kg/m^2)				
N	12	12	12	12
Mean (SD)	21.6 (3.35)	16.6 (1.73)	16.1 (2.66)	17.2 (2.67)
Median	21.4	16.7	16.2	16.6
Range	(17;29)	(14;19)	(13;23)	(14;25)

mons=months; SD=standard deviation.
Subjects ≥3 months to <2 years of age: received Doripenem 10 mg/kg i.v;
Subjects ≥2 to <18 years of age: received Doripenem 15 mg/kg i.v. with a maximum dose of 500 mg.
* The exact age range for ≥3 months to <2 years age-group was 0.27 - 1.85 years (3 months 5 days - 1 year 10 months 5 days)

- Pharmacokinetic results

The mean (SD) plasma concentration-time profiles of doripenem are presented below.



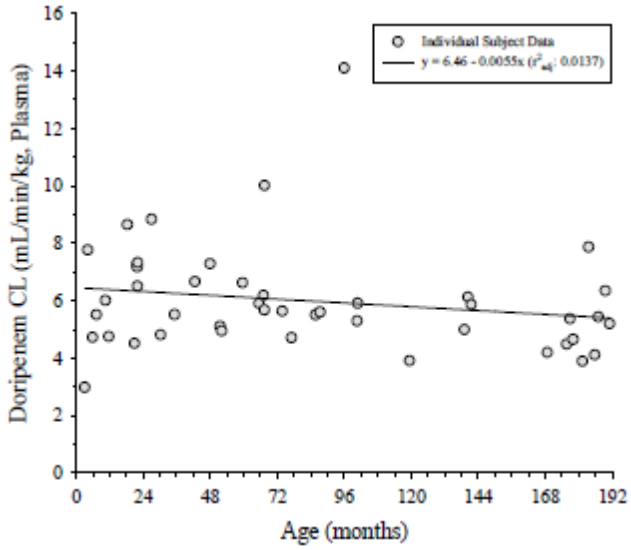
Note: Inlay plot represents log-linear doripenem concentration-time profile.
* All subjects 12 years to <18 years of age received a total dose of 500 mg doripenem.

The plasma and urine pharmacokinetic parameters for doripenem across all age groups studied following administration of doripenem are presented below.

PK Parameter		3 mon to <2 yr 10 mg/kg	2 yr to <6 yr 15 mg/kg	6 yr to <12 yr 15 mg/kg[g]	12 yr to <18 yr 15 mg/kg[h]
n		12	13	11	10
C_{max}	(µg/mL)	16.7 (4.43)	26.1 (3.02)	29.1 (6.34)[c]	18.9 (5.90)
t_{max}	(h)[a]	1.00 (0.97-1.50)	1.00 (0.92-1.02)	1.00 (0.50-1.10)[c]	0.98 (0.52-1.13)
AUC_∞	(µg•h/mL)	29.8 (10.2)	40.6 (8.47)[b]	44.8 (11.1)	31.1 (6.13)
$t_{½}$	(h)	1.01 (0.426)	0.937 (0.355)[b]	0.919 (0.211)	0.944 (0.225)
Vd_{ss}	(L)	4.86 (3.56)	6.34 (1.32)[b]	10.6 (4.38)	17.8 (4.71)
Vd_{ss}	(L/kg)	0.462 (0.291)	0.393 (0.0770)[b]	0.350 (0.138)	0.326 (0.0773)
CL	(L/h)	3.88 (1.67)	6.29 (1.62)[b]	10.5 (4.78)	16.7 (3.60)
CL	(mL/min/kg)	6.09 (1.64)	6.46 (1.59)[b]	6.14 (2.71)	5.15 (1.21)
CL_R	(L/h)	2.18 (3.02)[d]	3.33 (2.00)[e]	6.80 (1.68)[f]	12.4 (5.78)
CL_R	(mL/min/kg)	3.12 (3.57)[d]	3.17 (1.94)[e]	4.00 (1.04)[f]	3.81 (1.74)
CL_{CR}	(mL/min/kg)	16.6 (8.63)[d]	11.3 (7.84)[c]	5.52 (1.94)	3.06 (0.770)
Ae	(%,dose)	50.6 (50.0)[d]	48.1 (24.8)[e]	72.4 (24.5)[f]	74.4 (24.9)

[a] Median (range)
[b] n=12; [c] n=10; [d] n=11; [e] n=9; [f] n=8
[g] 3 subjects received the maximum dose allowed by the protocol (500 mg).
[h] All subjects received the maximum dose allowed by the protocol (500 mg).

Doripenem clearance versus age in individual subjects is presented below.



- Safety results

In total, TEAEs were reported by 28 of 50 (56%) subjects. The incidence of TEAE was the highest in the ≥2 years to <6 years age-group (77%) and the lowest in the ≥3 months to <2 years age-group (33%).

Investigations (n=9), gastrointestinal system (n=8), respiratory, thoracic and mediastinal disorders (n=6), and metabolism and nutrition disorders (n=5) were the commonly reported adverse events by system organ class.

Overall, vomiting was the most frequently reported adverse event (n=5), followed by diarrhea (n=4), increased GTT (n=3), abdominal pain, hypokalemia, pyrexia, rash, and hypertension (n=2 each).

All adverse events were mild (67%) and moderate (31%) in severity with one exception. One subject (Subject 000009) in the ≥3 months to <2 years age-group had a severe adverse event of cardiac failure; this event occurred 6 days after the administration of doripenem and was considered by the investigator as not related to study drug.

The majority of the adverse events were considered by the investigator to be not related or doubtfully related to the study drug. Adverse events considered by the investigator as possibly related to study drug were most often gastrointestinal disorders, including diarrhea (n=4), vomiting (n=4) and abdominal pain (n=2). In addition, crystalluria, presence of crystals in urine, and proteinuria were each reported once as adverse events possibly related to study drug. The only adverse event that was considered by the investigator to be probably related to study drug was the rash experienced by Subject 00001, which led to discontinuation of study drug.

No deaths occurred in this study. Two subjects experienced serious adverse events several days after study drug administration; both events were considered by the investigator to be not related to study drug.

The majority of the treatment-emergent adverse events had resolved by the end of the study. Five subjects experienced 7 persisting adverse events at the end of the study and all were considered by the investigator to be not related or doubtfully related to study drug. Three subjects had 8 adverse events with unknown outcome, all of which were adverse events considered by the investigator as not related to study drug.

No tolerability of infusion issues was noted. There were no reports of infusion-related reactions such as local irritation or potential necrosis, including pain. Adverse reactions associated with carbapenems such as seizures, hypersensitivity reactions and *C. difficile* colitis were not reported.

3. Discussion on clinical aspects

This well performed study will help the MAH to choose correct doses for the larger pivotal studies in the paediatric population. No new safety signals, which potentially would impact the paediatric plan, were seen in the study. No questions are raised.

The future studies to be performed are presented below (the current study is the first study in the package).

Area	Subarea	Number	Description
Clinical	PK, safety and tolerability	2	1) Multi-centre, open-label, study to evaluate the PK, safety/ tolerability and to identify the appropriate dose for children from 3 months to less than 18 years. 2) Multi-centre, open-label, study to evaluate PK, safety and tolerability in neonates including preterm infants with GA below 28 weeks, and in infants less than 3 months old.
	Descriptive safety and Efficacy	4	1) Randomized double-blind, multicenter, comparative study in hospitalized children 3 months to less than 18 years of age with complicated intra abdominal infections (cIAI) requiring intravenous antibiotic therapy. 2) Randomized, double-blind, multicenter, comparative study in hospitalized children 3 months to less than 18 years of age with complicated urinary tract infections (cUTI) requiring intravenous antibiotic therapy. 3) Randomized, double-blind, multicenter, comparative study in hospitalized children 3 months to less than 18 years of age with pneumonia requiring intravenous antibiotic therapy. 4) Multi-centre, open-label, descriptive safety, tolerability and efficacy study in neonates including preterm infants with GA below 28 weeks, and in infants less than 3 months of age.

There was no comparative analysis by the Company regarding identified and expected AE with regard to data from adults. While the majority of the reported adverse events considered to be at least possible related to doripenem are well known, crystalluria and presence of crystals in urine is currently not listed and should be closely monitored in the ongoing paediatric clinical program.

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