22 May 2014
EMA/594076/2014
Committee for Medicinal Products for Human Use (CHMP)

Doribax
(Doripenem)

Procedure No. EMEA/H/000891/P46/032

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

Medicinal product no longer authorised
## ADMINISTRATIVE INFORMATION

<table>
<thead>
<tr>
<th>Invented name of the medicinal product:</th>
<th>Doribax</th>
</tr>
</thead>
<tbody>
<tr>
<td>INN (or common name) of the active substance(s):</td>
<td>doripenem monohydrate</td>
</tr>
<tr>
<td>MAH:</td>
<td>Janssen-Cilag International NV</td>
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<tr>
<td>Currently approved Indication(s):</td>
<td>Doribax is indicated for the treatment of the following infections in adults: Nosocomial pneumonia (including ventilator-associated pneumonia) Complicated intra-abdominal infections Complicated urinary tract infections</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>J01DH04</td>
</tr>
<tr>
<td>Pharmaceutical form(s) and strength(s):</td>
<td>powder for solution for infusion, 250 mg and 500 mg</td>
</tr>
</tbody>
</table>

Medicinal product no longer authorised
1. INTRODUCTION

On 7 March 2014, the MAH submitted an abbreviated clinical study report for a completed paediatric study for Doribax in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The DORI-PED-3001 study was terminated early (05 August 2013) for business reasons and not for any safety concerns and was completed on 09 September 2013. At the time of study termination, only 41 of the planned 120 subjects were enrolled.

Given the limited enrollment, meaningful conclusions about the efficacy and safety of doripenem compared with meropenem could not be drawn.

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 for injection is a sterile, synthetic, parenteral antibiotic of the carbapenem class of β-lactam antibiotics with broad-spectrum, potent antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria.

On 25 July 2008, the European Commission (EC) granted authorization of DORIBAX (doripenem) 500 mg powder for solution for infusion (EU/1/08/467/001). DORIBAX (doripenem) 500 mg 1-hour and 4-hour infusions are approved for the treatment of adults with nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), and 500 mg 1-hour infusions are approved for the treatment of adults with complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs). An optional dose of doripenem 1g 4-hour infusion was approved by the EC for the treatment of adults with VAP on 23 August 2012.

A 250-mg vial strength has also been approved in the European Union (EU/1/08/467/002; date of approval, 15 March 2010). This strength was developed to address the recommendation of the European Medicines Agency’s (EMA) Pediatric Committee (PDCO; EMEA-000015-PIP01-07) to develop pediatric dose vials with a smaller content of drug (250 mg) to adjust for the lower total dose needed in young patients and to avoid wasting drug product.

Clinical aspects

2.1. Introduction

The MAH submitted an abbreviated final report for:
**DORI-PED-3001 Phase 3**

A Prospective, Randomized, Double-Blind, Multicenter Study to Establish the Safety and Tolerability of Doripenem Compared With Meropenem in Hospitalized Children With Complicated Intra-Abdominal Infections

### 2.2. Clinical study

**Description**

**Protocol No.: DORI-PED-3001**

**Study Period:** 23 December 2010 – 09 September 2013; database lock 13 December 2013. The DORI-PED-3001 study was terminated early (05 August 2013) for business reasons and not for any safety concerns and was completed on 09 September 2013.

**Study Centers:** There were 22 study centers across 8 counties (Argentina, Brazil, Chile, Colombia, Latvia, Lithuania, Panama and United States of America [USA]). Subjects were screened and enrolled at 10 study centers when the study was early terminated on 05 August 2013.

**Methods**

**Objectives**

The **primary objective** of this study was to

- establish the safety and tolerability of doripenem compared with that of meropenem in hospitalized children 3 months to <18 years of age with complicated intra-abdominal infections (cIAI).

**Secondary objectives** were to

- determine clinical cure rates and microbiological response rates at the test of cure (TOC) visit;
- determine clinical improvement rates at end-of-treatment for the IV study drug therapy (EIV) visit;
- and to determine clinical cure rates and microbiological response rates at the late follow-up (LFU) visit;
- characterize the pharmacokinetics (PK) of doripenem based on a sparse PK sampling scheme.

The **exploratory objective** was to

- determine the fraction of simulated subjects that met the pharmacodynamic (PD) goal of 35% T>MIC (plasma drug concentrations were greater than the minimal inhibitory concentration [MIC] for at least 35% of the dosing interval) for selected MICs over a single dosing interval utilizing the PK model developed from sparsely sampled PK data.
Study design

The DORI-PED-3001 study was 1 of 3 pediatric Phase 3 studies that made up Janssen’s overall pediatric clinical development plan.

Study DORI-PED-3001 was a prospective, randomized, double-blind, double-dummy, active comparator-controlled, multicenter study to establish the safety and tolerability of doripenem compared with meropenem in the treatment of hospitalized children 3 months to <18 years of age with clinical evidence of complicated intra-abdominal infection (cIAI) and required both operative drainage of an infective intra-abdominal focus and antimicrobial treatment.

Secondary objectives were to determine clinical cure rates at the test-of-cure (TOC) visit, to determine clinical improvement rates at the end-of-treatment for intravenous (IV) study drug therapy (EIV) visit, to determine clinical relapse rates at the late follow-up (LFU) visit, to determine microbiological response rates at the TOC and LFU visit, and to characterize pharmacokinetics (PK) of doripenem based on a sparse PK sampling scheme.

Study population /Sample size

Approximately 420 subjects were to be enrolled in total across the 3 studies (cIAI, complicated urinary tract infection [cUTI], pneumonia), with each study enrolling a minimum of 90 subjects in the doripenem treatment group and a minimum of 25 subjects in the comparator group. At least half of the total number of doripenem-treated subjects in all 3 studies combined must have been <6 years of age with at least 50 doripenem-treated subjects <2 years of age and at least 100 doripenem-treated subjects 2 to <6 years of age in all 3 studies combined.

Planned: A minimum of 120 subjects were to be randomly assigned to IV doripenem or IV meropenem in DORI-PED-3001 study in approximate 3:1 ratio.

Analyzed: 41 subjects were enrolled and treated in this study.

Diagnosis and Main Criteria for Inclusion:

- Boy or girl, 3 months to <18 years of age, with clinical evidence of cIAI, and requiring surgical intervention (eg, laparotomy, laparoscopic surgery, or percutaneous drainage) to manage the cIAI as well as antibacterial therapy for 5 to 14 days in addition to the surgical intervention.

Main exclusion criteria:

- History of hypersensitivity reactions to any β-lactam antibiotics;
- Concomitant infection including meningitis or other CNS infection requiring systemic antibiotic or antifungal therapy;
  - more than 24 hours of systemic antibiotic therapy immediately preceding start of infusion of first dose of study drug;
- Diagnosis of abdominal wall abscess confined to abdominal wall musculature, small bowel obstruction or ischemic bowel disease without perforation, traumatic bowel perforation requiring surgery within 12 hours of perforation, or perforation of gastroduodenal ulcers requiring surgery within 24 hours of perforation;
- spontaneous bacterial peritonitis or peritonitis associated with cirrhosis or chronic ascites;
- enrolled intra-operatively or post-operatively with simple, non-perforated appendicitis or gangrenous appendicitis without rupture into the peritoneal cavity identified during the surgical procedure;
- history or suspected history of uncomplicated intra-abdominal infection;
- gangrenous or suppurative cholecystitis without rupture or extension beyond gallbladder wall, acute suppurative cholangitis, infected necrotizing pancreatitis, or pancreatic abscess;
- failed prior surgical and or medical therapy with presumed ongoing or recurrent intra-abdominal infection;
- cIAI caused by at least one pathogen non susceptible to doripenem or meropenem;
- had (or suspected) intra-abdominal process in which primary etiology was unlikely infectious;
- was to be managed by Staged Abdominal Repair or open abdomen technique;
- girls who were pregnant, nursing, or menarchal, and if sexually active not practicing, before screening, and did not agree to continue using a highly effective method of birth control for 30 days after last dose of study drug therapy;
- any rapidly progressing disease or life-threatening illness;
- clinically significant laboratory abnormalities of hematocrit, absolute neutrophil count, platelet count, serum alanine aminotransferase, aspartate aminotransferase, or total bilirubin;
- acute or chronic renal insufficiency;
- profoundly immunodeficient and requiring prophylactic antimicrobial therapy to prevent *Pneumocystis jirovicei* infection, *Toxoplasma gondii*, or herpes viruses, and/or required chronic or intermittent immunoglobulin replacement therapy;
- receiving chemotherapy for current malignancy;
- had organ or bone marrow transplant and treated with chronic immunosuppressive therapy for prevention of organ transplantation rejection;
- receiving imuran, methotrexate, or chronic corticosteroid therapy;
- cystic fibrosis diagnosis;
- history of uncontrolled epilepsy;
- receiving probenecid or valproic acid.

**Treatments**

**Test Product, Dose and Mode of Administration, Batch No.:**

Doripenem was supplied as fine white to slightly yellowish off-white powder for IV administration in vials containing 500 mg of sterile powder.
Reference Therapy, Dose and Mode of Administration, Batch No.:

Meropenem, the comparator, was supplied in pharmacy-use vials containing 1 g of sterile powder. Meropenem is a white to pale yellow crystalline powder.

Duration of Treatment: Subjects were to receive a 5- to 14-day course of study drug therapy, which consisted of IV study drug only or at least 3 days of IV study drug followed by oral amoxicillin/clavulanate potassium. If, at any time after receiving at least 9 paired doses (approximately 72 hours) of IV study drug therapy, the subject did not demonstrate improvement in signs or symptoms of cIAI, or continued to have a fever that was not resolving, and was without an alternative explanation, or had clinical evidence of recurrent cIAI, and required alternative non study antibiotic therapy (other than adjunctive therapy with vancomycin or other approved alternative), the subject was to be considered a treatment failure and should have discontinued from study drug therapy and been followed for safety.

Outcomes/endpoints

Efficacy:

Clinical and microbiological outcome assessments were performed at the EIV, TOC, and LFU visits. Clinical outcomes were based on an assessment of the signs and symptoms of cIAI. The clinical outcomes at EIV were rated as clinical improvement, clinical failure, or indeterminate. The clinical outcomes at the TOC and LFU visits were rated as clinical cure, clinical failure, or indeterminate. Microbiological assessments were based on the culture results of intra-abdominal specimens. An overall per-subject microbiological response was determined at EIV, TOC, and LFU.

Pharmacokinetics:

Four blood samples (0.4 mL each) for determination of doripenem and doripenem M-1 or meropenem plasma concentrations were collected from all subjects. Pharmacokinetic sample collection occurred relative to the start of the infusion of the scheduled fourth, fifth, sixth, or seventh 60-minute dose of doripenem/doripenem placebo. PK blood samples of meropenem plasma concentration were not analyzed for drug concentration.
Safety:

Safety evaluations included the measurement of vital signs, monitoring of reported adverse events, including serious adverse events, concomitant therapy, serum chemistry and hematology assessments, and urinalysis with microscopy. A urine pregnancy test was performed for menarchal girls unless a serum pregnancy test was preferred at the discretion of the investigator or if required by local regulations.

Statistical Methods:

The cumulative sample size for all 3 pediatric studies (cIAI, cUTI, and pneumonia) was based on obtaining sufficient safety data in children. The primary focus of this study was safety. No pre-specified statistical hypothesis for efficacy was tested in this study. Safety data were summarized for the intent-to-treat (ITT) population. For efficacy, a 95% CI of the difference in the event rate (doripenem minus meropenem) was calculated to compare the clinical outcome rate between the two treatment groups in the clinical ITT (CITT; subjects who met the minimal disease definition of cIAI regardless of whether a baseline pathogen was isolated from the intra-abdominal cavity) and in the microbiological ITT (MITT, CITT subjects who had at least one baseline bacterial pathogen isolated from a specimen obtained from the intra-abdominal cavity which was susceptible to both doripenem and meropenem; subjects from whom the only documented intra-abdominal pathogen was Enterococcus or MRS were not included in this analysis set).

Results

Recruitment/ Number analysed

Study population:

A total of 41 subjects were randomized and treated in the study and included in the safety analysis set. Of the 41 subjects, 31 subjects were assigned to treatment with doripenem and 10 subjects were assigned to treatment with meropenem. All subjects were included in ITT and CITT analyses sets.

A total of 31 subjects were included in the MITT analysis set (23/31) doripenem-treated subjects and 8/10 meropenem-treated subjects). All doripenem-treated subjects were evaluated through the TOC and LFU visits and completed the study.

Eight of the 10 subjects treated with meropenem completed the study. Eight subjects in the doripenem group and 2 subjects in the meropenem group were excluded from the MITT analysis set.

Of these 10 subjects, 7 had a negative baseline culture (6 in the doripenem group and 1 in the meropenem group). One subject in each treatment group had no culture at baseline and 1 subject in the doripenem group had a pathogen with unknown susceptibility to both study drugs.

Approximately half of the subjects in the doripenem treatment group were male (51.6%) while all of subjects in the meropenem group were male. The majority of the subjects in both treatment groups were white (80.5%). Age distribution within each treatment group was similar with the greatest percentage of subjects in the 6 to 12 years of age category; 18 (58.1%) subjects in the doripenem treatment group and 4 (40%) subjects in the meropenem treatment group. No subjects were enrolled in the 3 months to 2 years of age group.
Baseline data

At baseline, the majority of subjects in both treatment groups had infections at the site of the appendix (95.1% [93.5% in the doripenem group and 100% in the meropenem group]).

A total of 17/41 (41.5%) subjects in both treatment groups were diagnosed with generalized peritonitis (13/31 [41.9%] in the doripenem group and 4/10 [40.0%] in the meropenem treatment group) and a total of 24/41 (58.5%) subjects in both treatment groups (18/31 [58.1%] in the doripenem group and 6/10 [60.0%] in the meropenem group) were reported to have other infection processes which included localized peritonitis, localized infection, multiple and single abscesses with visceral perforation.

More than half of the subjects (19/31 [61.3%] in the doripenem treatment group and 8/10 [80%] in the meropenem treatment group) required an open abdominal operative procedure and the remaining subjects in both treatment groups underwent “other” procedures for intra-abdominal infections (laparoscopy, laparoscopy converted to an open procedure, and percutaneous drainage). The majority of the subjects (27/31 [87.1%] in the doripenem treatment group and 10/10 [100%] in the meropenem treatment group) received prior antibacterial therapies for cIAI.

Less than 30% of subjects in each treatment group (29.0% [9/31 subjects] in the doripenem group and 20.0% [2/10 subjects] in the meropenem group) received concomitant bacterial therapy. None of the subjects had bacteremia at baseline or received vancomycin as adjunctive therapy for cIAI.

The total median duration of IV study drug therapy for the doripenem treatment group was 7 days (range: 4 to 14 days) and 4 days (range: 2 to 11 days) for the meropenem treatment group. For subjects who switched to oral therapy, the median duration of oral treatment for doripenem-treated and meropenem treated subjects was the same, 7 days (with a range of 2 to 10 days for doripenem-treated subjects and 4 to 10 days for meropenem-treated subjects). The maximum duration of treatment per protocol was 14 days or fourteen 24-hour treatment periods.

Efficacy results

The clinical improvement rates at EIV were 93.5% (29/31) for the doripenem group and 80.0% (8/10) for meropenem-treated subjects.

At the TOC visit the cure rates were 74.2% (23/31) for doripenem-treated subjects and 70.0% (7/10) for meropenem-treated subjects.

At LFU, the cure rates were essentially unchanged from TOC for the doripenem treatment group but lower for meropenem treatment group (71.0% [22/31] and 60.0% [6/10], respectively).

The efficacy analyses were considered exploratory because there was no pre-specified statistical hypothesis for this study. Furthermore, the CIs for the difference between the clinical improvement/cure rates of doripenem vs. meropenem treatment groups were wide due to the small sample size. Therefore no meaningful conclusions can be made.

No subjects included in the MITT analysis set had a post baseline intra-abdominal culture at the predefined windows of the EIV, TOC, and LFU visits. Consequently, all the microbiological outcomes reported in this study were derived from the clinical outcomes.

A favorable microbiological response rate was observed for 91.3% (21/23) of doripenem-treated subjects and 75.0% (6/8) of meropenem-treated subjects at the EIV visit.
At the TOC and LFU visits, the microbiological response rates were favorable for 73.9% (17/23) of doripenem-treated subjects and favorable for 62.5% (5/8) of meropenem-treated subjects.

At the EIV visit, the microbiological response rate in doripenem-treated subjects was favorable for >90% of subjects with *E. coli* (94.7% [18/19]), *Streptococcus anginosus* (92.3% [12/13]), and *Bacteroides fragilis* (90.9% [10/11]). The microbiological response rate in meropenem-treated subjects was favorable for 75.0% (6/8) subjects with *Escherichia coli*.

At the TOC and LFU visits, there was a favorable microbiological response rate in 81.8% (9/11) doripenem-treated subjects with *B. fragilis*, 78.9% (15/19) with *E. coli*, and 69.2% (9/13) with *S. anginosus*. The favorable microbiological response rate in meropenem-treated subjects with *E. coli* was 62.5% (5/8). Overall, the microbiological response rate was favorable at the EIV, TOC, and LFU visits for most baseline pathogens isolated in only a single subject.

The clinical response rates and microbiological outcomes were in agreement for all subjects in both treatment groups included in the MITT analysis set because all the microbiological outcomes were derived from the clinical outcomes.

One super infection was identified in a doripenem-treated subject. The pathogen was isolated from an abscess on Day 8 while on IV therapy. The pathogen isolated was *Bacteroides stercoris*, which was reported as susceptible to doripenem.

**Pharmacokinetic results**

Thirty-nine subjects had pharmacokinetic blood samples obtained, of which 31 subjects received doripenem. Three subjects were excluded from all PK assessments due to insufficient number of samples or protocol violations with respect to sampling time. Two samples were excluded from descriptive statistics due to protocol violation with respect to sampling time: Subject, 2 hour PK blood sample; Subject, 1 hour PK blood sample.

The mean (SD) doripenem and doripenem-M-1 PK data is presented in the table below.

**Table 1 Mean (SD) Doripenem and Doripenem-M-1 Plasma Pharmacokinetic Parameters Following Administration of 20 mg up to maximum of 500 mg Doripenem as a 60 min IV infusion q8h**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Doripenem</th>
<th>Doripenem-M-1</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>29.0 (10.9)</td>
<td>2.19 (0.716)</td>
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<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>0.92 (0.83-1.43)</td>
<td>0.92 (0.83-1.43)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt; (µg·h/mL)</td>
<td>50.3 (18.9)</td>
<td>5.76 (1.78)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24h&lt;/sub&gt; (µg·h/mL)</td>
<td>52.6 (19.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.22 (2.06)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.09 (0.222)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.93 (0.561)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CL &lt;sub&gt;(L/h)&lt;/sub&gt;</td>
<td>10.3 (5.70)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13.1 (8.09)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>V &lt;sub&gt;(L)&lt;/sub&gt;</td>
<td>0.404 (0.267)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>187 (64.5)</td>
</tr>
<tr>
<td>V&lt;sub&gt;B&lt;/sub&gt;/BW (L/kg)</td>
<td>4.04 (2.97)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>187 (64.5)</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>187 (64.5)</td>
<td>187 (64.5)</td>
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</table>

<sup>a</sup> Median (range); <sup>b</sup>n=26

**NOTE:** τ equals 8 hours

**Cross-reference:** TablePK3
The doripenem and doripenem-M-1 concentrations observed in this study overlapped with previously observed concentrations in children and adult subjects administered 500 mg or 1000 mg (or equivalent) doses.

Safety results

The safety analyses was based on 41 subjects (31 subjects in the doripenem treatment group and 10 subjects in the meropenem treatment group) who were randomized, received at least a partial dose of double-blind study drug.

For both treatment groups, the highest incidence of treatment-emergent adverse events (TEAEs) was in the system organ class of gastrointestinal disorders. The most common TEAEs reported in the doripenem treatment group were abdominal pain (5 subjects) and nausea (3 subjects). In the meropenem treatment group, the most commonly reported TEAEs were diarrhea (2 subjects) and vomiting (2 subjects).

Ten of 41 subjects had study drug-related TEAEs. Nine subjects from doripenem treatment group had 13 study drug-related TEAEs. Seven of those TEAEs have already been identified as adverse drug reaction (ADRs) in the adult population treated with doripenem: diarrhea, infusion-site pain, alanine transaminase (ALT) increased, aspartate aminotransferase (AST) increased, hepatic enzyme increased, rash papular, and phlebitis. The other study drug-related TEAEs, hematuria, eosinophilia and gamma-glutamyl transpeptidase (GGT) elevation, were confounded by multiple concomitant medications including anesthetics and analgesics, baseline abdominal infections, and recent abdominal surgery.

Finally, a case of overdose was reported in 1 doripenem-treated subject which was considered to be a serious adverse event. One subject in the meropenem treatment group had a study-drug related TEAE of diarrhea.

There were no deaths or TEAEs leading to study discontinuation in either treatment group.

A total of 7 subjects reported treatment-emergent serious adverse events (SAEs); all were in the doripenem treatment group (abdominal pain [3 subjects], and 1 subject each of functional gastrointestinal disorder, abdominal abscess, overdose, and seroma). All treatment-emergent SAEs were considered by the investigator to be unrelated to study drug, except the SAE of overdose. In this case, the subject received the correct dose of doripenem every 6 hours instead of every 8 hours for 4 days. The investigator reported the adverse event as serious. The remaining 6 treatment-emergent SAEs were consistent with the natural progression of the abdominal infection or complications related to the surgical procedure.

Two doripenem-treated subjects were discontinued from oral amoxicillin/clavulanate when an SAE of abdominal pain was reported. Both subjects completed the study.

There were no clinically relevant differences between the 2 treatment groups in the mean values of hematology, chemistry, or urinalysis parameters over time except a slight increase in ALT in the doripenem treatment group. Increases in ALT and AST have already been identified as ADRs in the adult population treated with doripenem.

Three of 31 doripenem-treated subjects experienced TEAEs of special interest of local site reactions. In general, the adverse events reported in this study were related to the underlying baseline infection or its complications. The safety findings from this study are consistent with the safety profile for doripenem observed in adults and no new safety issues were identified.
Study limitations

This study was terminated early due to business reasons and not related to safety concerns or issues. As such, the limited enrollment precludes a meaningful conclusion about the efficacy and safety of doripenem compared with meropenem.

3. Discussion on clinical aspects by the MAH

The major limitation of the study was limited enrollment, which precludes a meaningful conclusion about the efficacy and safety of doripenem compared with meropenem for the pediatric population under study.

Doripenem administered as 20 mg/kg per dose (up to a maximum of 500-mg dose) as a 1-hour infusion in subjects 3 months to <18 years of age was generally safe and well tolerated in the subjects who enrolled in this study. There were no new safety findings identified in subjects treated with doripenem in this study. The doripenem and doripenem-M-1 concentrations and exposures observed in this study fall within the range of those previously measured in adults and children administered 500 mg or 1000 mg (or mg/kg equivalent) doses.

The clinical response rates and microbiological outcomes were in agreement for all subjects in both treatment groups included in the MITT analysis set because all the microbiological outcomes were derived from the clinical outcomes.

One super infection was identified in a doripenem-treated subject. The pathogen was isolated from an abscess on Day 8 while on IV therapy. The pathogen isolated was Bacteroides stercoris, which was reported as susceptible to doripenem.

Doripenem administered as 20 mg/kg per dose (up to a maximum of 500-mg dose) as a 1-hour infusion in subjects 3 months to <18 years of age was generally safe and well tolerated in this study. In general, the adverse events reported in this study were related to the underlying baseline infection or its complications. The safety findings from this study are consistent with the safety profile for doripenem observed in adults and no new safety issues were identified.

No specific benefits or special precautions can be derived from these limited data. Because the data from this study do not influence the benefit-risk balance for the product, no changes to the current labeling are proposed at this time.

Conclusions

- Enrollment in this study was too limited to determine the comparable efficacy and safety with meropenem for the pediatric population under study.
- Doripenem administered as 20 mg/kg per dose (up to a maximum 500-mg dose) as a 1-hour infusion in subjects 3 months to <18 years of age was generally safe and well tolerated in the subjects who enrolled in this study. There were no new safety findings identified in subjects treated with doripenem in this study.
- The percentage of subjects who were clinically cured at the TOC visit was 74.2% (23/31) in the doripenem group and 70.0% (7/10) in the meropenem group. However, there was no pre-
specified statistical hypothesis for this study. Efficacy analyses were considered exploratory and meaningful conclusions cannot be made given the limited subject enrollment in the study.

- The doripenem and doripenem-M-1 concentrations and exposures observed in this study fall within the range of those previously measured in adults and children administered 500 mg or 1000 mg (or mg/kg equivalent) doses.

4. **Rapporteur’s Overall Conclusion AND RECOMMENDATION**

**Overall conclusion**

The outlined study protocol can be considered satisfactory.

The major limitation of the study was limited enrollment and early termination, which precludes a meaningful conclusion about the safety and tolerability of doripenem compared with meropenem in hospitalised children with complicated intra-abdominal infections.

Doripenem administered as 20 mg/kg per dose (up to a maximum 500-mg dose) as a 1-hour infusion in subjects 3 months to <18 years of age was generally safe and well tolerated in this study.

The doripenem and doripenem-M-1 concentrations and exposures observed in this study fall within the range of those previously measured in adults and children administered 500 mg or 1000 mg (or mg/kg equivalent) doses.

Safety data is not sufficient to draw any conclusions regarding the efficacy and safety of doripenem compared with meropenem in the present patient population.

No specific benefits or special precautions can be derived from these limited data.

**Recommendation**

- [ ] Fulfilled –

No further action required.

5. **ADDITIONAL CLARIFICATIONS REQUESTED**

Not applicable