EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2014
EMA/594074/2014
Committee for Medicinal Products for Human Use (CHMP)

Doribax

(Doripenem)

Procedure No. EMEA/H/000891/P46/026.1

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 Indication	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 21 March 2013, the MAH submitted a Response to Request for Supplementary Information (RSI) on the Article 46 submission of DORI-PED-1003 (P46 026).

The MAH stated that the submitted Response to RSI 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(ies)

NA

Clinical aspects

In this section, the CHMP Questions, MAH Responses are outlined together with a critical assessment.

2.1. CHMP Question 1

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.

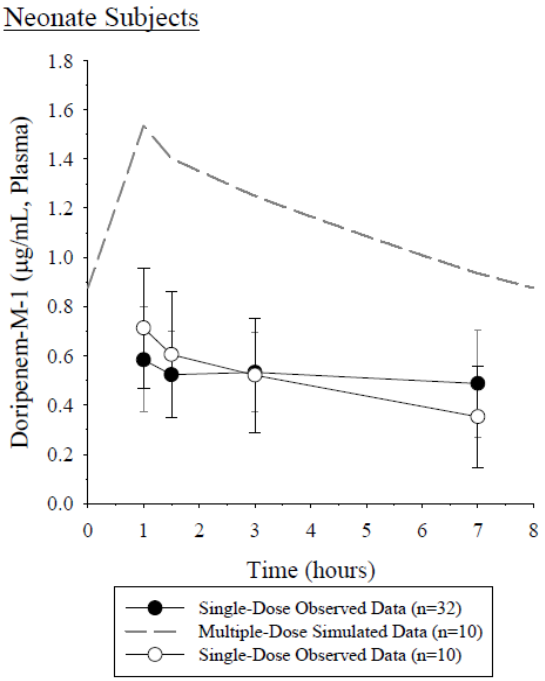
Summary of MAH's Response

Steady-state doripenem-M-1 concentration-time profiles after 14 days of doripenem dosing (5 mg/kg or 8 mg/kg) were simulated for infant and neonate subjects using nonparametric superposition methods. The predictions are based upon an accumulation ratio computed from the terminal slope, therefore only those subjects where the terminal slope of the doripenem-M-1 concentration-time profile could be estimated were included in the nonparametric superposition analysis (neonate subjects [n=10]; infant subjects [n=8]). Based on the steady-state simulated concentration-time data, Cmax, tmax, and AUCτ were determined using non-compartmental analysis methods, and then summarized descriptively by population.

The observed single-dose and simulated multiple-dose data in neonates are presented in Figure 1. The predicted steady state exposure to doripenem-M-1 in neonates was 9.19 µg.h/mL.

In adult patients with renal impairment, substantial accumulation of doripenem-M-1 has been observed. For example, an AUCτ of 40.9 µg.h/mL was observed following IV infusion of Doribax 500 mg q8h for 7 days to subjects with severe renal impairment (DORI-03). No safety issues were noted in small numbers of subjects in Studies DORI-NOS-1005 (Mod5.3.3.3/DORI-NOS-1005/CSR) and DORI-NOS-1010 (Mod5.3.3.3/DORI-NOS-1010/CSR) requiring either intermittent or continuous dialysis who received doripenem 500 mg single doses, and where levels of doripenem-M-1 were sustained at levels substantially higher than those predicted for infants after multiple-dose doripenem.

Figure 1 Observed single dose and simulated steady state exposure to doripenem-M-1 in neonate subjects following 5 mg/kg or 8 mg/kg q8h as a 1 h IV infusion.



Up to the cut-off date of February 14, 2013, safety data from 66 paediatric subjects who received at least a partial dose of study drug therapy have been reviewed. A total of 25 subjects in DORI-PED-3001, 34 subjects in DORI-PED-3002, and 7 subjects in DORI-PED-3003 were included in the analyses. Due to the blinded nature of the studies, doripenem and comparator safety data are combined into a single treatment group for the summary presented below. Of the 66 subjects, 41 (62%) reported treatment-emergent adverse events (TEAEs). Three subjects (5%) reported TEAEs of special interest (infusion site reaction). Nine of the subjects (14%) have treatment-emergent SAEs in the database, treatment-emergent SAEs included pneumonia, empyema, functional gastrointestinal disorder/ileus, appendicitis, acute pyelonephritis, diarrhoea, pseudomembranous colitis, seroma, urinary tract infection, urinary tract infection relapse, and pyuria. Two subjects who had treatment-emergent SAEs, empyema and appendicitis, discontinued from the study drug. No deaths have occurred in any of the studies. There were no relevant differences with regard to the type or severity of TEAEs across the 3 studies. Thirteen (59.1%) of 22 subjects in study DORI-PED-1001 reported at least 1 TEAE. The most common TEAEs reported in more than 10% of subjects, belonged to the system organ class of general disorders and administration site conditions (22.7%), gastrointestinal disorders (13.6%), investigations (13.6%), and skin and subcutaneous tissue disorders (13.6%). TEAEs reported during the study at an incidence rate of 5% or greater were alanine transferase increased, hyperhidrosis, hypokalaemia, and cough; each of these events was reported for 2 subjects. The number of TEAEs reported was too small to identify trends with respect to age groups and frequency of TEAEs. There were no deaths or serious adverse events reported in the study. There was 1 TEAE (infusion site extravasation) that led to withdrawal of the subject from the study. There was no specific trend observed with respect to age groups and frequency of TEAEs. All TEAEs reported in this study were mild in severity. No consistent patterns in changes from baseline were observed across haematology, serum chemistry, or urinalysis analytes. No clinically meaningful changes in mean vital sign parameters were reported in the study.

Doripenem-M-1 has also been considered in pre-clinical toxicology studies. Juvenile toxicity studies were conducted in rats and dogs. No treatment related findings were observed at any dose level. Exposure to doripenem-M-1 following multiple dosing in juvenile beagle dogs (200 mg/kg/day by IV infusion once daily for 7 days) was approximately 19 µg.h/mL.

Assessor's comment

The calculation of steady-state exposure neonates did not take all available data into account. Due to exclusion of subjects with very long (not estimable) terminal half-life, a larger accumulation of doripenem-M-1 than presented by the MAH is expected. The true accumulation factor remains uncertain.

No specific safety concern has been raised due to increased doripenem-M-1 exposure. Further, considerably higher accumulation has been observed in adult patients with renal impairment. Thus, the potentially high accumulation in neonates is not alarming as such but should be closely monitored in further clinical development of Doribax.

Issue resolved

2.2. CHMP Question 2

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.

Summary of MAH's Response

Unfortunately, this supporting information was omitted from the original submission and therefore an updated version of the study report including this data is being provided with this response document (please refer to Mod5.3.3.2/Study Report DORI-PED-1003).

Collected urine data was extremely limited; concentration data was only available in 5 subjects (3 neonate and 2 infants) and the concentrations, volumes, and amount excreted in urine in these subjects are summarized in the Clinical Study Report attachment TablePK6 of the CSR.

The amount of doripenem and doripenem-M-1 excreted over the 8-hour period for the infants was approximately 54% and 7.2% of the administered dose. The amount of doripenem and doripenem-M-1 excreted over the 8-hour period for the neonates was approximately 39% and 6.4% of the administered dose. These data were also very variable and compare most with the data collected in children 3 months to < 6 years of age.

Assessor's comment

The requested data was provided. Limited data suggest that the amount of doripenem and doripenem-M-1 excreted in urine over the 8-hour period was similar to what has been observed previously in children.

Issue resolved

2.3. CHMP Question 3

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

Summary of MAH's Response

NA

Assessor's comment The requested data was provided. **Issue resolved**

3. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

No major concern is raised regarding safety due to potential accumulation of doripenem-M-1 in neonates following repeated dosing of Doribax. Due to remaining uncertainty of the true accumulation ratio, the MAH is advised to monitor the concentration of doripenem-M-1in future clinical studies in neonates.

Recommendation

☒ Fulfilled –

No further action required

4. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable