EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 January 2013
EMEA/594075/2014
Committee for Medicinal Products for Human Use (CHMP)

Doribax

(Doripenem)

Procedure No. EMEA/H/000891/P46/026

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 delete

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Doribax
INN (or common name) of the active substance:	Doripenem monohydrate
MAH:	Janssen-Cilag International NV
Currently approved indications:	Treatment of the following infections in adults: - Nosocomial pneumonia (including ventilator-associated pneumonia) - Complicated intra-abdominal infections - Complicated urinary tract infections Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Pharmaco-therapeutic group (ATC Code):	J01DH04
Pharmaceutical form and strengths:	Powder for solution for infusion, 250 mg, 500 mg

1. INTRODUCTION

On 30 October 2012, the MAH submitted a completed paediatric study for Doribax (doripenem), 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

Doribax used in the study was supplied as single use type 1 clear glass vials containing

500 mg (on an anhydrous basis) of sterile doripenem powder

Clinical aspects

2.1. Introduction

The MAH submitted a final report for:

- DORI-PED-1003: An Open-Label Study to Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Doripenem in Infants (Term and Preterm), Less Than 12 Weeks Chronological Age

2.2. Clinical study

DORI-PED-1003: An Open-Label Study to Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Doripenem in Infants (Term and Preterm), Less Than 12 Weeks Chronological Age

Description

This was a multicenter, open-label, single-dose PK study in hospitalized but medically stable infants (term and preterm), <12 weeks chronological age (CA), who had documented, were presumed to have, or were at risk for bacterial infection(s) and were undergoing treatment with IV antibiotics. Doripenem was administered alone at any time after the first dose of a nonstudy antibiotic was administered to treat an infection, colonization, or prophylaxis. Doripenem was not used in this study to treat infection and did not replace the subject's prescribed antibiotic(s).

Methods

- Objective(s)

The primary objective of this study was to evaluate the PK of doripenem after single-dose administration of Doribax to infants (term and preterm) <12 weeks CA. Safety and tolerability were also assessed.

- Study design

  multicenter, open-label, single-dose PK study

- Study population /Sample size

  Thirty-two neonatal male and female subjects, and 16 infant male and female subjects, were planned to be included in the study to ensure that at least 48 subjects completed all required assessments. Subjects were stratified by gestational age (GA), and neonate subjects were further stratified by chronological age (CA). Subjects were stratified into the following groups:

  - Age Group 1 (n=8; 5mg/kg): Neonates (<32 weeks GA and <14 days CA)
  - Age Group 2 (n=9; 5mg/kg): Neonates (<32 weeks GA and ≥14 days to <4 weeks CA)
  - Age Group 3 (n=9; 5mg/kg): Neonates (≥32 weeks to ≤44 weeks GA and <14 days CA)
  - Age Group 4 (n=8; 5mg/kg): Neonates (≥32 weeks to ≤44 weeks GA and ≥14 days to <4 weeks CA)
  - Age Group 5 (n=7; 5 or 8mg/kg): Infants (<32 weeks GA and 4 weeks to <12 weeks CA)
  - Age Group 6 (n=11; 5 or 8mg/kg): Infants (≥32 weeks to ≤44 weeks GA and 4 weeks to <12 weeks CA)
  - Treatments

    Doribax was administered as a single IV infusion. Subjects <8 weeks CA received a 5-mg/kg Doribax 1-hour infusion, and subjects ≥8 weeks CA received an 8 mg/kg Doribax 1-hour infusion. All subjects received Doribax as a 5 mg/mL IV infusion solution.

  - Outcomes/endpoints

    Safety assessments were conducted for all enrolled subjects. Safety from screening to the follow-up visit was evaluated by examining incidence, severity, relationship to study drug and type of AEs; changes in clinical laboratory results, physical examination and vital sign measurements; and concomitant medication/therapy.

  - Four blood samples, 0.2 mL each, for determination of doripenem and doripenem-M-1 plasma concentrations were collected at 1 hour (immediately before end of infusion), 1.5 hours, 3 hours and 7 hours after start of infusion. Urine samples for PK assessment were to be collected from catheterized subjects.
  - Statistical Methods

    Plasma concentration data for doripenem and doripenem-M-1 were summarized and plotted vs time after start of infusion. Pharmacokinetic parameters, e.g. Cmax, AUC and t½ were calculated using non-compartmental analysis and summarized.

Results

- Recruitment/ Number analysed

  The study was conducted from 19 Nov 2009 to 30 Apr 2012. A total of 52 subjects were assigned to 1 of the 6 age groups, of which 51 (98%) subjects completed the study. One subject was withdrawn from the study due to personal reasons.

- Baseline data

  The majority of subjects enrolled in this study were white (43 [83%] of 52 subjects). The mean age of subjects enrolled in this study was 23.2 days (range: 1 to 74 days) and the mean (±SD) baseline weight was 2.53±1.259 kg. The proportion of female subjects was slightly higher as compared with male subjects (54% vs 46%).

- Efficacy results

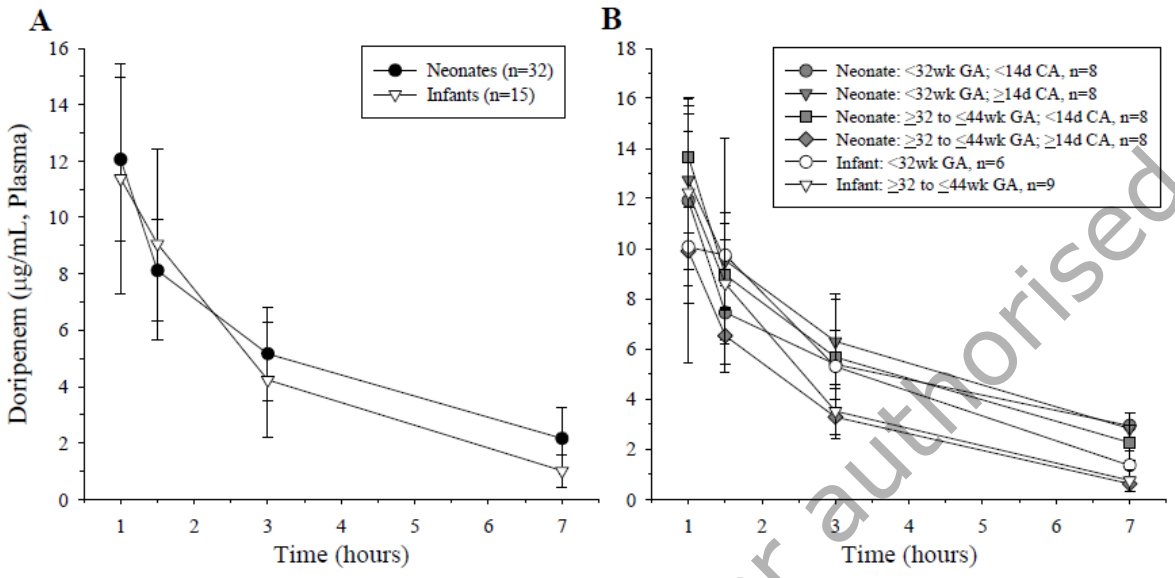
  The final PK analysis included data from 46 subjects. Of the 51 subjects completing the study, 5 were excluded from PK assessment due to protocol deviation (e.g. not receiving Doribax) or undetectable plasma concentration. Of the 46 evaluable subjects, 5 were excluded from non-compartmental analysis due to incomplete data.

  Due to high variability in the terminal phase of the doripenem-M-1 concentration-time profile, parameters calculated based on the terminal phase (AUCinf and t1/2) could not be determined.

  Urine was collected from catheterized subjects only, over the interval of 0 (start of the Doribax infusion) to 8 hours after the start of the infusion for the assessment of doripenem and doripenem-M-1 concentrations in urine. Data was obtained from 5 subjects. It is not clear from the listing (LSUB16) which numerical result that belong to each of the analytes (doripenem and doripenem-M-1), thus hampering analysis.

  The mean (SD) plasma concentration-time profiles of doripenem for neonates and infants respectively are shown in Figure 1

Figure 1 **Mean (SD) Concentration-Time Profiles of Doripenem Per Study Population and Age Group**



Pharmacokinetic parameters summarized by the initial protocol stratification of neonate (<4 weeks CA) vs infant (≥4 weeks to <12 weeks of age) are presented in Table 1.

Table 1 **Arithmetic Mean (SD) Doripenem Plasma Pharmacokinetic Parameters Per Study Population**

(Study DORI-PED-1003: Pharmacokinetic Analysis Set)

Parameter	Neonates (<4 wk CA)	Infants (4 wk to <12 wk CA)
N	32	15
C_{inf} (µg/mL)	12.1 (2.90)	11.4 (4.23)[c]
C_{max} (µg/mL)	12.2 (2.70)	11.7 (4.02)[c]
t_{max} (h)[a]	1.00 (0.98-1.50)	1.00 (0.98-1.58)[c]
AUC_{last} (µg.h/mL)	35.8 (8.95)	32.2 (10.8)[c]
AUC_{∞} (µg.h/mL)	45.7 (15.3)[b]	32.4 (9.56)[d]
$t_{1/2}$ (h)	2.98 (1.11)[b]	1.79 (0.577)[d]
CL/BW (mL/min/kg)	2.08 (0.849)[b]	3.03 (0.455)[d]
Vdz/BW (L/kg)	0.474 (0.0956)[b]	0.464 (0.142)[d]
CrCL (mL/min/kg)		
Baseline	21.4 (7.69)[e]	23.6 (8.39)[f]
End of Study	22.0 (7.93)[e]	26.4 (9.14)[f]

BW: Body Weight
[a] Median (range); [b] n=30; [c] n=14; [d] n=12; [e] n=31; [f] n=13
NOTE: Subjects <8 weeks CA: 5-mg/kg doripenem 1-hour IV infusion and subjects ≥8 weeks CA: 8 mg/kg doripenem 1-hour IV infusion
NOTE: Creatinine clearance was calculated using the Schwartz equation

The mean doripenem half-life (t1/2) was 66% longer (2.98 vs 1.79 h) and clearance normalized for body weight (CL/BW) was 31% lower (2.08 vs 3.03 mL/min/kg) in neonates as compared to infants. No evident difference in Volume of distribution (Vdz) normalized for body weight was seen between

neonates and infants although infants <32 weeks GA and neonates <32 weeks GA and <14 days CA seemed to have a slightly higher Vdz as seen in Table 2.

Table 2 Arithmetic Mean (SD) Doripenem Plasma Pharmacokinetic Parameters Per Stratification and Age Group

(Study DORI-PED-1003: Pharmacokinetic Analysis Set)

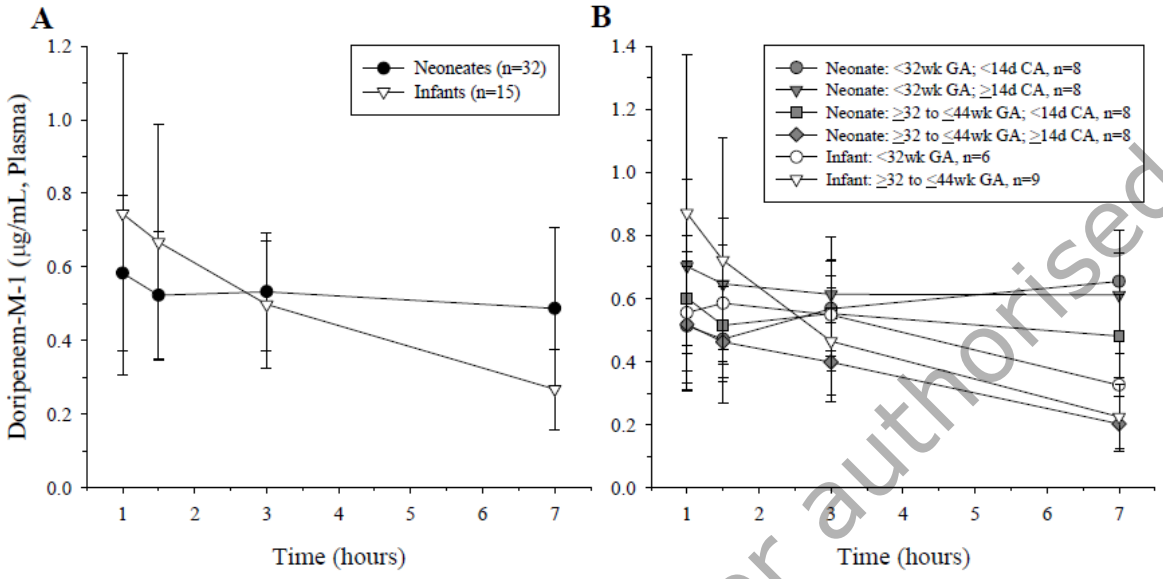
	Neonate (<4 wk CA)				Infant (4 wk to <12 wk CA)	
	<32 weeks GA		≥32 to ≤44 weeks GA			
Parameter	<14 days CA	≥14 days CA	<14 days CA	≥14 days CA	<32 weeks GA	≥32 to <44 weeks GA
N	8	8	8	8	6	9
C_{inf} (µg/mL)	11.9 (4.11)	12.7 (2.65)	13.7 (2.03)	9.91 (0.723)	9.90 (5.13)[c]	12.3 (3.71)
C_{max} (µg/mL)	12.2 (3.67)	13.2 (2.12)	13.7 (2.03)	9.91 (0.723)	10.8 (4.83)[c]	12.3 (3.71)
t_{max} (h)[a]	1.00 (1.00-1.50)	1.00 (1.00-1.50)	1.00 (1.00-1.00)	1.00 (0.98-1.00)	1.00 (1.00-1.58)[c]	1.00 (0.98-1.07)
AUC_{last} (µg.h/mL)	37.2 (5.93)	42.0 (7.72)	39.4 (6.39)	24.6 (3.77)	35.0 (14.8)	30.0 (6.91)[e]
AUC_{∞} (µg.h/mL)	55.3 (10.1)[b]	54.6 (11.7)[b]	49.2 (10.9)	26.2 (4.62)	32.9 (15.1)[d]	32.2 (6.80)[e]
$t_{1/2}$ (h)	4.22 (0.429)[b]	3.40 (0.894)[b]	2.85 (0.641)	1.66 (0.385)	2.03 (0.369)[d]	1.67 (0.644)[e]
CL/BW (mL/min/kg)	1.56 (0.340)[b]	1.59 (0.370)[b]	1.78 (0.434)	3.27 (0.589)	3.07 (0.474)[d]	3.01 (0.476)[e]
Vdz/BW (L/kg)	0.564 (0.0975)[b]	0.455 (0.0859)[b]	0.424 (0.0597)	0.461 (0.0907)	0.548 (0.151)[d]	0.422 (0.125)[e]
CrCL (mL/min/kg)						
Baseline	18.8 (4.98)	28.5 (7.27)[b]	15.1 (5.49)	24.2 (6.44)	29.7 (7.74)	18.4 (4.71)[b]
End of Study	17.8 (4.89)	30.3 (6.80)[b]	16.1 (6.07)	24.7 (5.66)	31.2 (10.1)	22.2 (6.15)[b]

[a] Median (range)
[b] n=7; [c] n=5; [d] n=4; [e] n=8
NOTE: Subjects <8 weeks CA: 5-mg/kg doripenem 1-hour IV infusion and subjects ≥8 weeks CA: 8 mg/kg doripenem 1-hour IV infusion
NOTE: Creatinine clearance was calculated using the Schwartz equation

Systemic exposure, at the doses evaluated in infants (5 mg/kg or 8 mg/kg), were generally within the range of what has previously been observed in older children and healthy adult subjects administered a single doripenem 500 mg dose over 1 hour (approximate mean [SD] AUC: 36.3 µg.h/mL [8.77]).

The mean (SD) plasma concentration-time profiles of doripenem-M-1 for neonates and infants respectively are shown in Figure 2.

Figure 2 **Mean (SD) Concentration-Time Profiles of Doripenem-M-1 Per Study Population and Age Group**



Pharmacokinetic parameters summarized by the initial protocol stratification of neonate (<4 weeks CA) vs infant (≥4 weeks to <12 weeks of age) are presented in

Table 3 **Arithmetic Mean (SD) Doripenem-M-1 Plasma Pharmacokinetic Parameters Per Study Population**

(Study DORI-PED-1003: Pharmacokinetic Analysis Set)

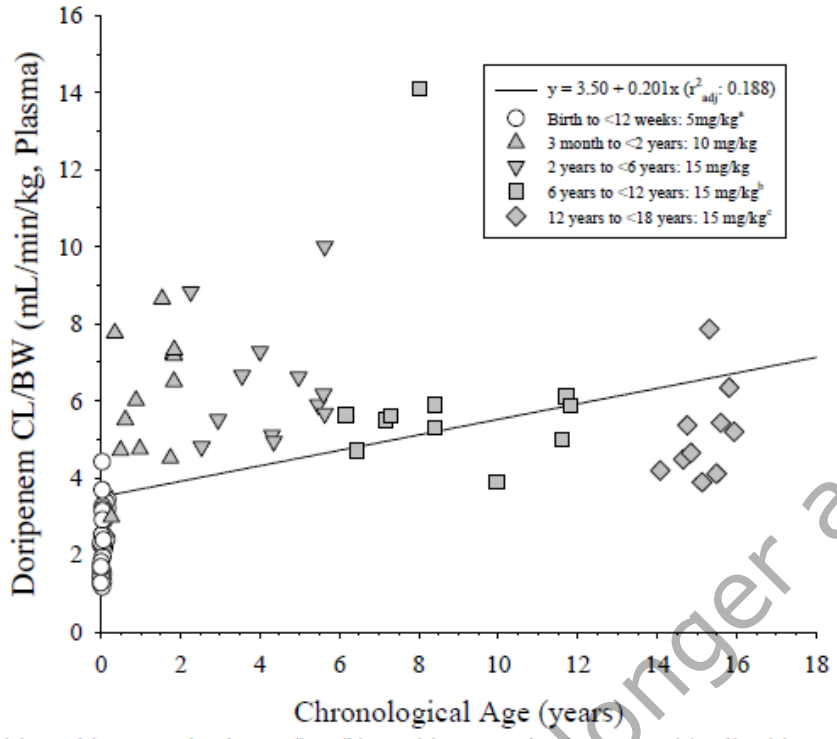
Parameter	Neonate (<4 wk CA)	Infant (4 wk to <12 wk CA)
N	32	15
C_{inf} (µg/mL)	0.584 (0.213)	0.759 (0.449)[b]
C_{max} (µg/mL)	0.658 (0.181)	0.781 (0.431)[b]
t_{max} (h)[a]	1.00 (1.00-7.08)	1.00 (0.98-1.58)[b]
AUC_{last} (µg.h/mL)	3.41 (1.01)	3.04 (1.02)[b]
M/P C_{max} Ratio	0.0572 (0.0160)	0.0738 (0.0457)[b]
M/P AUC_{last} Ratio	0.0992 (0.0165)	0.104 (0.0417)[b]

[a] Median (range)
[b] n=14
NOTE: Subjects <8 weeks CA: 5-mg/kg doripenem 1-hour IV infusion and subjects ≥8 weeks CA: 8 mg/kg doripenem 1-hour IV infusion

For doripenem, a modest decreasing trend in weight-corrected systemic clearance with increasing age was previously noted, with CL values approaching those observed in healthy adult subjects between 15 to 17 years of age [Study DORI-NOS-1008]. To appreciate this change from birth to adulthood, the data from infants was plotted with previously collected doripenem data from children <18 years of age, and the relationship between doripenem CL/BW to CA was evaluated by fitting a linear regression model to the data, see Figure 3.

Figure 3 Individual Subject Doripenem CL/BW Versus Chronological Age

(Study DORI-PED-1003: Pharmacokinetic Analysis Set)



(a) 5 subjects received 8 mg/kg; (b) 3 subjects received 500 mg; (c) All subjects received 500 mg
White symbols: Individual subject data from DORI-PED-1003;
Grey symbols: Individual subject data from DORI-NOS-1008
Linear Regression: A linear regression model was fitted with CL/BW as the dependent variable and CA as a linear predictor. The slope of the regression line (0.201) was found to be statistically significant (i.e., there was an increase in CL/BW with CA [p=<0.0001])

- Safety results

  Twenty-one (40.4%) of 52 subjects reported at least 1 TEAE in this study. The most common TEAEs reported in more than 10% subjects, belonged to the SOC of Infections and infestations and Metabolism and nutrition disorders; 13.5% each. The most common TEAE (<10%) reported in this study was neonatal anemia (4 of 52 subjects). Other TEAEs reported during the study at an incidence rate of 2% or greater were hypoalbuminemia, fungal infection, nosocomial infection, hyperglycemia, edema peripheral, dermatitis diaper, and patent ductus arteriosus. No trends with respect to age groups and frequency of AEs were observed. The incidence of TEAE was higher in Age Group 2 (Neonates [<32 weeks GA and ≥14 days to <4 weeks CA]; 7 of 9 subjects had at least one TEAE) as compared with other age groups.

  Most of the TEAEs reported in this study were mild to moderate in severity except 1 TEAE of sepsis (Subject Age Group 5), which was assessed as severe in severity and considered not related to study drug by the investigator.

  All the TEAEs were considered by the investigator as doubtfully or not related to the study drug except 2 TEAEs (oral candidiasis in Subject [Age Group 4] and neonatal agitation in Subject [Age Group 6]) which were considered as possibly related to study drug.

Most of the TEAEs were resolved by the EOS. There were 2 TEAEs reported in 2 subjects, which were persistent at the EOS; hyponatremia reported in Subject (Age Group 2) and leukocytosis reported in Subject (Age Group 6). Both these TEAEs were considered by the investigator to be mild in severity and not related to the study drug.

There was 1 TEAE of infusion site hematoma (Reported term: subcutaneous infusion/hematoma right hand [doripenem infusion was at left feet]) reported in Subject (Age Group 4) which was considered by the investigator as mild in severity and not related to the study drug.

The majority of the subjects received concomitant medication or additional treatment for TEAEs during the study.

There were no deaths reported during the study. No AEs led to the discontinuation of study drug. One SAE was reported in 1 subject during the study.

2.3. Discussion on clinical aspects

Pharmacokinetics

The CL and t½ of doripenem in healthy young adults is reported to be 3.8 mL/min/kg (assuming 70 kg body weight) and 1 hour respectively (Doribax SmPC). In this study CL and t½ was estimated for neonates and infants to 2 and 3 mL/min/kg and 3 and 1.8 hours respectively. Compared to adults and adolescents the clearance per kg body weight is lower in neonates and infants as expected considering maturation of the kidney.

The pharmacokinetics of the metabolite doripenem-M-1 was not well determined in this study and there is uncertainty about accumulation during repeated dosing in neonates. This should be considered for future studies and a discussion about risks associated with metabolite accumulation should be provided, if possible, supported by a simulation of exposure to doripenem and doripenem-M-1 following repeated dosing.

The kidney undergoes significant maturation during the first year and drug clearance during this period is a non-linear function of age. The proposed linear regression of CL/BW vs age for the age range neonates-adolescents is probably not a valid representation of the maturation effect.

Safety

The single-dose exposure to doripenem in term and pre-term infants less than 12 weeks of age, at the doses evaluated in this study of 5 mg/kg in infants <8 wks of age and 8 mg/kg in infants ≥8 wks of age, were generally similar to what have been previously observed in older children administered single doripenem 500 mg equivalent doses and healthy adult subjects administered single doripenem 500 mg dose, noting that the systemic exposure in terms of AUC generally increased in subjects born at younger gestational ages along with a slower elimination of doripenem from the systemic circulation.

Doripenem administered as a single dose of 5 mg/kg 1-hour infusion in infants

<8 weeks CA, and 8 mg/kg 1-hour infusion in infants ≥8 weeks CA, as a 5 mg/mL infusion solution in medically stable infant subjects <12 weeks CA was generally safe and well tolerated in this study.

3. Rapporteur's Overall Conclusion AND RECOMMENDATION

Overall conclusion

The data from DORI-PED-1003 will support the doripenem dosage selection for future studies in paediatric subjects. The sample sizes in all cohorts were relatively small (n<12) which limits the ability to draw firm conclusions regarding trends in the safety profile of single 5 or 8 mg/kg doses in neonates and infants <12 weeks CA. However, there were no signals of a different safety profile for these age groups compared to that of older children and adults.

Based on the submitted data, the outcome from this single study does not influence the benefit-risk balance for Doribax. Changes to the current labelling are currently not needed, but as more data become available an integrated summary of the clinical pharmacology of doripenem in paediatric patients should be amended.

Further clarification is needed regarding risk of accumulation of doripenem-M-1 following repeated dosing of Doribax to neonates.

Recommendation

Fulfilled, provided that adequate responses to the questions listed below are provided.

Further clarifications are requested below.

4. ADDITIONAL CLARIFICATIONS REQUESTED

The MAH should provide a discussion around the risk and consequences of accumulation of doripenem-M-1 in neonates following repeated administration of Doribax, if possible, supported by a simulation of exposure to doripenem and doripenem-M-1 following repeated dosing.

The MAH should list the results of the analysis of urine data so each concentration measurement is linked to its analyte. Furthermore the MAH should comment on the amount excreted during the 8 hour sampling interval and compare to results obtained in adults, adolescents and children, if available.

The study data sets including plasma concentration-time data for doripenem and doripenem-M-1 should be provided along with dosing information and demographic and clinical chemistry data in a format suitable for data analysis (e.g. csv format). If the MAH have compiled the data in a format suitable for analysis in NONMEM, this data set should be provided.