European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Doribax

International Nonproprietary Name: doripenem

Procedure No. EMEA/H/C/000891

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 27 June 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Doribax, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 14 December 2006.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies)

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
A new application was filed in the following countries: USA (12 December 2006).
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: T. Salmonson
Co-Rapporteur: A. Irs

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 27 June 2007.
- The procedure started on 20 July 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 October 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 October 2007.
- During the meeting on 12-15 November 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 November 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 February 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 April 2008.
- During the CHMP meeting on 21-24 April 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 30 April 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 9 May 2008.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 23 May 2008.
- During the meeting on 27-30 May 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a

Marketing Authorisation to Doribax on 30 May 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 27 May 2008.

- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 25 July 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Carbapenems as broad spectrum antibacterial agents are often used as empiric therapy since they provide coverage against both gram positive and gram negative pathogens. Multiple studies have shown that patients with severe infections if treated early with agents that are effective against infecting organisms have better survival rate than those treated initially with agents of suboptimal antibacterial activity. Therefore in most guidelines carbapenems are first option for empiric therapy of sepsis. At present three carbapenems (meropenem, imipenem/cilastatin and ertapenem) are available in European markets. Resistant pathogens, and especially multi-drug resistant strains, can be associated with increased mortality and morbidity. At present carbapenems would fulfill most of the criteria being potentially effective in difficult to treat infections. The applicant is seeking approval for doripenem for following indications: complicated urinary tract infections (cUTI), complicated intraabdominal infections (cIAI) and nosocomial pneumonia (NP) including ventilator associated pneumonia (VAP)

Urinary tract infections (UTIs) are associated with a high risk of morbidity, especially in the elderly population, and are the leading cause of gram-negative bacteremia in subjects of all ages. Complicated lower UTIs (cLUTIs) occur in subjects with a functionally, metabolically, or anatomically abnormal urinary tract and range from cystitis to life-threatening urosepsis. The predisposing conditions that constitute functional or anatomical abnormalities of the urinary tract include the presence of an indwelling catheter, increased residual urine after voiding or neurogenic bladder, obstructive uropathies such as nephrolithiasis or fibrosis, and urinary retention in men, often due to benign prostatic hypertrophy. Complicated UTIs are caused by a broad range of bacteria, many of which are becoming increasingly resistant to multiple antibacterial agents. For this reason, the carbapenems may become the optimal choice for first-line antibacterial therapy.

Complicated intra-abdominal infections are commonly encountered in general surgery, and require both operative drainage and empiric, broad-spectrum antibacterial therapy. Since antibacterial therapy must be initiated before culture results are available, the antibacterial agent chosen must cover the gram-positive and gram-negative aerobic and anaerobic bacteria that comprise the usual gastrointestinal (GI) flora. As reported in the literature, the pathogens most frequently encountered in cIAI include *E. coli*, other common *Enterobacteriaceae*, *B. fragilis*, and a wide variety of other anaerobes. Often these infections are polymicrobial caused by aerobic and anaerobic bacteriae. Due to the broad spectrum of antibacterial activity against aerobic and anaerobic pathogens that cause cIAI, it is expected that doripenem would be effective in the treatment of cIAIs, including those caused by pathogens resistant to other antibacterial agents.NP is the second most common hospital-acquired infection, with VAP the most common intensive care unit (ICU)-acquired infection. It caused by a broad range of bacteria, and is associated with a high risk of morbidity, especially in mechanically-ventilated subjects. The pathogens most frequently encountered in NP vary from center to center and include *S. aureus*, *K. pneumoniae, E. coli*, *P. aeruginosa*, *Acinetobacter* species, *H. influenzae*, and *S. pneumoniae*. Because the mortality rate and other complications (e.g., acute respiratory distress syndrome [ARDS], empyema, and lung abscess) from NP can be high, effective management of these infections requires early diagnosis and treatment with an optimal antibacterial agent with a spectrum of activity to cover all these pathogens. Carbapenems have the broad spectrum of antibacterial activity and most of them have good activity against more resistant species, such as *P. aeruginosa*, which in many centres is the predominant organism among causative agents of NP.

- **About the product**

Doripenem monohydrate (JNJ-38174942, S-4661), a synthetic antibiotic, is a new chemical entity that belongs to the carbapenem class of beta-lactams. Doripenem monohydrate is sparingly soluble in water, slightly soluble in methanol, and practically insoluble in ethanol. Doripenem is administered via intravenous route.

Doripenem is active against a range of Gram positive and Gram negative bacteria, as shown in vitro and in animal models. Doripenem is resistant to hydrolysis by a variety of β-lactamases, including penicillinases, cephalosporinases, and extended spectrum β-lactamases. Doripenem exhibits time-dependent bactericidal activity and moderate and short post-antibiotic effect in vitro and in animal models.

The approval is sought for the indication of:

Treatment of the following infections caused by strains of bacteria sensitive to doripenem:

- Complicated urinary tract infections (UTI), including complicated and uncomplicated pyelonephritis and cases with concurrent bacteremia.
- Complicated intra-abdominal infections

- Nosocomial pneumonia, including ventilator-associated pneumonia (VAP)

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibility to doripenem. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Several Phase 1 studies, one Phase 2 study and 6 pivotal Phase 3 studies have been submitted to support the application.

Doripenem was initially developed in Japan and has received approval there in 2005 as Finibax. Finibax is indicated for multiple bacterial infections, the majority of which are respiratory indications. The usual dose, according to the Japanese label, is 250 mg intravenously (i.v.) infused over 30 to 60 minutes 2 or 3 times a day; the maximum dose is 500 mg per administration up to a total dose of 1,500 mg/day

2.2 Quality aspects

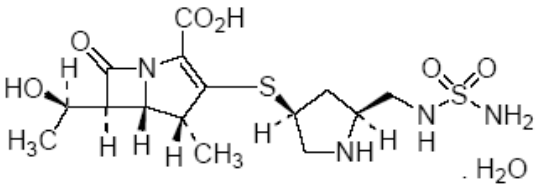
Introduction

Doripenem monohydrate is a new active substance and is a synthetic carbapenem antibiotic structurally related to other β-lactam antibiotics. It is formulated as a dry powder for solution for infusion due to hydrolysis of the drug substance in water.

The drug product contains doripenem monohydrate equivalent to 500 mg of doripenem (on an anhydrous basis). The product is a sterile powder for solution for infusion with no excipient.
It is supplied in Ph.Eur. Type I flint glass vials with butyl rubber stoppers covered with fluororesin on top and bottom. The vials are capped with aluminium seal a plastic cap.

Active Substance

Doripenem (INN) or (4*R*,5*S*,6*S*)-3-[((3*S*,5*S*)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl)thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate (IUPAC) is a new chemical entity and hence an in-house monograph has been proposed.



It is a white to slightly yellowish, off-white crystalline powder, soluble in N,N-dimethylformamide, sparingly soluble in water and slightly soluble or insoluble in most of the organic solvents. It is not hygroscopic. Doripenem possesses 6 asymmetric carbons but only one pure isomer is used (see structural formula above). Polymorphism: Doripenem has not been found to exhibit true polymorphism, it can however co-crystallize with water to form a monohydrate.

- Manufacture

The synthesis of doripenem monohydrate can be summarised in three steps: hydrolysis, condensation and hydrogenation steps starting from two chirally-pure materials. The final step of the synthesis consists of purification under aseptic conditions. The route of synthesis is well described and possible impurities specified.

Appropriate specifications have been provided and justified for starting materials, solvents, reagents, catalysts materials used in the synthesis. Several batch analysis data for both starting materials are presented. Suitable specifications for intermediates of doripenem have also been presented.

Sterilisation methods were investigated, and the aseptic processing technique was the method chosen and validated. Based on the presented data the procedure adequately guarantees sterility of the active substance.

Manufacturing development: During the course of development doripenem monohydrate was found to have superior stability over other forms. Therefore it was the form selected for late stage development studies and commercial manufacturing.

The structure of doripenem was fully elucidated by elemental analysis, UV, IR, MS, ^{13}C-NMR, ^{1}H-NMR, mass spectrometry. The doripenem molecule contains 6 chiral carbon centers. Theoretically, maximal 2^6, or 64 stereoisomers may occur. However, the current manufacturing process consistently produces drug substance with the desired stereochemistry (see structure above). The molecular structure of doripenem and the absolute stereochemistry configuration were confirmed by single crystal X-ray crystallography.

The physico-chemical characterisation was conducted by X-ray powder diffraction, IR spectroscopy, thermogravimetry analysis (TGA) and differential thermal analysis (DTA). Doripenem exists as different forms, however, as a result of the manufacturing process, the monohydrate is consistently formed. The above analytical methods allow the differentiation of the possible forms.
In addition, the hygroscopicity of the drug substance was extensively discussed.

An extensive discussion on potential and found impurities/degradation products was presented including organic, inorganic (heavy metals and residual catalysts) compounds.The information presented is considered sufficient, and the specification limits for impurities/degradation products, in line wih the PhEur Monograph, the guideline on the limits of genotoxic impurities and ICH-guidelines Q3A and Q3C, are acceptable taking into consideration the short duration of the treatment and the severity of the indications.

- Specification

A satisfactory specification for the active substance has been developed.
Methods have been described and validated in accordance with ICH requirements.

Batch analysis data have been presented for batches used for toxicological studies, clinical studies, registration stability studies, process validation, and production-scale batches. Batches have been tested for all parameters included in the drug substance manufacturer's specification. Results comply with the proposed specification and demonstrate consistency of the manufacturing process

Doripenem primary packaging complies with PhEur 3.1.3. The packaging was found to be compatible with the active substance and has been suitably characterised. The immediate container is sterilised and based on the presented data the sterility of the primary package is guaranteed.

- Stability

Stability studies were conducted on three consecutive pilot batches packed into the commercial packaging under long-term and accelerated ICH conditions (24 months at 2-8°C and 25°C/60% RH) as well as under stress conditions (3 months at 25°C/85% RH, 40°C/75% RH and light exposure). All tests were performed using the analytical procedures used for the active substance.
Results showed that no significant trend of degradation was noticed under long-term and accelerated conditions.

Medicinal Product

Doripenem powder for solution for infusion is provided as single-use vials containing 500 mg (anhydrous basis) of sterile white to slightly yellowish, off-white crystalline powder. The dry powder is constituted at the time of use and administered by intravenous infusion.

The container-closure system for the drug product consists of a 20 ml Type I clear glass vial, grey fluororesin-coated elastomer stopper and aluminium seals with ivory-coloured flip-off cap.

- Pharmaceutical Development

Choice of the Drug Substance: The drug substance selected for development and commercialization is the monohydrate form of doripenem, based on stability considerations.

Excipients: There are no excipients used in the manufacture of the product.

Formulation Development: Two candidate formulations were considered during initial development: 1) a lyophilized powder formulation, and 2) a powder-filled formulation. The powder-filled formulation was retained since it produced the more stable monohydrate.

Overages: There are no overages used in the manufacture of doripenem powder for infusion.

Sterility Assurance: The drug product is manufactured by aseptic filling of sterile doripenem monohydrate powder. The manufacturing procedures for the drug product ensure microbiological control at each step of the drug product manufacturing process. The aseptic processes all occur under Class A conditions.

Container Closure System: The choice of the container was extensively discussed, and consists of Type I borosilicate glass and a butyl elastomer closure with a fluororesin coating. Type I glass vials and type I stoppers should be adequate for the formulation and in accordance with Ph.Eur. requirements (PhEur 3.1.6 and 3.2.9*).* The proposed packaging materials were considered adequate to support the stability and use of the product.

Microbiological Attributes: The integrity of the container closure system is ensured through a combination of routine testing and validation studies. Sterility testing is a routine product release test.

- Adventitious Agents

There are neither excipients of human nor animal origin used in the manufacture of doripenem powder for infusion. There are no starting materials, fermentation steps, or intermediates of human and animal origin used in the synthesis of doripenem powder for infusion.
Based on the above information, it is concluded that there is no transmissible spongiform encephalopathy (TSE) risk for doripenem powder for infusion.

- Manufacture of the Product

The manufacture of the finished product has been fully described with a flow chart starting from the doripenem monohydrate sterile powder to be aseptic filled into the vials to the labelling and packaging of the filled vials.The manufacturing process takes place in a dedicated building to minimize the possibility of cross-contamination from other products.
Process validation has been performed on three consecutive production-scale batches. Results were found acceptable. The validation for sterility assurance was also provided.

- Product Specification

Analytical methods have been described and validated in accordance with ICH requirements. Validation of the sterility procedure for the drug product has been validated comparably to the validation of the sterility procedure for the drug substance.
The specifications were adequately justified including the impurities limits and no safety concern can be anticipated.

Batch analysis data are provided for full scale commercial batches, pilot scale batches, batches used in non-clinical and clinical phase I studies and batches used in clinical studies. Results were found in accordance with the specification.

The package consists of a clear 20 ml Type I glass vial; a grey butyl elastomer stopper with fluororesin coating; a silver aluminium crimp seal and a polypropylene flip-off cap. Adequate specifications for the packaging including criteria such as appearance, material identification, particulate matter in line with PhEur. requirements have been proposed (type I glass vials according to PhEur 3.2.1, type I stoppers according to PhEur 3.2.9, and fluororesin conform to PhEur 3.1.6) .
The container closure system has been shown to be suitable for its intended use by adequate protection of the dosage form, by compatibility with the dosage form, and by use of materials that are considered appropriate for use with the dosage form and the route of administration.

- Stability of the Product

Stability studies have been performed on three consecutive pilot-scale batches with vials stored in the inverted position and protected from light under long-term, intermediate, accelerated ICH conditions (25C/60% RH, 30C/65% RH and 40C/75% RH). Stability studies under ICH light exposure conditions (1,200,000 lux per hr and 200 W per hr/m^2) were also conducted.
The drug product was tested according to the analytical procedures used for the finished product.
All results remained within the specification under all storage conditions and no significant trend was observed. In addition, stability studies after reconstitution have also been conducted.

In total, the accumulated results support the shelflife and storage conditions as defined in the SPC.

2.3 Non-clinical aspects

Introduction

Pivotal non-clinical studies including studies on general toxicity, genotoxicity, reproduction toxicity as well as some safety pharmacology studies were conducted in compliance with the principles of GLP.

Pharmacology

- Primary pharmacodynamics

For primary pharmacological data reference is made to the clinical pharmacodynamics assessment of this report.

- Secondary pharmacodynamics

Some β-lactam antibiotics have been noted for their seizure potential and doripenem was tested in a range of systems for such effects. Doripenem was tested for GABA receptor binding using mouse synaptic membranes (S-4661-SB-552-N) since the ability to act as a ligand at the gamma-aminobutyric acid $(GABA)_A$ receptor has been implicated in the molecular mechanism of a seizure inducing potential. At 0.3 to 10 mM doripenem did not significantly displace the agonist ^{3}H-muscimol (IC_{50} 46.4 mM, extrapolated). At 10 mM, imipenem, panipenem and cefazolin caused over 90% displacement and corresponding IC_{50} values for imipenem, meropenem, panipenam and cefazolin were 0.48, 15.63, 0.63 and 0.99 mM, respectively.

A series of studies (S-4661-SB-553-N, S-4661-SB-554-N, S-4661-SB-570-N) investigating the potential of doripenem to affect the CNS, in particular the potential for convulsive activity, have been submitted. In some studies meropenem was also included as comparator. *In vivo* studies in mouse, rat and dog indicated a low potential of doripenem to induce seizures, siezure-like brain activities or enhance seizures induced by external stimuli. Intracerebroventricular administration of imipenem or imipenem/cilastin caused seizures and enhanced pentylenetetrazol induced seizures in mice. In mouse given 50, 250 or 500 mg/kg intravenously (P11-K-13) there was no potentiation of electroshock or pentylentetrazole induced convulsions while imipenem/cilastin caused potentiation. Intracisternal administration of up to 1000 µg/mouse did not cause seizures while reference compounds imipenem/cilastin, cefazolin and biapenem caused clonic and tonic extension convulsion in 20 to 90% of the animals. Further studies in mouse showed no enhancement of minimal electroshock or pentylentetrazole induced convulsions or any effect on convulsive thresholds by up to 400 mg/kg intravenously.

Table **1**. Overview of studies on seizure potential

Test system	Species	Dose/Route	Major findings
Behaviour	Mouse (Slc-ddY)	50, 250 mg/kg, IV	Doripenem: No significant effects Imipenem/Cilastin: Spasms/Straubs tail
Proconvulsive activity	Mouse (Slc-ddY)	50, 250, 500 mg/kg, IV	Doripenem: No potentiation electroshock, PTZ Imipenem/Cilastin (500/500): Potentiation PTZ
	Mouse (Slc-ddY)	30, 100, 300 mg/kg, IV	Doripenem: No significant effects
	Mouse (CD-1/ICR)	100, 200, 400 mg/kg, IV	Doripenem: Convulsive threshold unaffected Imipenem/Cilastin: No effect
	Mouse (CD-1/ICR)	250, 500 mg/kg, IV	Doripenem: No effect on PTZ convulsions Imipenem/Cilastin: (250/250): Potentiation PTZ
Seizure activity	Mouse (Slc-ddY)	30, 300, 1000 µg/mouse ICV	Doripenem: No seizures Imipenem/Cilastin (30/30): clonic convulsions, tonic extension
	Mouse (CD-1/ICR)	30, 300, 1000 µg/mouse ICV	Doripenem: No seizures Imipenem/Cilastin: dose-dependent clonic convulsions
Behaviour and EEG	Rat (SD)	100, 200, 400 mg/kg, IV	Doripenem: No effects Imipenem/Cilastin 200/200): Spikes EEG, hyperactivity
	Dog (Beagle)	300, 1000 µg/dog ICV	Doripenem: No effects Imipenem (300): seizure discharges, circling behaviour
	Dog (Beagle)	1000 µg/dog ICV	Doripenem: No effects
	Dog (Beagle)	100, 300, 1000 µg/dog ICV	Doripenem: No effects Imipenem (100): seizure discharges, clonic convulsions

ICV: intracerebroventricular, PTZ: pentylenetetrazol. Table adapted from Applicants Pharmacology summary

No effects on behaviour or EEG by doripenem at intravenous doses up to 400 mg/kg in rat (S-4661-SB-555-N) were reported while meropenem induced wet dog shakes and imipenem/cilastin caused spike or multiple spike complexes on EEG. Similarly in dog (S-4661-SB-556-N) doripenem up to 1

mg intracerebroventricularly had no effect on behaviour or on EEG while imipenem/cilastin produced seizure discharges with clonic convulsions and meropenem caused localized seizure discharges without behavioural convulsions.

- Safety pharmacology programme

Table **2**. Overview of studies

Organ system	Species (#)	Dose/Duration	Major findings
Cardiovascular and Respiratory (SBL35-87, GLP, S-4661-SB-542-L, GLP, FBM02-2870, GLP, FBM02-4871, GLP)	Rat (SD) (6 M) Dog Purkinje fibers Human CHO-K1 cells expressing HERG Rat (SD) (4 M) Dog (beagle) (4) Dog (beagle) (4 M) (conscious)	30, 100, 300 mg/kg, IV 3, 30, 300 µM 3, 30, 300 µM 30, 100, 300 mg/kg, IV 30, 100, 300 mg/kg, IV 10, 30, 100 mg/kg, IV	No effects on respiratory rate, tidal volume, minute volume in conscious animals. No effect RMP, APA, MRD, ADP_{50}, ADP_{90} at 1 or 0.5 Hz. At 30 µM a stat. sign. decrease, but small (10%) and not dose-dependent. No effect on respiratory rate, ECG, heart rate, arterial blood flow. No effect on respiratory rate, blood pressure, heart rate. No effect on heart rate, blood pressure, ECG, behaviour, no clinical signs.
Gastrointestinal	Mouse Rabbit Guinea pig	30, 100, 300 mg/kg, IV 10^{-5}-10^{-3} g/ml *in vitro* 10^{-5}-10^{-3} g/ml *in vitro*	No effect on intestinal transit of charcoal. No effect isolated ileum spontaneous motility No effect ileum anticontractile response.
CNS	Mouse (4-10 M), Rat (8 M)	30, 100, 300, 1000 mg/kg, IV	Abnormal posture at HD. General behaviour, spontaneous motor activity, analgesic activity, body temperature not affected.
CNS (FBM02-2869, GLP)	Rat (16 M)	30, 100, 300 mg/kg, IV	No effects in the Functional Observational Battery method.

In the HERG assay a small but statistically significant, not dose-dependent decrease was noted. *In vivo,* in the conscious dog no significant effects of doripenem on cardiovascular/respiratory parameters were reported. A pharmacokinetic study in dog (FBM-4049, GLP) was conducted using the same animals. Systemic exposure increased from 35.5 to 98.9 and 309.9 (µgxh/ml) from 10, 30 and 100 mg/kg, intravenously, values approximately up to x3 expected clinical levels. Elimination half-life ranged from 35.9 to 38.1 minutes.

Single intravenous doses in mouse and rat had no effect on parameters recorded reflecting CNS function. A separate pharmacokinetic study in rat (FBM03-2048, GLP) showed that exposure increased from 9.6 to 29.9 and 99.4 (µgxh/ml) at 30, 100 and 300 mg/kg, intravenously. Elimination half-life increased from 6.3 to 10.3 minutes.

- Pharmacodynamic drug interactions

The potential for interactions of doripenem with valproic acid was studied in rat (S-4661-B-53-N). Doripenem at 100 to 1000 mg/kg intravenously had no effect on the anticonvulsive effects of valproic acid in a pentylentetrazol-induced model. Similarly no effect of doripenem on anticonvulsive effects of valproic acid was reported in a bicuculline induced seizure model. Meropenem at doses of 100 to 1000 mg/kg appeared to attenuate responses in both seizure models.

Pharmacokinetics

The pharmacokinetics of doripenem have been extensively investigated in species used in toxicology studies including juvenile animals and pregnant rat and rabbit. Limited data indicated that the methods used for determination of doripenem, band culture assay and HPLC, produced similar results.

Single dose pharmacokinetic studies following intravenous doses showed a short elimination half-life in plasma ranging from 0.1-0.3 hour in mouse, 0.1 hour in rat, 0.2-1.0 hour in rabbit and 0.7-1.2 hours in monkey. The corresponding human value was 1 hour. Dose proportional pharmacokinetics with no

evident gender differences were reported. No accumulation after repeated doses was seen. Exposure to the major metabolite, the dicarboxylic acid, was highest in rat. Further, it was shown in a mouse pulmonary infection model that drug levels in plasma and liver tissue were comparable to those in non-infected groups.

Doripenem had low plasma protein binding in all species with values ranging from 25, 35 (mouse, rat) to 6 and 8% (monkey, human). Tissue distribution studies indicated highest levels in plasma, kidney, liver and lung in mouse. In rat highest levels were detected in plasma, blood, trachea, skin and lung. At 2 hours post dose values had declined to below 1 μg/g except in liver, cecum, kidney and bone. In the pigmented rat initial high levels in kidney, lung, liver, blood and skin were reported. At 24 hours post dose values were less than 0.141 μg/g in all tissues except kidney and liver. After repeated administration in fed male rats high concentrations in kidney, plasma, blood, trachea and lung were recorded. In the fed male dog given a single intravenous dose of 20 mg/kg highest levels of radioactivity were detected in kidney, cecum, blood, plasma, skin, lung and tongue. Adult and juvenile dogs exhibited similar distribution.

Studies in pregnant rat showed transfer of doripenem radioactivity to the fetus. At 6 hours postdose only trace amounts of label in tissue in dams were detected but the amniotic membrane retained label. Levels in fetuses were overall low and as expected highest in blood and kidney.

No cytochrome P450 dependent metabolism of doripenem was evident in microsomes. Renal DHP-1 (dehydropeptidase-I) is known to mediate cleavage of the β-lactam ring. The activity of DHP-1 was determined to be highest in tissue from rat lung and monkey kidney while liver overall had lower activity. Hydrolysis of doripenem was similar to imipenem in monkey kidney, but less than for imipenem and meropenem in kidney tissue from other species. Overall data were in line with that administration of doripenem can proceed without an inhibitor of DHP-1. The major metabolite of doripenem was identified as the ring-opened product dicarboxylic acid in both rat, dog and monkey. In monkey small amounts of the metabolite were found in plasma and cumulative excretion in urine amounted to 24% of dose up to a 2 hour collection time. The metabolite had no biological activity. In dog and human a minor amount was further converted to taurine and glycine conjugates.

Doripenem was mainly excreted in urine in all species. In rat, 93-94% was excreted in urine in 96 hours. In dog and monkey given single intravenous doses also 90-96% of dose was found in urine in 24 hours. Radiolabelled doripenem was also excreted into milk of lactating rat. The mechanism of renal excretion of carbapenems may differ depending on species. Doripenem was shown to be excreted by tubular secretion and glomerular filtration in rabbits and primarily by glomerular filtration in dog.

Carbapenem antibiotics may decrease blood concentrations of valproic acid thereby interfering with the anticonvulsive efficacy of the drug. Carbapenems including doripenem were shown to decrease the AUC of valproic acid by inhibiting hydrolysis of the corresponding glucuronide. Other studies indicated that doripenem had little potential to displace bilirubin from its binding site. Studies on doripenem interactions with cilastatin in rat indicated some inhibition of metabolism of doripenem while studies in monkey were consistent with that co-administration of a DHP-1 inhibitor such as cilastatin would not be required.

Overall, the general pharmacokinetics of doripenem seemed comparable to those of imipenem/cilastatin and the parameters characterised indicated that species used in toxicity studies are relevant to use for evaluating the toxicity of the compound.

Toxicology

- Single dose toxicity

Table **6**. Single dose toxicity studies

Study ID	Species/Sex/Number/Group	Dose/Route	Approx. lethal dose / max non-lethal dose	Major findings
S-4661-B-10-L, GLP	Rat SD (6F+6M)	2000 mg/kg, IV	>2000 mg/kg	Mild hypopnea, loose faeces, dark, yellow urine.
S-4661-B-19-L, GLP	Rabbit, Japanese white (4 M)	200, 400, 600 mg/kg, IV infusion	>600 mg/kg	3 day observation period. Body weight ↓. Glucose, protein in urine, Creatinine, BUN ↑. Tubular necrosis renal cortex >400 mg/kg.
S-4661-B-41-N	Rabbit, Japanese white (4 M)	250, 400 mg/kg, IV infusion	250-400 mg/kg	3 day observation period. Food intake ↓, Tubular necrosis in renal cortex. 1death-400 mg/kg
S-4661-B-09-L, GLP	Dog, Beagle (1M+1F)	1000, 2000 mg/kg, IV infusion	>2000 mg/kg	Vomiting, faecal changes. Body weight ↓. Occult blood in urine. Creatinine, BUN ↑. Necrosis renal cortex (HD), degeneration glandular mucosa stomach.

Signs of renal effects were evident in rabbits after single doses of 400 mg/kg or higher. Nephrotoxicity of doripenem was further investigated in a non-GLP rabbit study and determined to be lower than for cefazoline, cefotiam and cefmenoxime, but higher than for the carbapenem antibiotic tienam (imipenem/cilastatin). Target organs for toxicity in the dog after single high doses were determined the digestive tract and kidneys.

- Repeat dose toxicity (with toxicokinetics)

Rat

Table **7**. Overview of rat studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL	Major Findings
T-Mizushima Y-001	Rat SD (6M+6F, 6M in 100 and 300 mg/kg group)	0, 100, 300, 1000 mg/kg, IV inj.	14 days	<100 mg/kg	100, 300 mg/kg: loose feces, ketones, urobilinogen, occult blood in urine. Neutrophils ↓, (M), spleen, cecum w.↓ hypertrophy spleen. 1000 mg/kg: loose feces, ketones, urobilinogen, occult blood in urine. Neutrophils ↓, (M),WBc, lymph. ↑. AST, amylase, ALP slight ↑ spleen, cecum w.↓ hypertrophy spleen.
R-442	Rat SD (8M+8F)	0, 30, 100, 300, 1000 mg/kg, IV inj.	Males: 4 weeks Females: 3 weeks	100 mg/kg	30, 100 mg/kg: Cecum w. ↑. 300 mg/kg: Cecum w. ↑, abnormal urine colour. 1000 mg/kg: Cecum w. , spleen w (M) ↑. Bw. slight ↓.(F). Abnormal colour urine, atrophy testes, epididymides.
5972, GLP	Rat SD (10M+10F)	0, 5, 10, 15 mg/kg, ***Inhalation***	120 min/day, 4 weeks+2 week rec.	>15 mg/kg	Perivascular mononuclear cell inflammation. No effects following 2 weeks recovery.
S-4661-B-13-L, GLP	Rat SD (10-16M+10-16F)	0, 100, 300, 1000 mg/kg, IV inj.	1 month	300 (NOEL) 1000 mg/kg	Transient ↓ food intake, loose faeces. Neutr. ↓. WBC, lymph, ↑ HD (sign. females). Cecum w. ↑, spleen w. ↑ HD. Activation germinal center spleen, axillary lymph node HD.
JBC-92-RVSA-217, GLP	Rat SD (10-16M+10-16F)	0, 100, 300, 1000 mg/kg, IV inj.	3 month	300 mg/kg	Body weight gain ↓ HD. Loose faeces, transient in LD females and MD. Kidney w. ↑ HD. Cecum enlarged MD-HD.

At high doses in the "pretoxicity" study (Y-001) in rat, hypertrophy of the germinal center in the white pulp of spleen was noted. Increased spleen weight has also been reported with imipenem and meropenem.

The study R-442 was a preliminary fertility study to determine doses for the reproduction toxicity study. As in other studies increased cecum and spleen weight was noted in males and a trend towards increased cecum weight in females. There were no significant differences in estrus cycles or estrus periods between controls and treated groups.

In the 1 month study positive reaction in the occult blood urine test likely was due to a false positive reaction also seen in other studies. Ophthalmological and auditory examinations did not indicate any effects of treatment.
In the 3 month rat study, body weight gain was still decreased at end of recovery period. Loose stool, cecum enlargement and decreases in urinary electrolytes were judged related to the antimicrobial activity of the compound and as such not representative of toxicity. There were occasional statistically significant changes in haematology parameters, but these were slight and did not appear dose related. Two males in the high dose group had bilateral or unilateral atrophy in the epididymides. This was also seen in one control male.

Toxicokinetics of doripenem and its major metabolite were determined using HPLC in a separate 5 day repeated dose study (S-4661-TF-612-L). Tmax was 2 minutes after administration.

Table **8**. Toxicokinetics in rat after intravenous administration for 5 days

Dose (mg/kg)	AUC (µgxmin/ml) M D1	AUC (µgxmin/ml) F D1	AUC (µgxmin/ml) M D5	AUC (µgxmin/ml) F D5
30	762.9 (1710.2)	747.5 (1496.8)	712.5 (1640.2)	793.9 (1529.9)
100	2825.5 (5394.4)	2455.6 (5553.1)	2450.0 (5726.9)	2960.2 (4903.9)
300	9775.5 (17713.9)	8205.3 (15401.7)	9677.7 (16562.2)	7933.4 (14825.0)

Values for the metabolite JNJ-39399191 are in parenthesis. M=males, F=females, D=day.

Rabbit

Table **9**. Overview of rabbit studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL	Major Findings
S-4661-40-N	Rabbit, Jap. white (4M)	0,50, 100, 200 mg/kg, IV infusion	5 days	50 mg/kg	100 mg/kg: 1 death, bw, food intake ↓, creatinine ↑. Early death had tubular necrosis. 200 mg/kg: 1 death, bw, food intake ↓, creatinine ↑, potassium ↓. Early death had tubular necrosis
S-4661-TB-569-N	Rabbit, Jap. white (4M)	0,50, 100, 200 mg/kg, IV infusion	5 days	>200 mg/kg	200 mg/kg: Food consumption ↓.
S-4661-B-32.Y1-L	Rabbit, Jap. white (3 F)	0,25, 50, 100, 200 mg/kg, IV infusion	14 days	25 mg/kg	25 mg/kg: Cecum w. ↑. 50 mg/kg: Cecum w. ↑, diarrhea, red/brown urine, deaths. 100 mg/kg: Cecum w. ↑, diarrhea, red/brown urine, glucose, occult blood in urine, deaths. 200 mg/kg: Cecum w. ↑, diarrhea, Bw, food intake ↓, red/brown urine, glucose in urine, deaths.

In the 5 day rabbit study, nephrotoxicity of doripenem was estimated to be similar to that of Cefotiam but greater than for Tienam. In a second 5 day study in rabbit nephrotoxicity was estimated to Cefmenoxamine>Cefazolin=Biapenem>Imipenem/cilastin>Meropenem trihydrate=doripenem. In this latter study systemic exposure levels to doripenem on the first day were reported to 70.7, 138 and 333 µgxh/ml for the 50, 100 and 200 mg/kg groups, respectively.

The 2 week study in rabbit was a preliminary dose finding study to estimate doses to be used in a subsequent teratology study. Some animals in groups dosed 50 mg/kg and above developed diarrhea and died.

Dog

Table **10**. Overview of dog studies

Study ID	**Species/Sex/ Number/Group**	**Dose/Route**	**Duration**	**NOEL/ NOAEL**	**Major Findings**
S-4661-B-14-Y1-N (2966)	Dog, Beagle (1M+1F, 1 M at 500 mg/kg)	0, 250, 500, 1000 mg/kg, Intravenous infusion	14 days	250 mg/kg	250 mg/kg: WBC, Neut. slight ↑, kidney w. ↑. 500 mg/kg: Vomiting, diarrhea, hypoactivity. Food intake, Bw. ↓, protein, ketone in urine. WBC, Neut. ↑, lymph. ↓, kidney, adrenal w. ↑, thymic atrophy, degen. germinal epithelium, giant cells in testes. 1000 mg/kg: 1 death, Vomiting, diarrhea, hypoactivity. Food intake, Bw. ↓, protein, occult blood in urine. WBC, Neut. ↑, lymph., plat. ↓, kidney, adrenal w. ↑, nephritis, tubular necrosis, necrosis digestive tract, thymic atrophy, degen. germinal epithelium, giant cells in testes.
SG06104, GLP	Dog, Beagle (3M+3F)	0, 10, 30, 100 mg/kg, Intravenous infusion	14 days	100 mg/kg	Toxicokinetics
S-4661-B-14-L, GLP	Dog, Beagle (3-5M+3-5F)	0, 125, 250, 500 mg/kg, Intravenous injection	1 month+1 month recovery	<125 mg/kg	Deaths-HD. Bw. ↓ MD-HD. Vomiting, loose, tarry/bloody, faeces, emaciation, hypoactivity, salivation, HD. RBC, Hb, platelets ↓, MD-F, HD. Alb., Na, glucose, creatinine ↓ mainly HD. AP, triglycerides, ↑ mainly in HD. Kidney, liver w. ↑ MD-F, HD-F. Epithelial vacuolization proximal tubule, hypertrophy spleen –LD-HD.
TOX 8083, GLP	Dog, Beagle (3-5M+3-5F)	0, 20, 50, 100 mg/kg, Intravenous infusion, ***twice daily***	1 month+1 month recovery (control+HD)	50-100 mg/kg bid	APTT slight ↑ MD-HD. Creatinine slight ↓ HD. Cholesterol slight ↑ HD. AP slightly increased in all groups, also after recovery.
S-4661-B-34-L, GLP	Dog, Beagle (3-6M+3-6F)	0, 40, 100, 250 mg/kg, Intravenous injection	3 month+1 month recovery	40-100 mg/kg	Mucus faeces-HD. RBC, Hb, Hct ↓,LD-HD. Bilirubin in urine HD. Red point cecum-MD-HD. Epithelial vacuolization proximal tubule-HD (+1 MD), thymus hyperplasia (MD-HD), hypertrophy spleen LD-HD. Inflammatory cell infiltration cecum HD.

In a 2 week range-finding study the 2 dogs at the high dose of 1000 mg/kg exhibited subcutaneous bleeding across the entire body which was attributed to a reduction in platelets. A 2 week intravenous toxicity study (S-4661-TF-618-L) with doripenem hydrate was conducted in dog (3M+3F/group) using doses of 10, 30 and 100 mg/kg and included a direct Coomb's test. There were no treatment related findings and the Coomb's test was negative.

Toxicokinetics of doripenem and its major metabolite were determined using HPLC in a separate 5 day repeated dose study (S-4661-TF-613-L). Tmax was 2 minutes after administration.

Table **11**. Toxicokinetics in dog after intravenous administration for 5 days

Dose (mg/kg)	**AUC (µgxmin/ml) M D1**	**AUC (µgxmin/ml) F D1**	**AUC (µgxmin/ml) M D5**	**AUC (µgxmin/ml) F D5**
10	1700.5 (145.5)	1734.8 (144.3)	1726.3 (154.1)	1754.9 (146.6)
30	5600.3 (365.6)	5035.9 (323.6)	5337.4 (427.1)	5127.1 (422.1)
100	19473.9 (1292.8)	19665.3 (1378.7)	17972.8 (1631.6)	17481.8 (1668.6)

Values for the metabolite JNJ-39399191 are in parenthesis. M=males, F=females, D=day.

Day 1 Cmax values in males for doripenem were 30.4, 107.7 and 404.7 µg/ml for the 10, 30 and 100 mg/kg groups, respectively. Corresponding values for females were 32.9, 90.9 and 436.8. Day 5 values in males were 24.5, 90.9 and 367.97 µg/ml for the 10, 30 and 100 mg/kg groups, respectively. Corresponding values for females were 28.7, 100.3 and 404.5.

For doripenem dicarboxylic acid Day 1 Cmax values in males were 0.99, 2.41 and 10.09 µg/ml for the 10, 30 and 100 mg/kg groups, respectively. Corresponding values for females were 1.00, 2.27 and 11.13. Day 5 values in males were 0.81, 2.47 and 12.12 µg/ml for the 10, 30 and 100 mg/kg groups, respectively. Corresponding values for females were 0.91, 2.53 and 13.31.

In the 2 week intravenous infusion study in dog toxicokinetic parameters were monitored.

Table **12**. Toxicokinetics in the 2 week intravenous infusion study

Dose (mg/kg)	**Cmax (µg/ml) M D1**	**Cmax (µg/ml) F D1**	**Cmax (µg/ml) M D14**	**Cmax (µg/ml) F D14**
10	45.26	40.45	44.56	42.81
30	136.16	137.85	129.64	117.14
100	479.03	387.12	479.41	276.16

Vales are 2 minutes post-dose

In the 1 month intravenous injection study (S-4661-B-14-L) deaths occurred at the high dose. Histopathology of early deaths showed perivascular hemorrhage in lung, vacuolisation epithelial in kidney proximal tubule, hepatocyte vacuolisation, congestion in pancreas, thymus atrophy, thrombus in testes, neutrophil infiltration testes, mucosal erosion in cecum, pyloric gland erosion among other changes. The severity of gastrointestinal damage seemed reduced after repeated administrations since abnormal feces decreased in incidence towards the end of the administration period. After the recovery period body weight in high dose animals remained lower than in control animals. Reductions of RBC, HGB and HCT were considered to reflect hemorrhagic anemia caused by hemorrhage in the gastrointestinal tract, but other causes may also have been involved. One female in the high dose group was noted for decreased hematopoiesis in the bone marrow caused by poor nutritional status contributing to decreases in red blood cell parameters. Further, haematological parameters showed evidence of recovery mainly in females, as did serum chemistry values. Spleen weight remained increased and hypertrophy and erythropoietic hyperplasia was recorded in one female. Kidney vacuolisation was also noted in animals in the mid and high dose group and changes were reversible. Deaths appeared related to gastrointestinal effects, including erosions or ulcer in the mucosa. Gastrointestinal damage showed reversibility during the recovery period. Changes in haematology in part reflected hemorrhage in the gastrointestinal tract.

In a second 1 month toxicity study with lower doses administered twice daily there were no adverse clinical signs and ophthlmological and electrocardiographic examinations were negative. Some changes in clinical pathology were noted, but were overall slight and showed evidence of recovery. Increased eosinophil count in males at mid dose and in high dose animals was noted but was minor and similar to control after the recovery period. Toxiocokinetics were determined in the 1 month intravenous infusion study.

Table **13**. Toxicokinetics in the 1 month (twice daily) intravenous infusion study

Dose (mg/kg)	**AUC (µgxh/ml) M D1**	**AUC (µgxh/ml) F D1**	**AUC (µgxh/ml) M D30**	**AUC (µgxh/ml) F D30**
20	72.1 (7.45)	69.3 (7.35)	138 (12.6)	137 (12.8)
50	179 (18.0)	174 (20.5)	372 (33.0)	363 (36.3)
100	326 (32.2)	363 (35.7)	629 (59.8)	580 (53.4)

Values are 0-∞ day 1 (after the first dose) and 0-24 h day 30. Values for the metabolite JNJ-39399191 are in parenthesis)

In the 3 month dog study two animals in the high dose group went into shock after administration of the whole injection volume on the first day. The animals subsequently recovered. Electrocardiographic

examinations showed a tendency for prolongation of the QTc interval in mid and high dose males. There was also tendency for prolongation of the APTT in treated females. Slight haematological changes were still evident after recovery in the high dose animals and hemosiderin deposition was increased in one male. A slight increase in alkaline phosphatase in males was present up to 3 months. Thymus hyperplasia was also seen in one control animal, but occurred at a higher incidence in treated animals. Hemorrhage and inflammatory cell infiltration in stomach were noted in females given the mid dose as well as at the high dose. One female in the high dose group had localized necrosis of the proximal tubule.

- Genotoxicity

Standard tests *in vitro* for genotoxic activity as well as an *in vivo* mouse micronucleus test were negative.

- Carcinogenicity

No carcinogenicity studies have been conducted and such studies are not required in view of results from mutagenicity studies and the treatment duration.

- Reproduction Toxicity

A full range of studies to investigate potential effects on reproduction parameters was conducted using rat and rabbit and intravenous doses of up to 1000 mg/kg. In a fertility and embryonic development study where males were treated 9 weeks prior to mating and females 2 weeks prior to mating no effects on fertility indices were reported. However, in one dog study at high doses intravenous infusion (500 to 1000 mg/kg) degeneration of germinal epithelium and giant cells in testes were observed. In a rat embryofoetal study 1 to 3 dams in doripenem treated groups had all pups dead by day 4 after parturition resulting in a trend for decreased survival rate, but with no clear dose-response. The NOAEL for general toxicity in dams was considered 300 mg/kg, and this was also judged representative for reproductive toxicity inferred from a case of abnormal parturition in one animal in the high dose group. The study included postnatal development tests of F1 pups up to puberty and production of F2 generation. The NOAEL for developmental toxicity and maintenance of pregnancy and nursing performance was identified as 1000 mg/kg. At this dose an effect on parturition possibly due to secondary effects linked to aggravation of clinical signs prior to parturition was reported and the NOAEL for parturition was set to 300 mg/kg. Pre and postnatal function in rats did not seem affected by doripenem treatment. In rabbits treated with doripenem no significant effects on external, skeletal and visceral anomalies of live fetuses were evident. Taken together while reproduction toxicity studies include the different stages of the reproductory process the studies seem deficient in that administration was once daily likely resulting in drug holidays and this should be reflected in the information on reproduction toxicity to be included in the SPC. Potential effects relative to fertility and parturition should be further considered.

- Studies in which the offspring (juvenile animals) are dosed and /or further evaluated

A series of studies in juvenile animals is available. No specific toxicity in juvenile dogs not recorded in adult animals was noted. In both rat and dog studies red/brown urine was frequently noted and data were consistent that in most cases this was an artefactual reaction due to the physical characteristics of the compound. Positive results in the occult blood urine test were noted in some studies and likely this represented false positive reactions. The NOEL in two one month juvenile dog toxicity studies using once daily and twice daily administration ranged from 40 to 200 mg/kg/day.

- Local tolerance

A local irritation study in Japanese white rabbits was conducted (S-4661-B-18-L, GLP) using bolus intravenous injection into auricular vein once per day for 8 days. Vascular irritancy was determined by an intravenous retention method. Concentrations used ranged form 0.25 to 2.0% (per dose volume

0.05 ml). Erythema and induration at all sites was noted and there were no differences in frequency or severity of findings with the test formulation and vehicle control (physiological saline).

In another rabbit study (S-4661-B-30-L, GLP) a single bolus intramuscular injection was administered at a concentration of 1%, 1 ml at 0.1 ml/sec. Acetic acid was used as a positive control. Two days after injection necrosis of muscle fiber, mononuclear cell infiltration and hemorrhage and edema was evident, but was not considered marekedly different from that of physiological saline.

- Other toxicity studies

A mouse study (TOX7610, GLP) was conducted to investigate phototoxicity. In the acute tolerance phase mice (3 females/group) were given an intravenous injection of 10, 50 and 100 mg/kg/day for 5 days followed by a 3 day observation period. A slight decrease in body weight was recorded (1-3%). In the phototoxicity phase 6 females per group were given a daily intravenous injection of doripenem up to 100 mg/kg/day for five days followed by exposure to simulated sunlight for 15 ±5 minutes. No indication of a cutaneous response related to phototoxicity was reported up to 3 days following irradiation. The positive control 8-methoxypsoralen gave expected responses.

Antigenicity

A passive cutaneous anaphylaxis (PCA) study (AG-1110-1) was conducted using a mouse/rat system. Mice were sensitised with 1 mg doripenem and FCA (Freunds Complete Adjuvant) given intravenously/subcutaneously/intraperitoneally 5 days a week for 2 weeks or 2 days per week for 3 weeks (plus FCA) or 3 days per week for 3 weeks (conjugate plus alum). Doripenem had no sensitizing antigenicity in the PCA test using the BALB/c mouse, but slight eliciting antigenicity was reported. Doripenem had no sensitizing or eliciting antigenicity in the PCA test using the C3H/He mouse. Sensitizing antigenicity of doripenem and imipenem was noted in the ELISA (BALB/c mouse, C3H/He). No cross reactivity with respect to imipenem and other beta-lactam antibiotics was recorded.

In an antigenicity study (AG-1110-2) using a guinea pig model and intravenous (doripenem plus vehicle), subcutaneous (doripenem plus FCA) administration doripenem exhibited sensitizing antigenicity detected by the guinea pig active systemic anaphylaxis test (ASA), guinea pig passive cutaneous anaphylaxis test and ELISA. Eliciting antigenicity was detected by the guinea pig passive cutaneous anaphylaxis test and possible eliciting antigenicity was reported in the active systemic anaphylaxis test using guinea pig. Imipenem had sensitizing antigenicity in the guinea pig active systemic anaphylaxis test and guinea pig passive cutaneous anaphylaxis test. Eliciting antigenicity of imipenem was detected in the guinea pig passive cutaneous anaphylaxis test. Doripenem showed weak immunological cross reactivity with imipenem.

Ecotoxicity/environmental risk assessment

An environmental risk assessment was conducted in compliance with applicable guidelines and is to be updated with some additional studies. A rapid degradation in aerobic aquatic sediment systems was noted and the potential for bioaccumulation appeared low. Toxicity to early stages of zebra fish was evident at 9.2 mg/L while no specific effects on water-flea mobilization were evident at doses up to 88 mg/mL.

2.4 Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics
The PK and PD of doripenem were characterized in 9 clinical pharmacology studies in subjects from the Western population. In addition, one population PK analysis was performed using sparse data from one Phase 2 study and two Phase 3 studies. Doripenem PK was also assessed in 8 clinical pharmacology studies with subjects from the Japanese population. Penetration of doripenem in various tissues and fluids was assessed in 10 additional Phase 2 and 3 studies in Japanese subjects. Several bioanalytical methods have been used during the development program.

- Absorption

Doripenem is to be injected intravenously and bioavailability is then by definition 100%.
In the application, one-hour infusions are recommended for treatment of patients with nosocomial pneumonia and four-hour infusions are recommended patients who are at risk for infection with less susceptible pathogens. Bioequivalence, in terms of exposure, has been demonstrated between the two dosing regimes.

- Distribution

The volume of distribution, 18 L, is approximately equal to the extracellular fluid volume in humans. Mean serum protein binding across these studies was 8.1% and was independent of serum drug concentration. The partitioning of doripenem into red blood cells was determined to be low, based on the blood to plasma ratios of radioactivity of about 0.5. Doripenem penetration into various body tissues and fluids was assessed in ten phase II/III Japanese studies. On an average, with some exceptions, reported doripenem concentrations in various tissues were ≤ 35% of plasma peak concentration. Doripenem concentrated into urine where its levels exceeded several fold these of plasma.

- Elimination

Doripenem is excreted to a large part unchanged in the urine. The major elimination pathways are filtration, active tubular secretion and metabolism. A microbiologically inactive metabolite of doripenem, M-1, is formed via cleavage of its β-lactam ring, likely by dehydropeptidase.
In the Western population, mean doripenem CL, CL_R, and Ae (% dose) were 15.9 L/hr (265 mL/min), 10.3 L/hr (170 mL/min), and 70.4%, respectively when pooled across studies. Doripenem mean renal clearance 10.3 L/hr (170 mL/min) exceeds the glomerular filtration rate in humans, 7.5 L/hr (125 mL/min), indicating that both glomerular filtration and active tubular secretion are involved in its renal excretion. An interaction study with probenecid indicates that there is also re-absorption involved in the elimination process of doripenem.
Based on the elimination data from Study DORI-NOS-1007 (metabolism and excretion of doripenem in healthy men after a single i.v. dose of ^{14}C-doripenem 500 mg given as a 1-hour infusion), doripenem CL consists of metabolism via dehydropeptidase, filtration, the combination of active secretion and re-absorption and phase II metabolism constituting approximately 18 %, 43%, 35 % and < 3 % of total CL, respectively. Urinary recovery or doripenem was complete within 24 hours post start of infusion, with a mean 78.7% and 18.2% of the administered dose recovered as doripenem and M-1, respectively.

The PK-characteristics of M-1 in subjects with normal renal function are well described. The elimination of M-1 seems not formation rate limited as the terminal half life is approximately 120 min in comparison to doripenem´s 70 minutes. There is no accumulation of M-1 in subjects with normal renal function.

- Dose proportionality and time dependencies

Doripenem displays linear pharmacokinetics. There is no apparent accumulation of doripenem in plasma after doses as high as 1000 mg t.i.d. in healthy volunteers.

- Variability

Inter-individual variability in systemic exposure to doripenem was generally less than 20%. Based on the population analysis, inter occasion variability on clearance and volume of distribution (Vp) was 15 % CV and 30 % CV, respectively.

- Special populations

As doripenem does not undergo hepatic metabolism, the pharmacokinetics of doripenem is not expected to be affected by hepatic impairment. No study has been performed.

Two formal studies in patients with renal impairment have been performed. Study DORI-02 was performed in patients with varying degree of renal function and Study DORI-NOS-1005 in haemodialysis patients. Further, the impact of renal impairment was evaluated in the Phase 2 Study DORI-03 which was included in the population PK analysis. The results obtained in DORI-02 showed that administration of a single dose of 500mg subjects with mild, moderate and severe renal impairment resulted in approximately 1.6, 2.8 and 5.1 fold higher AUC as compared to subjects with normal renal function. The currently proposed dose regimes for patients with moderate and severe renal impairment are a 2- and 3- fold reduction of the normal daily dose, respectively, which will not fully compensate for the decreased clearance in these patients in study DORI-02. With responses to questions raised, non-compartmental analysis of DORI-03 data were provided. The influence of renal impairment on doripenem exposure seems to be somewhat lower in this study than that observed in study DORI-02 with a 1.3 and 1.9-fold increase in exposure at 500 mg qd in mild and moderate renal impairment on Day 7, which supports the proposed dose recommendation. Data in severe renal impairment group was limited to two subjects with creatinine clearance close to 30 ml/min (25 and 29 ml/min respectively). Hence, based on data from DORI-02 and -03, the currently proposed dose reduction will not compensate for the decreased clearance in patients with severe renal impairment and it is expected that this patient group will get a higher exposure of doripenem compared to what is expected in patients with normal renal function.

Information regarding the pharmacokinetics of M-1, in relation to renal function status, was obtained from the Phase 2 cUTI study DORI-03. The data presented in the response to Day 120 LoQ clearly show the influence of renal function on the M-1 exposure with large increases in M-1 exposure patients with creatinine clearance <50 ml/min (if the dose is not adjusted). With the proposed dose adjustment the M-1 exposure will be increased in both mild and moderate renal impairment but to a moderate extent which seems acceptable. The data in severe renal impairment are, however, very limited. There are only two subjects with severe renal impairment and both these subjects had creatinine clearance >25 ml/min. Previous data in dialysis patients (DORI-NOS-1005) showed extremely large increases in exposure of M-1 (15- fold increase in AUC_t when doripenem was administered pre-dialysis and 39-fold increase when doripenem was administered post-dialysis with an expected much greater increase in AUC_∞). Hence, very large increases in M-1 exposure are expected in patients with creatinine clearance 10-20 ml/min. Given the limited safety data in patients with severe renal impairment at the proposed dose and the pharmacokinetic data which suggest increased doripenem exposure and probably very large increases in M-1 exposure, Doribax should be used with caution in patients with severe renal impairment.

Doripenem and M-1 is dialyzable but considering the extensive accumulation of M-1, its use in dialysis patients is not recommended. Doripenem AUC and Cmax in female subjects were 13% and 15% higher, respectively, compared to the values in male subjects. Compared to Caucasians, mean doripenem clearance was 29% higher in subjects of Hispanic or Latino ancestry. No significant difference was observed for subjects of African-American ancestry. PK parameters in average were similar in Asian and Western populations. As these differences in exposure are not considered to be clinically important, no dosage adjustment is recommended based on gender, race or weight.

Pharmacokinetics of doripenem in children has not been studied.

- Target population

The pharmacokinetics in patients with cUTI and NP was evaluated in a population analysis. A two-compartment model with zero-order input and first order elimination best described the plasma concentration time profile after intravenous administration of doripenem.

The exposure to doripenem was primarily governed by renal function status, where a reduction in renal function was associated with a reduction in clearance to the drug. Disease state was not a significant covariate and it could be concluded that there is no major difference in PK between healthy subjects and patients.

- Pharmacokinetic interaction studies

The in vitro studies suggest no potential for inhibition or induction of CYP450 isoenzymes by doripenem and M-1. Doripenem is eliminated through active tubular secretion but the transport protein/s responsible for this secretion has not been identified. An in-vivo interaction study with concomitant administration with probenecid resulted in an increase in doripenem AUC by 75%.

Based on experience with meropenem, there are indications that doripenem may reduce serum concentrations of sodium valproate to subtherapeutic levels.

Pharmacodynamics

Doripenem is a new beta-lactam agent of the carbapenem class, expressing an antimicrobial spectrum resembling that of meropenem. Doripenem was selected for development because of the sulfamoylamino-ethyl-pyrrolidinylthio group in its side chain at position 2 that enhances its activity against non-fermentative gram-negative rods.

- Mechanism of action

Like other beta-lactam agents, doripenem acts by targeting penicillin-binding proteins (PBPs) to inhibit the biosynthesis of the bacterial cell wall. The binding of the beta-lactam molecule to the PBPs prevents bacteria from completing transpeptidation (cross-linking) of peptidoglycan strands, thus preventing the synthesis of an intact bacterial cell wall. The metabolite of doripenem, M1, has been shown to be microbiologically inactive.

- Primary and Secondary pharmacology

Doripenem exhibits a broad-spectrum bactericidal antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria. Of approximately 10,000 recent worldwide clinical isolates tested, the majority of species, including most β-lactamase-producing organisms, had a MIC_{90} value of ≤1 µg/mL. Doripenem is less active against *Enterococcus faecalis* and certain non-fermentative gram-negative bacteria, and inactive against most isolates of methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium*, *Corynebacterium* spp., and *Stenotrophomonas maltophilia.* Doripenem is slightly less active than imipenem, but more active than meropenem and ertapenem, against gram-positive bacteria. Against gram-negative bacteria, the activity of doripenem is similar to that of meropenem, and similar to or more active than imipenem and ertapenem. Doripenem seems to be slightly more (1-2 fold) potent against *Pseudomonas* isolates than imipenem or meropenem.

Doripenem was shown to exhibit bactericidal activity, in line with other carbapenems.

Although the spectrum of activity of carbapenems is very broad, some organisms demonstrate intrinsic resistance. The poor binding affinity of all beta-lactams to PBP2a in meticillin resistant staphylococci (e.g. MRSA) and to PBP5 in *E. faecium* render these bacteria to be intrinsically resistant to all carbapenems developed so far. Like imipenem and meropenem, doripenem susceptibility is generally not affected by common cephalosporinases, including the extended-spectrum beta-lactamases (ESBL), while the susceptibility is markedly decreased for organisms producing carbapenemases, such as KPS

enzymes and metallo-betalactamases. *Acinetobacter* spp. positive for the classD OXA beta-lactamases, do also express reduced susceptibility. In addition, AmpC overproduction combined with loss of OprD in *Pseudomonas* spp., results in increased MIC-values to doripenem, as for other carbapenems. Thus, the vulnerability for beta-lactamase encoded resistance as well as permeability and efflux mediated resistance for doripenem, seems to be in line with that of other carbapenems, especially meropenem. A combination of several of these mechanisms is often present in resistant gram-negative strains. For gram-positive bacteria, reduced affinity for altered PBPs remains the most common resistance mechanism.

Two studies, using checker-board assays, indicated that combinations of doripenem and glycopeptides were synergistic or additive for tested clinical MRSA strains. It was demonstrated that doripenem could be combined with a range of antimicrobials without risk of antagonism, suggesting that co-administration with other agents would not lead to loss of activity.

Pooled susceptibility data from cUTI, IAI and NP infections from the current clinical studies revealed that MIC_{90}-values were ≤ 0.5 µg/mL for all gram-negative isolates regardless of resistance mechanisms, except for *Morganella morganii* and non-fermentative organisms. Among gram-positive organism, the activity of doripenem was somewhat poorer, but MIC_{90} values against streptococci and methicillin susceptible staphylococci (MSSA) were consistently low, ≤ 0.5 µg/mL. This is in accordance with previous surveillance data and very similar to the activity of meropenem.

Molecular typing of pre- and post treatment isolates, revealed pairs of isolates that exhibited > 4-fold increases in doripenem MIC during doripenem treatment, mainly *P. aeruginosa* from the NP studies. Resistance development during doripenem treatment was in line with that of imipenem treated subjects. The resistance was probably due to multiple mechanisms as would be expected for a carbapenem. Increased levels of AmpC β-lactamase activities were demonstrated, but could not fully explain the decreased susceptibility. Efflux/permeability likely played a role and requires further investigation. The applicant is asked to submit final results regarding the mechanisms of resistance in these pairs of isolates.

As with other carbapenems, animal model studies have demonstrated that time (T) >MIC is the best predictor of microbiologic outcome (key pharmacodynamic index) for doripenem. Animal models as the neutropenic thigh model and human population PK designated the conservative target of 35% T>MIC, which predicted that 500 mg of doripenem administered for 1 h every 8 h would be effective against organisms with an MIC <2 µg/ml, and that less susceptible strains could be treated with prolonged (4 h) infusions. Clinical species specific and non-species related breakpoints based on PK/PD variables and epidemiological cut-off vales will be established in cooperation with EUCAST. The Applicant has provided data in support of tentative breakpoints, which have been preliminary used for the analyses in this dossier.

Specific Target Attainment for NP+cIAI+ UTI Pathogens Based on Doripenem Dosing Regimens

	Dosing regimens used					
Species specific target attainment	500 mg, q8h, 1 h infusion			500 mg, q8h, 4 h infusion		
	25% T>MIC	30% T>MIC	35% T>MIC	25% T>MIC	30% T>MIC	35% T>MIC
Enterobacteriaceae	99.88	99.82	99.72	99.91	99.9	99.9
Non-Enterobacteriaceae	92.34	90.13	87.83	93.96	93.69	93.3
Pseudomonas aeruginosa	91.42	88.96	86.41	93.25	92.95	92.51
*Acinetobacter*spp.	82.13	80.95	78.99	82.26	82.2	82.16
*Burkholderia*spp.	59.38	49.89	41.05	64.83	62.27	59.41
Stenotrophomonas maltophilia	7.41	4.74	3.16	8.57	7.85	7.08
Other gram-negative	99.43	98.01	96.06	100.02	100.02	100.01
*Haemophilus*spp.	100	99.97	99.88	100	100	100
*Enterococcus*spp.	62.53	51.05	41.98	73.22	71.93	69.86
Enterococcus faecalis	76.79	62.42	50.79	90.61	89.4	87.18
*Staphylococcus*spp.	86.88	86.04	85.36	87.41	87.26	87.04
*Staphylococcus aureus*Oxa-S	100	100	99.99	100	100	100

Streptococcus pneumoniae	100	99.91	99.7	100.01	100.01	100.01
*Streptococcus*spp. (other than *S. pneumoniae)*	99.81	99.66	99.54	99.96	99.96	99.93
Other gram-Positive	90.13	89.74	89.02	90.08	90.05	90.03
All Anaerobes	97.75	97.26	96.66	98.09	98	97.89

However, a target attainment of 35% T > MIC might not be optimal for all patients since it is calculated for bacteriostatic effect, which may not be sufficient in seriously ill patients with impaired immune defence. Extending the infusion time of doripenem to 4 hours maximizes the %T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. As a precaution in this group of seriously ill and often immunocompromised patients, 40-50% T>MIC would likely be more warranted. Based on PK/PD data aiming at least 95% of patients achieving 50% T > MIC, four-hour infusion should be recommended for isolates with MIC $\geq$ 0.5 mg/l (Figure 7 below (Module 2.7.2.4) and Tables 3 and 4, Appendix 2.1, Target attainment report).

Overall, there were limited numbers of isolates with doripenem MICs in the 8-16 µg/ml range from the clinical studies. MIC values of the isolates from the clinical studies were not clearly predicttive for clinical failure.

The Applicant has not performed any study on the impact of doripenem on the normal microflora.

The effect of doripenem on QT/QTc was assessed by measuring the time-matched mean differences in ΔQTcF between doripenem treatments at therapeutic and supratherapeutic doses and placebo in a randomized, double-blind Phase I study in 60 healthy adults (DORI-NOS-1001). Neither dose of doripenem had a significant effect on QT/QTc and no relationship between ΔQTcF and doripenem concentration was observed in either the 500 mg or 1000 mg treatment groups.

Clinical efficacy

The clinical efficacy of doripenem for the indications cUTIs, cIAIs and NP was studied in one Phase 2 study and in 6 multi-center Phase 3 studies. Three of the Phase 3 studies were double-blinded studies with active comparators, whereas the other three were open labeled, of which two with active comparators. Overall, the design of the clinical trials was in agreement with current guidelines. The highlights and main features across the studies are presented in the table below.

Main characteristics of phase 2 and phase 3 studies in the doripenem clinical programme

Study	Design	Population	Posology (doripenem dosing vs)	N of subjects treated/ completed	Primary endpoint
Dose finding study; phase 2					
DORI-03	DB, randomised, comparative	cUTI	250 mg over 1 h q8h vs 500 mg over 1 h q8h	121/107	Microb. response at TOC visit in ME at TOC population
Complicated urinary tract infections; phase 3					
DORI-05	DB, randomised, DD, comparative	Complicated lower UTI (symptomatic, asymptomatic and pyelonephritis)	500 mg over 1h q8h vs levofloxacin 250 mg/q24h with option to switch to oral levofloxacin (250 mg qd) after 9 doses of doripenem Concomitant AB: not allowed except those that do not have activity against UTI-associated organisms	748/597	Microb. response at TOC visit in ME at TOC and mMITT populations
DORI-06	OL, single arm	Complicated lower UTI (symptomatic,	500 mg over 1h q8h with option to switch to oral levofloxacin (250 mg qd) after	423/328	Microb. response at TOC visit in ME at TOC and mMITT

		asymptomatic and pyelonephritis)	9 doses of doripenem Concomitant AB: not allowed except those that do not have activity against UTI-associated organisms		populations
Complicated intra-abdominal infections; phase 3					
DORI-07	DB, randomised, DD, SRP; Option to discharge after 48h of treatment	cIAI and planned or recently performed drainage of an infection	500 mg over 1h q8h vs meropenem bolus injection 1g/q8h option to switch to amoxicillin/clavunate (875 mg/125 mg q12h) Concomitant AB: vancomycin for proven/(suspected) MRSA or *Enterococcus* infection	471/414	Clinical cure at TOC visit in ME at TOC and mMITT population
DORI-08	DB, randomised, DD, SRP; Option to discharge after 48h of treatment	cIAI and planned or recently performed drainage of an infection	500 mg over 1h q8h vs meropenem bolus injection 1g/q8h option to switch to amoxicillin/clavunate (875 mg/125 mg q12h) Concomitant AB: vancomycin for proven/(suspected) MRSA or *Enterococcus* infection	475/412	Clinical cure at TOC visit in ME at TOC and mMITT population
Nosocomial pneumonia incl. VAP; phase 3					
DORI-09	OL, randomised, comparative, BEC	Non-ventilated HAP or early-onset VAP	500 mg over 1h q8h vs pip/tazo 4.5 g over 30 min q6h with option to switch levofloxacin (750 mg qd) after Day 3 7 to 14 days (iv + oral) Concomitant AB: amikacin (or other AG) for suspected *P.aeruginosa* required; vancomycin for suspected MRSA	444/382	Clinical cure at TOC visit in CE at TOC and in cMITT population
DORI-10	OL, randomised, comparative	VAP	500 mg over 4 h q8h vs imipenem 500 mg over 30 min q6h or 1 g over 1h q8h 7 to 14 days (iv only) Concomitant AB: amikacin (or other AG) for suspected *P.aeruginosa* was allowed; vancomycin for suspected MRSA	525/353	Clinical cure at TOC visit in CE at TOC and in cMITT population

AG – aminoglycoside; AB – antibiotic; BEC – blinded evaluation committee; DB – double blind; DD – double dummy; CE – clinically evaluable; microb. – microbiological; ME – microbiologically evaluable; cMITT – clinical modified intention to treat; mMITT – microbiological modified intention to treat; MRSA – methicillin resistant *Staphylococcus aureus*; OL – open label; SRP – surgical review panel; TOC – test of cure

- Dose response study(ies)

The dose finding study (DORI-03) conducted in patients with cUTI was double blinded. Two doses of doripenem (250 mg/q8h or 500 mg/q8h) were given as one hour infusion for 7 to 14 days. The 1:1 randomisation was used and the primary objective was to compare the microbiological response rate in patients with cUTI at Days 5 to 9 post-therapy. The secondary objectives included clinical response at days 5 to 9, safety of doripenem and obtaining pharmacokinetics data. The populations and evaluation criteria were similar to those used in cUTI studies (see below under cUTI studies). The study randomised 121 patients of which 107 (55 in 250 mg/q8h and 52 in 500 mg/q8h group) completed the study (mMITT population). The demographic findings in both groups were similar.

The microbiological eradication rate was slightly greater in patients who received the dose of 500 mg/q8h than in those given dose of 250 mg/q8h (68% vs 64%, respectively). There was a higher eradication rate of the most common pathogen, *E. coli*, in the 500 mg arm (25/31; 81%) versus (24/35; 69%) in the 250 mg arm. The combined per pathogen eradication rates at TOC for all of the most frequently isolated organisms typically found in cUTI infections (*E. coli*, *P. mirabilis*, *K. pneumoniae*,

S. saprophyticus, *E. faecalis* and *P. aeruginosa*) were 82% and 69% in the 500 mg and 250 mg treatment arms, respectively.

Secondary outcome measures 250 mg/q8h vs 500 mg/q8h were Microbiological response at TOC (mMITT) – 59% vs 64%, clinical response at TOC (CE at TOC) – 93% vs 90%, clinical response at TOC (cMITT) – 82% vs 84%, clinical response at TOC (ME at TOC) – 93% vs 90%, clinical response at LFU (CE at LFU) – 80% vs 78%, microbiological response at LFU (ME at LFU) – 47% vs 55%, and clinical response at LFU (ME at LFU) – 79% vs 74%.

The safety profiles of the 2 doripenem dosing regimens were similar. In both groups 6 new pathogens emerged at TOC visit, in both groups there were 2 Gram-negative organisms, rest of them were Gram-positives or *Candida*. The most common AEs were headache (11.6%) and gastrointestinal disorders, including constipation, diarrhoea, and dyspepsia, each reported by 5.0% of patients.

For the indications cIAI and NP no formal dose finding studies have been conducted. Therefore the final choice of dose is mainly based on PK/PD approaches (see above). As highlighted in the SPC there is an option to prolong the duration of infusion (500mg given over 4 hours) in NP patients in order to cover less susceptible pathogens, such as *P. aeruginosa*. PK/PD data indicate that 1g q8 hours, administered during 4 hours, may further enhance the efficacy for pathogens with decreased susceptibility, although clinical efficacy and safety data for this regimen is currently lacking.

- Main study(ies)

Complicated Urinary tract infection (cUTI)

Study DORI-05 and Study DORI

Methods

(DORI-05 and DORI-06) have a similar study design, with the important exception that only DORI-05 included an active comparator, while DORI-06 was an open single arm study where the levofloxacin arm from DORI-05 was used for comparative analyses. The DORI-06 study was designed to provide independent supportive confirmation of the response rate for doripenem observed in the double-blind, levofloxacin-controlled study in cUTI (DORI-05).

- **Study Participants**

Male and female patients of 18 years of age or older, with a confirmed diagnosis of complicated lower urinary tract infections or pyelonephritis (complicated or uncomplicated) were included in the studies.

Exclusion criteria for both studies (DORI-05 and DORI-06) included a history of moderate or severe hypersensitivity reactions to carbapenems, penicillins, other beta-lactam antibiotics, or any quinolone, a complete permanent obstruction of the urinary tract, a confirmed fungal UTI with a colony count greater than or equal to 10^3 CFU/mL, a suspected or confirmed perinephric or intrarenal abscess and suspected or confirmed prostatitis.

Patients were defined as having completed the study if they had received study drug therapy as directed during the 10 days of treatment and had attended the TOC and LFU visits as specified in the protocol. At the time of a possible study withdrawal, EOT (i.v.) visit procedures were performed if the patient was on i.v. study drug therapy, and TOC visit procedures were performed if the patient was on oral levofloxacin.

- **Treatments**

In study DORI-05 patients were randomised to receive either doripenem as a 1-hour i.v. infusion (500 mg q8h) or levofloxacin, administered as a 1-hour i.v. infusion (250 mg q24h).

In study DORI-06 all subjects received doripenem +/- oral levofloxacin according to the protocol of DORI-05.

The total treatment duration (i.v. and oral) in both studies was 10 days. However, 14 days was allowed for subjects with documented bacteraemia at study entry.

Patients with severe renal impairment were excluded from this study. Any patient who required dialysis after enrollment was removed from study drug therapy. The doripenem dose was adjusted according to renal function.
Levofloxacin was adjusted in case of renal impairment according to labeling and current clinical practice. Patients who were bacteraemic with the same uropathogen responsible for the current cUTI may have continued in the study if no concomitant systemic antibacterial therapy was required.

- **Objectives**

In studies DORI-05 and DORI-06 the primary objective of the studies was to compare the safety and to demonstrate equivalent efficacy of doripenem to that of levofloxacin in the treatment of patients with cLUTI and pyelonephritis. In order to establish the non-inferiority of doripenem to levofloxacin in the single-armed study DORI-06, levofloxacin data from DORI-05, for the per-patient microbiological cure rates (in the co-primary analysis sets and per patient microbiological cure rates by subgroups) and the key secondary efficacy endpoint clinical cure rate in the CE at TOC analysis set were presented. Other efficacy outcomes from study DORI-06 were described without comparisons.

- **Outcomes/endpoints**

Primary endpoints were per-patient microbiological cure rate at the TOC visit in the microbiological evaluable (ME) at TOC analysis set and per-patient microbiological cure rate in the microbiological modified intent-to-treat (mMITT) analysis set (mMITT_1) at the TOC visit.
Secondary endpoints and analyses included clinical cure rate in the clinically evaluable at TOC (CE at TOC) analysis set and per-baseline uropathogen microbiological outcomes for E. coli.

Additional secondary analyses included per-patient microbiological cure rate in subgroups: symptomatic and asymptomatic cLUTI, pyelonephritis (including complicated pyelonephritis), and patients who had concurrent bacteraemia at baseline, sustained microbiological cure rate (i.e., sustained eradication of all baseline pathogens) in the ME at LFU analysis set, sustained clinical cure rate in the CE at LFU analysis set, occurrence of emergent infections (superinfections and new infections), per-patient microbiological cure rate and the clinical improvement rate at EOT(i.v.), time to defervescence while on i.v. study drug therapy in patients in the CE at TOC analysis set who had fever at study entry, time to negative urine culture in the ME at TOC analysis set and time to meeting criteria to switch from i.v. to oral therapy in the CE at TOC analysis set.

Sampling for culture procedures
A urine sample for culture was obtained at baseline and after administration of the third dose of i.v. study drug therapy of each day until two consecutive urine cultures were reported with no growth at 24 hours or growth with a colony count less than 10^4 CFU/mL.

A blood sample for culture was obtained at screening from patients who presented with clinical signs/symptoms of pyelonephritis or bacteremia and from all catheterized patients from whom the baseline urine culture specimen was obtained through the catheter, and on Day 2 if the screening blood culture was positive. Repeat blood cultures were taken approximately every 24 hours until 2 consecutive cultures obtained on separate days were without growth. In addition, blood cultures were performed at anytime signs/symptoms of sepsis were present.

Evaluation of microbiological response

Microbiological outcome (by pathogen) and response (by patient) were determined at the EOT(IV), TOC, and LFU visits. An overall per-patient microbiological response was determined based on individual microbiological outcomes for each baseline pathogen. For the patient to have a microbiological cure, all baseline pathogens had to be eradicated at the specified visit.

Definitions of per-pathogen microbiological outcomes were:

Eradication (EOT(i.v.), TOC): The last interpretable urine culture result from a specimen found at entry reduced to less than 10^4 CFU/mL.

Persistence (EOT(i.v.), TOC): At least 1 interpretable urine culture result from a specimen $\geq 10^4$ CFU/mL of the original uropathogen(s).

Sustained Eradication (LFU): An interpretable urine culture result from a specimen at LFU where baseline pathogens remained less than 10^4 CFU/mL.

Recurrence (LFU): An interpretable urine culture result from a specimen obtained any time after documented eradication at the TOC visit, up to and including the LFU visit, grew greater than or equal to 10^4 CFU/mL of the original uropathogen.

Indeterminate (EOT(i.v.), TOC, LFU): No urine culture was obtained, or the culture result could not be interpreted for any reason.

Evaluation of clinical response

Clinical signs and/or symptoms of cUTI, including dysuria, frequency, suprapubic pain, urgency, or flank pain/costovertebral angle tenderness, were assessed at screening to obtain a pre-infection status score. These signs and symptoms were also assessed on each study day while the patient was receiving IV study drug therapy, and at the EOT(**i.v.**), TOC, and LFU visits.

Definitions of clinical outcomes were:

Clinical Cure (TOC): Patients had resolution or improvement of signs or symptoms of cUTI, or return to pre-infection baseline (if known) at the TOC visit, such that no additional antibacterial therapy was required for the treatment of the current infection.

Improvement (EOT(i.v.)): Patients had resolution or improvement of signs or symptoms of cUTI since before the first dose of study drug therapy.

Clinical Failure (EOT(i.v.), TOC): Patients had no apparent response to therapy, persistence of signs and/or symptoms of cUTI infection, such that use of additional antibacterial therapy was required for the current infection.

Sustained Clinical Cure (LFU): All pre-therapy signs and symptoms showed no evidence of resurgence after administration of the last dose of study drug therapy.

Clinical Relapse (LFU): Signs and/or symptoms of cUTI that were absent at the TOC visit reappeared at LFU.

Indeterminate (EOT(i.v.),TOC, LFU): No determination of clinical response (improvement or failure) could not be made.

- **Sample size**

DORI-05: The original study sample size of 450 patients which was based on previous cUTI studies on oral levofloxacin treatment of cUTIs, were revised after interim evaluation of blinded data from the DORI-05 study, according to Amendment 4. Data indicated that approximately 66% of the randomly assigned patients met the criteria to be included in the ME at TOC analysis set and the overall microbiological cure rate was approximately 84%. Estimation of sample size based on these interim data and a decision to increase the a priori power from 80% to 85% at the (1-sided) 2.5% significance level, indicated that approximately 248 patients per study arm were required to meet the criteria for inclusion in the ME at TOC analysis set in order to demonstrate non-inferiority of i.v. doripenem to i.v. levofloxacin. In order to achieve this and assuming a 66% evaluability rate, a revised sample size of approximately 750 patients was enrolled.

DORI-06: The aim of DORI-06 was to provide an independent confirmation of the microbiological cure rate for doripenem observed in DORI-05, by establishing non-inferiority of doripenem compared

with the levofloxacin treatment arm in DORI-05. For this objective, a sample size close to that expected in each treatment arm in DORI-05 was selected for DORI-06.

- **Randomisation**

In study DORI-05 eligible patients were randomized to treatment according to a computer-generated randomization code. Randomization was stratified by region (North America, South America, or Europe) and, within each region, stratification by baseline diagnosis (symptomatic cLUTI, asymptomatic cLUTI, or pyelonephritis). In addition, within the combinations of region and baseline diagnosis, patients were randomly assigned to a treatment arm by the order in which study drug was infused.

- **Blinding (masking)**

In study DORI-05 the study was conducted double-blinded, thus both study personnel (with the exception of the pharmacist) and patients remained blinded to study drug therapy assignment. Since doripenem and levofloxacin required different administration in terms of volume and interval, a double-dummy design approach was implemented with normal saline infusions to match the doripenem and levofloxacin administration. Unblinding of study drug therapy assignment was permitted only in situations when knowledge of the treatment received was absolutely necessary for patient management.

- **Statistical methods**

The primary efficacy analysis was to test the hypothesis of non-inferiority of i.v. doripenem to i.v. levofloxacin. While DORI-05 was a double-blind comparative study enabling this analysis, the results from DORI-06, which was a single-armed study, were compared with the levofloxacin arm from DORI-05. Non-inferiority was to be concluded if the lower bound of the 2-sided 95% CI for the difference (doripenem minus levofloxacin in the proportion of patients who were classified as microbiological cures) was greater than or equal to -10%. This 2-sided 95% CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method). Analysis of the per-patient microbiological response in the mMITT-1 analysis set was considered a co-primary analysis. A sensitivity analysis was performed for the primary endpoint by adjusting for the effects of the baseline cUTI diagnosis (cLUTI or pyelonephritis) on the microbiological response. This analysis was performed using a continuity-adjusted Cochran-Mantel-Haenszel (CMH)-type method weighted by the sample sizes.

Efficacy analyses were performed on the following study populations (DORI-05 and DORI-06):

Intent-to-Treat (ITT): All randomly assigned patients who received any dose of study drug therapy. Safety analyses, but not efficacy analyses, were conducted in this analysis set.

Microbiological Modified Intent-to-Treat (mMITT): All randomly assigned patients who received any dose of study drug therapy and who had a study-qualifying pre-treatment urine culture, whether or not they met the protocol definition of cUTI were met or not. Two different mMITT analysis sets were evaluated.
mMITT_1: all patients who met the criteria for inclusion in the mMITT analysis set, including those who did not have an interpretable urine culture result available after completing study drug therapy. Indeterminate cultures were considered failures.
mMITT_2: patients without interpretable urine culture result after completing study drug therapy were excluded.

Microbiologically Evaluable at Test-of-cure (ME at TOC): All randomly assigned patients who met the protocol definition of cUTI, had a bacterial uropathogen isolated from a study-qualifying baseline

urine culture, had no entry criteria or in-study protocol deviation likely to impact the microbiological outcome, were compliant with study drug therapy or were classified as an evaluable microbiological failure after completing at least 3 days of i.v. study drug therapy and had an interpretable urine culture result from a specimen obtained in the appropriate TOC window.

Microbiological Evaluable at Late Follow-up (ME at LFU): Patients in the ME at TOC analysis set with an interpretable urine culture result at the LFU visit and who did not have any confounding event or receive any systemic antibacterial therapy with potential activity against the baseline uropathogen(s) between the time of the TOC and LFU visits, except resuming oral antimicrobial prophylaxis therapy after the TOC urine culture was obtained.

Clinically Evaluable at Test-of-cure (CE at TOC): This analysis set was similar to the ME at TOC analysis set except a clinical outcome assessment in the appropriate TOC window was required and an interpretable urine culture result at TOC was not. Patients who were classified as having an asymptomatic cLUTI at study entry because they had an indwelling catheter, a urinary obstruction, or a neurogenic bladder and did not experience symptoms of dysuria, frequency, suprapubic pain, or urgency were excluded from this analysis set.

Clinically Evaluable at Late Follow-up (CE at LFU): Patients in the CE at TOC analysis set who were evaluated clinically at the LFU. Two populations, ME at TOC and mMITT-1 at TOC were used as primary analysis sets.

Results

- **Participant flow**

Discontinuation information for each study (DORI-05 and DORI-06) ITT analysis sets.

	DORI-05				**DORI-06**		**Total**	
	Doripenem		**Levofloxacin**		**Doripenem**		**Doripenem**	
Subject Completed Treatent/trial	(N=376)		(N=372)		(N=423)		(N=799)	
Reason for Withdrawal/termination	n	(%)	n	(%)	n	(%)	n	(%)
Subject completed study per protocol through late follow-up visit	317	**(84.3)**	280	**(75.3)**	328	**(77.5)**	645	(80.7)
Subject did not complete study per protocol	59	(15.7)	92	(24.7)	95	(22.5)	154	(19.3)
Adverse event	6	(1.6)	**11**	**(3.0)**	6	(1.4)	12	(1.5)
At request of subject, investigator, or sponsor	2	(0.5)	5	(1.3)	1	(0.2)	3	(0.4)
Death	1	(0.3)	0		2	(0.5)	3	(0.4)
Lost to follow up	8	(2.1)	10	(2.7)	13	(3.1)	21	(2.6)
Need for additional antibacterial therapy for an infection other than index infection	1	(0.3)	4	(1.1)	2	(0.5)	3	(0.4)
Negative pretreatment culture	29	(7.7)	25	(6.7)	**60**	**(14.2)**	89	(11.1)
Non-compliance	3	(0.8)	2	(0.5)	1	(0.2)	4	(0.5)
Treatment failure	**2**	**(0.5)**	**26**	**(7.0)**	**2**	**(0.5)**	4	(0.5)
Other	7	(1.9)	9	(2.4)	8	(1.9)	15	(1.9)

- **Recruitment**

DORI-05: The study was conducted in North America, South America and Europe.
A total of 44 centres (18 in the United States; 7 in Germany; 7 in Argentina; 6 in Brazil; 5 in Poland; and 1 in Canada) randomized 753 patients in this study.

DORI-06: Patients were recruited from North America, South America and Europe. A total of 30 centers (11 in US, 9 in Argentina, 6 in Brazil, 3 in Austria and 1 in Canada) enrolled the 426 patients.

- **Conduct of the study**

DORI-05: The original study protocol was dated 23 September 2003. Five amendments were made; Amendment 1 was implemented 09 February 2004 after enrolment of the first two patients and reflected information learned from preparation of the final clinical study report for the Phase 2 study in cUTI (DORI-03) and discussions at investigator meetings. This amendment concerned among other issues changes in duration of study drug from 7-10 days to 10 days, in order to comply with prescribing practice for levofloxacin, and revised visit windows at TOC and LFU. Amendment 2 (31 August 2004) reflected a change in the dosing regimen for patients with impaired renal function, added Canada as a country where the study could be conducted, and provided clarification to investigator comments and commonly asked questions. Amendment 3 (10 February 2005) was an administrative amendment. Amendment 4 (18 April 2005) was made in order to increase the sample size; to strengthen and clarify methods to prevent, detect, and report pregnancies; and to exclude patients with asymptomatic cLUTI. Finally, Amendment 5 (15 September 2005) led to a further increase the sample size from 580 to approximately 750 patients.

DORI-06: The original study protocol was dated 29 October 2003. The same five amendments as for study DORI-05 was implemented for DORI-06 (Amendments 1 to 5). Thus the study protocols for the two studies were essential similar (except for the single armed nature of DORI-06).

- **Baseline data**

Treatment groups in DORI-05, doripenem and levofloxacin, were generally well matched with regard to demographic characteristics such as age, weight, sex, race and baseline disease diagnosis at entry.

Since the results of DORI-06 was compared to the levofloxacin arm of study DORI-05, the validity of the analyses is dependent on the similarity of patients underlying demographic and disease characteristics between the treatment arms. Some differences were a significant larger number of Caucasians in DORI-05 compared to DORI-06; 79% vs. 48%, largely depending on lower recruitment of patients in Europe in DORI-06. Notable, only one patient was included in Europe in DORI-06. The relative frequency of patients with a baseline diagnosis of cLUTI or pyelonephritis was comparable between the two treatment arms. However, for the cLUTI diagnosis, there were differences between the studies regarding the reasons for complications. In DORI-06, fewer subjects had instrumentation, obstructive uropathy and urogenital surgery compared to patients in DORI-05. It appears that subjects in DORI-05 more often suffered from multiple complicating factors. On the other hand, a higher percentage of subjects in DORI-06 had bacteraemia at entry. Regarding baseline renal function, 18% in DORI-06 and 13% in DORI-05 had moderate or severe renal impairment, CrCL <50 mL/min. The percentage of ME at TOC patients was clearly higher in DORI-05 than in DORI-06.

- **Extent of drug exposure**

The pooled extent of exposure data results were similar to those in the individual studies, with a median duration of total study drug therapy (10 days), i.v. therapy (5 days), and oral therapy (7 days). In the doripenem treatment arm, 16% of subjects received i.v. study drug therapy only, compared with 18% in the levofloxacin treatment arm. The median duration of exposure for subjects who received i.v. study drug therapy only was 11 days.
For subjects who were switched to oral study drug therapy, the mean duration of i.v. study drug therapy was 5 days before switching to oral therapy and the total mean duration of therapy was 10 days.

<u>Baseline uropathogens:</u>
The distribution of baseline uropathogens was generally similar in the two treatment arms in DORI-05, and in DORI-06. The most common baseline uropathogen isolated from patients overall was *E. coli*, of which 11% were resistant to levofloxacin while none to doripenem.

Baseline uropathogens and susceptibility characteristics in the mMITT population (DORI-05 and DORI 06).

Baseline Uropathogen	Doripenem (DORI-05) (N=327) NI/NT[a]	S or I	R	Levofloxacin (DORI-05) (N=321) NI/NT[a]	S or I	R	Doripenem (DORI-06) (N=337) NI/NT[a]	S or I	R
Gram-positive Aerobes	10/9	8	1	10/9	7	2	13/12	9	3
nterococcus faecal	7/7	6 (85.7%)	(14.3%	6/6	6 (100.0%)	0	6/ 5	5 (100.0%)	0
nterococcus faeciu	0/0	0	0	1/1	0	1 (100.0%)	1/ 1	0	1(100.0%)
nterococcus hirae	1/1	(100.0%)	0	0/0	0	0	0	0	0
nterococcus spp	1/0	0	0	0/0	0	0			0
ardnerella vaginal	0/0	0	0	1/0	0	0			0
aphylococcus aure	1/1	1 (100.0%	0	2/2	1 (50.0%)	1 (50.0%)	6/ 6	4 (66.7%)	2 (33.3%
Gram-negative Aerobes	321/302	302	0	312/299	257	42	328/300	297	3
Acinetobacter baumannii	4/3	3 (100.0%	0	1/1	1 (100.0%)	0	7/ 7	7 (100.0%)	0
urkholderia cepaci	0/0	0	0	1/1	1 (100.0%)	0	0/ 0	0	0
Chromobacterium violaceum	1/0	0	0	0/0	0	0	0/ 0	0	0
Citrobacter freunc	4/4	4 (100.0%	0	5/4	3 (75.0%)	1 (25.0%)	0/ 0	0	0
Citrobacter koseri	2/2	2 (100.0%	0	0/0	0	0	1/ 1)	1 (100.0%	0
Enterobacter aerogenes	1/1	1 (100.0%	0	2/2	2 (100.0%)	0	0/ 0	0	0
nterobacter cloaca	10/9	9 (100.0%	0	8/8	3 (37.5%)	5 (62.5%)	24/24	24 (100.0%)	0
Escherichia coli	232/222	22 (100.0%	0	245/237	212 (89.5%)	25 (10.5%	221/204	204 (100.0%)	0
Levofloxacin-resistant strains	23/23	23 (100.0%	0	25/25	0	25(100.0%	24/24	24 (100.0%)	0
Klebsiella oxytoca	5/5	5 (100.0%	0	5/5	5 (100.0%)	0	3/ 3	3 (100.0%)	0
Klebsiella pneumoniae	18/15	15 (100.0%	0	14/12	9 (75.0%)	3(25.0%)	31/25	24 (96.0%)	1 (4.0%)
Morganella morganii	1/1	1 (100.0%	0	1/1	1 (100.0%)	0	1/ 1	1 (100.0%)	0
asteurella multocic	1/0	0	0	0/0	0	0	0	0	0
Proteus mirabilis	24/24	24 (100.0%	0	18/18	14 (77.8%)	4 (22.2%)	13/12	12 (100.0%)	0
Proteus penneri	0/0	0	0	1/1	1 (100.0%)	0	0/ 0	0	0
Proteus vulgaris	0/0	0	0	2/0	0	0	0/ 0	0	0
Providencia rettgeri	1/1	1 (100.0%	0	0/0	0	0	1/ 1	1 (100.0%)	0
Providencia stuartii	1/1	1 (100.0%	0	0/0	0	0	0/0	0	0
Pseudomonas aeruginosa	11/9	9 (100.0%	0	7/7	3 (42.9%)	4 (57.1%)	20/18	16 (88.9%)	2 (11.1%)
Salmonella spp.	1/1	1 (100.0%	0	0/0	0	0	0/ 0	0	0
Serratia marcesce	4/4	4 (100.0%	0	2/2	2 (100.0%)	0	3/ 3	3 (100.0%)	0

[a] N is the number of subjects with the specified baseline isolate. NT is the number of subjects with the specified baseline isolate tested for which an interpretation of susceptibility results was available. For doripenem, pathogens were considered Susceptible(S), Intermediate(I) or Resistant(R) if the MIC level was ≤4µg/mL, = 8 µg/mL or ≥16 µg/mL, respectively. For levofloxacin, the number Susceptible, Intermediate or Resistant was defined according to the CLSI recommendations

Blood isolates

The most common uropathogen isolated from patients who were bacteremic at baseline was *E. coli*: 16 of 20 pathogens in the DORI-05 doripenem treatment arm and 20 of 23 in the levofloxacin treatment arm. In DORI-06, 22 of 27 uropathogens associated with bacteraemia were *E. coli.* None of the baseline pathogens isolated from both the blood and urine of patients in either treatment arm was resistant to any of the study drug received.

- **Outcomes and estimation**

Primary efficacy endpoint

Analyses were performed for the two co-primary variables, the ME at TOC and mMITT at TOC. The results from both studies individually and for the pooled data demonstrated that doripenem is non-inferior to levofloxacin in the treatment of cUTIs in the studied populations.

Per patient microbiological cure rates at the TOC visit (DORI-05 and DORI-06). All data on levofloxacin originate from DORI-05.

Analysis Set	Doripenem	Levofloxacin	Difference (2-sided 95% CI)
DORI-05			
ME at TOC	**230/280 (82.1%)**	**221/265 (83.4%)**	**-1.3% (-8.0%, 5.5%)**
mMITT_1	**259/327 (79.2%)**	**251/321 (78.2%)**	**1.0% (-5.6%, 7.6%)**
DORI-06			
ME at TOC	209/250 (83.6%)	221/265 (83.4%)	0.2% (-6.6%, 7.0%)
mMITT_1	278/337 (82.5%)	251/321 (78.2%)	4.3% (-2.1%, 10.7%)
Pooled data (DORI-05 and DORI-06)			
ME at TOC	439/530 (82.8)	221/265 (83.4%)	-0.6% (-6.4, 5.2)
mMITT_1	537/664 (80.9)	251/321 (78.2%)	2.7% (-3.0, 8.3)

The microbiological cure rates between the treatment arms for patients within the study-population of the original protocol were consistent with the results from the final population.

Secondary efficacy endpoints

Clinical cure rates at TOC overall and per subgroup are summarized as follows:

DORI-05: Per-Patient Clinical Cure Rates at TOC: Overall and by diagnosis (CE at TOC Analysis Set)

	Doripenem N=286	Levofloxacin N=266	Difference (2-sided 95% CI[a])
Overall	272 (95.1%)	240 (90.2%)	**4.9% (0.2%, 9.6%)**
By diagnosis			
Symptomatic cLUTI	**134/141 (95.0%)**	**105/124 (84.7%)**	10.4%
Pyelonephritis	138/145 (95.2%)	135/142 (95.1%)	0.1%
Bacteremic at baseline	23/23 (100.0%)	24/24 (100.0%)	0

DORI-06: Per-Patient Clinical Cure Rates at TOC: Overall and by Subgroups (CE at TOC Analysis Set). (Data on levofloxacin originates from DORI-05).

Outcome Clinical Cure	Doripenem (DORI-06) N=257	Levofloxacin (DORI-05) N=266	Difference (2-sided 95% CI)
Overall	239 (93.0%)	240 (90.2%)	2.8% (-2.4%, 7.9%)
By diagnosis			
Symptomatic cLUTI	117/132 (88.6%)	105/124 (84.7%)	4.0%
Pyelonephritis	122/125 (97.6%)	135/142 (95.1%)	2.5%
Bacteremic at Baseline	27/27 (100.0%)	24/24 (100.0%)	0

Outcome per symptom

For each symptom assessed, responses were similar between the treatment arms. Approximately, 94% to 99% of the patients in all three treatment arms (DORI-05 and DORI-06) indicated improvement in symptoms of dysuria, flank pain/costovertebral tenderness, frequency, suprapubic pain, and urgency at the EOT(i.v.) visit, and 95% to 100% indicated improvement at the TOC visit indicating that the majority of patients had improvement in individual symptoms while receiving i.v. study drug therapy.

Outcome at EOT

At the EOT(i.v.), microbiological cure in the ME at TOC population was demonstrated in 99.6%-100% of the doripenem-treated patients and in 88% of the levofloxacin-treated patients. In DORI-05, clinical improvement at EOT(i.v.) in the CE at TOC analysis set was 98% of doripenem-treated patients and 93% of levofloxacin-treated patients, while in DORI-06, clinical improvement at EOT(i.v.) was demonstrated in 99% of the patients. Although doripenem-treated patients had slightly

better outcome than those treated with levofloxacin, some doripenem-treated subjects who were infected with levofloxacin-resistant pathogens failed when switched to oral therapy. These microbiological failures may thus be caused by the too short duration of iv doripenem therapy in combination with an inappropriate oral agent. Although these studies were not designed to identify optimal treatment duration of iv doripenem they indicate that 3 to 4 days may not be sufficient and longer treatment period may be required. The data also suggest that when subjects are switched to oral therapy only agents to which initial organism is susceptible should be used.

Outcome at LFU

The sustained microbiological cure rate among patients who were ME at LFU and had eradication of all baseline uropathogens at the TOC visit was 89% and 87% for doripenem-treated patients in DORI-05 and DORI-06, respectively, and 90% for levofloxacin, respectively.

The sustained clinical cure rate at LFU, based on patients classified as clinically cured at the TOC visit, was 91% and 95% for doripenem and levofloxacin, respectively in DORI-05 and 89% in DORI-06.

Other secondary variables

For other secondary variables, similar results were recorded between the different treatment regimens; time to defervescence (9-10 hours for doripenem patients and 16 hours for levofloxacin), median time to negative urine culture (2 days in all three treatment arms) and median time to meeting criteria to switch to oral therapy (4-5 days in doripenem treated patients and 5 days in levofloxacin treated patients).

Efficacy in subgroups

The microbiological outcome per patient and subgroup were similar between the two treatment arms in DORI-05 and correspondingly in DORI-06.

For the subset of ME at TOC patients who received IV study drug only, the microbiological cure rate at TOC was 66% (56/85) for pooled doripenem-treated patients and 38% (18/48) for levofloxacin-treated patients. Generally, a higher percentage of levofloxacin resistant *E.coli* was isolated from i.v. drug only subjects, compared to the total population (39% vs 11 %).

For patients with reduced iv study drug due to renal impairment, 75% (54/72) had microbiological cure at TOC in the pooled ME doripenem population compared to 58% (15/26) in the levofloxacin arm.

Per pathogen eradication

The per pathogen eradication rates at TOC (ME-population) were similar between the two cUTI studies and are presented as pooled data for DORI-05 and DORI-06.

Eradication rates for all baseline uropathogens at the TOC visit for the ME at TOC. Pooled data from DORI-05 and DORI-06 (Data only for pathogens isolated from at least 10 doripenem subjects).

Baseline Uropathogen	**Doripenem F/NI (%)**	**Levofloxacin F/NI (%)**	**Difference (2-sided 95% CI)**
Gram Positive, aerobic	15/20 (75%)	1/4 (25%)	
Enterococcus faecalis	8/12 (66.7%)%)	1/3 (33.3%)	33.3%
Gram Negative, aerobic	516/429 (83.1%)	222/262 (84.7%)	-1.6% (-7.3; 4.1)
Enterobacteriaceae	401/476 (84.2%)	217/254 (85.4%)	-1.2% (-6.9%; 4.5%)
Enterobacter cloacae	18/28 (64.3%)	3/7 (42.9%)	21.4%
Escherichia coli	313/357 (87.7%)	184/211 (87.2%)	0.5% (-5.6%, 6.5%)a
Levofloxacin-resistant strains	**26/43 (60.5%)**	**6/21 (28.6%)**	31.9%
Levofloxacin-susceptible strains	**287/314 (91.4%)**	**178/190 (93.7%)**	-1.0 %
ESBL-producing strains	7/11 (63.6%)	1/3 (33.3%)	30.3%
Klebsiella pneumoniae	26/33 (78.8%)	5/8 (62.5%)	16.3%
Proteus mirabilis	22/30 (73.3%)	13/15 (86.7%)	-13.3%

Non-fermenters	27/38 (71.1%)	5/8 (62.5%)	8.6%
Acinetobacter baumannii	8/10 (80.0%)	0/1	80.0%
Pseudomonas aeruginosa	19/27 (70.4%)	5/7 (71.4%)	-1.1%

F = number of pathogens with a favorable outcome; NI = number of patients in which the pathogen was isolated at baseline and a follow-up culture was available at the TOC visit;

Clinical cure rates in CE patients at TOC with respect to specific species were generally similar between treatment groups, with the exception of levofloxacin resistant *E. coli,* where 95% of doripenem treated patients (pooled data) and 50% of levofloxacin treated patients were cured.

For subjects with *E. coli* isolated from both urine and blood at baseline, the eradication rates at the TOC visit were similar between the 2 treatment arms, with blood eradication rates of 100% in both treatment arms, and urine eradication rates of 97.4% (37/38) and 95.0% (19/20) for the doripenem and levofloxacin treatment arms, respectively, in the pooled ME at TOC analysis set.

Outcome by baseline pathogen and susceptibility

More than 95% of all tested gram-negative isolates had a doripenem MIC ≤ 0.5 µg/mL at baseline. There were too few doripenem resistant microorganisms to draw any conclusion of MIC-values and outcomes, while levofloxacin resistance was predictive for the outcome in levofloxacin treated patients. Seven baseline microorganisms in doripenem-treated patients (pooled data) in the ME at TOC analysis set had a MIC greater than 2 µg/mL for doripenem (6 *P.aeruginosa* (MIC 4- ≥16 µg/mL) of which four were eradicated, and one *Serratia marcescens* (MIC= 8 µg/mL) which was not eradicated). All *E. coli* isolates were susceptible to doripenem while approximately 11% of *E. coli* isolates were resistant to levofloxacin, according to CLSI breakpoints.

Among patients assessed as microbiological failures, most of the doripenem treated patients were infected with a doripenem susceptible uropathogen, whereas in failures in the levofloxacin group, fluoroquinolones resistance was common.

Baseline Uropathogen Susceptibility Characteristics for Subjects Assessed as Microbiological Failures From the Pooled Data Set (DORI-05 and DORI-06) ME at TOC Analysis Set.

	Doripenem (DORI-05 and DORI-06)				**Levofloxacin** (DORI-06)			
	N/NT	S	I	R	N/NT	S	I	R
Gram positive, aerobic	5/5	3(60%)	0	2(40%)	3/3	2(67%)	0	1(33%)
Staphylococcus aureus	0/0	0	0	0	1/1	0	0	1(100%)
Enterococcus faecalis	4/4	3(75%)	0	1(25%)	2/2	2(100%)	0	0
Enterococcus faecium	1/1	0	0	1(100%)	0/0	0	0	0
Gram negative, aerobic	87/81	78(96%)	2(2%)	1(1%)	40/39	10(26%)	5(13%)	24(62%)
Enterobacteriaceae	75/72	71(99%)	1(1%)	0	37/36	10(28%)	4(11%)	22(61%)
Citrobacter freundii	0/0	0	0	0	1/1	0	0	1(100%)
Enterobacter cloacae	10/10	10(100%)	0	0	4/4	0	1(25%)	3(75%)
Escherichia coli	44/44	44(100%)	0	0	27/27	9(33%)	3(11%)	15 (56%)
Klebsiella pneumoniae	7/5	5(100%)	0	0	3/2	1(50%)	0	1(50%)
Morganella morganii	1/1	1(100%)	0	0	0/0	0	0	0
Proteus mirabilis	8/8	8(100%)	0	0	2/2	0	0	2(100%)
Providencia alcalifaciens	1/0	0	0	0	0/0	0	0	0
Providencia stuartii	1/1	1(100%)	0	0	0/0	0	0	0
Serratia marcescens	3/3	2(67%)	1(33%)	0	0/0	0	0	0
Acinetobacter baumannii	2/2	2(100%)	0	0	1/1	0	1(100%)	0
Pseudomonas aeruginosa	8/7	5(71%)	1(14%)	1(14%)	2/2	0	0	2(100%)
Pseudomonas species	1/0	0	0	0	0/0	0	0	0
Pasteurella multocida	1/0	0	0	0	0/0	0	0	0

N is the number of subjects with the specified baseline isolate. NT is the number of subjects with the specified baseline isolate tested for which an interpretation of susceptibility results was available.

Emergence of resistance

Three patients in the doripenem treatment arm (DORI-05) and six patients in DORI-06 had persistent uropathogens that developed a 4-fold increase in MIC to doripenem; *Enterococcus faecalis* (n=1), *E. coli* (n=3), *Enterobacter cloacae* (n=2), *Klebsiella pneumoniae* (n=1), *Pseudomonas aeruginosa* (n=1) and *S. marcescens* (n=1). Only the *P. aeruginosa* strain had a MIC greater than 1 µg/mL (>2.0 µg/mL). In addition, for two of the *E. coli* isolates from DORI-05, MIC to levofloxacin increased 4-fold, up to 16 and 32 µg/mL, respectively. In the levofloxacin arm, 11 patients had persistent infection caused by uropathogens that had developed resistance to levofloxacin during therapy. In none of these isolates was an increased MIC for doripenem detected.

Emergent infections

Only three superinfecting organisms (one in doripenem arms and two in levofloxacin arm) were tested for susceptibility. These were all resistant to the treating agent.

Summary of Emergent Uropathogens (superinfections [during therapy] and new infections [after end of treatment]). Pooled data from DORI-05 and DORI-06.

	Doripenem pooled data		**Levofloxacin (N=318)**	
Emergent Pathogen	**No of pat (no of pathogens)**	**No of pathogens**	**No of pat (no of pathogens)**	**No of patghogens**
Superinfection				
Total no of patients (total no of pathogens)	**8 (10)**		**2 (2)**	
Candida spp.		4		0
Enterococcus spp.		1		1
Escherichia coli		1		1
Myroides species		1		0
Staphylococcus aureus		1		0
Stenotrophomonas maltophilia		2		0
New Infection				
Total no of patients (total no of pathogens)	**53 (59)**		**17 (18)**	
Acinetobacterspp		4		0
Enterococcus spp.		**18**		**5**
Klebsiella spp.		5		3
Proteus spp.		4		2
Escherichia coli		9		5
Pseudomonas aeruginosa		**10**		**1**

In the pooled doripenem group, four of the new infections were caused by doripenem-resistant strains, one *Enterococcus avium* and three *P. aeruginosa* strains. In the levofloxacin arm, there were five new infections caused by levofloxacin-resistant organisms (two *E. faecalis* and one each of *P. mirabilis*, *E. coli*, and *P. aeruginosa*).

If emergent infections occurring during TOC visit window were considered as failures, the microbiological eradication rate (primary efficacy end-point) with doripenem was numerically lower than that with levofloxacin (ME at TOC population at TOC in the pooled analysis 77.5% vs 82.6%, respectively; 95% CI -11.2; 0.9) suggesting that despite the excellent *in vitro* activity, *in vivo* doripenem might be less efficacious than levofloxacin. This all indicates that doripenem might effectively eradicate original micro-organisms but this effect is short-lasting and the re- or new infections are common after the therapy is discontinued.

Complicated intra-abdominal infections (cIAI)

Study DORI 07 and Study DORI 08

The study designs used in DORI-07 and DORI-08 were identical, but the two studies were performed as individual studies and at different study sites.

Methods

Both studies are multicenter, randomized, double-blind studies that compared the efficacy and safety of doripenem with that of meropenem in adult patients with a confirmed diagnosis of complicated intraabdominal infection (cIAI).

- **Study Participants**

The patients were males or females aged 18 years or older and presented either localized or generalized peritonitis secondary to appendix perforation, small or large bowel perforation, cholecystitis, or parenchymal (e.g., liver or spleen) abscesses. Patients who had a requirement for surgical intervention (e.g., laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) within 24 hours of study entry were also included.

Exclusion criteria included intra-abdominal processes in which the primary etiology was not likely to have been infectious (e.g. abdominal wall abscess; small bowel obstruction or ischemic bowel disease without perforation; traumatic bowel perforation with surgery within 12 hours; perforation of gastroduodenal ulcers with surgery within 24 hours).

- **Treatments**

The meropenem dosage regimen of 1 g q8h was chosen according to guidelines and clinical practice. The dosing schedule was as follows: initially, meropenem (1 g) or meropenem placebo (20 mL) was administered as an i.v. bolus (over 3 to 5 minutes) followed by doripenem (500 mg) or doripenem placebo i.v. infusion (100-mL bag) over 1 hour q8h. Patients could be switched to oral therapy with amoxicillin /clavulanate (875/125 mg twice daily) after 9 or more doses of IV study drug therapy, if body temperature and WBC count were decreased relative to pre-treatment values (if increased at baseline), if signs/symptoms of cIAI were absent/improved relative to those before the start of i.v. study drug therapy, and if normal bowel function had returned.

Additional treatment with open-label vancomycin was permitted if *Enterococcus* spp. or methicillin-resistant *Staphylococcus aureus* (MRSA) was suspected causative pathogens at baseline.
If, after 14 days of study drug therapy, a patient continued to have clinical symptoms of IAI requiring antibacterial therapy, that patient was considered a treatment failure.

Dosage adjustments
Patients with mild to moderate renal impairment had their study drug therapy dosage adjusted according to the following:
Doripenem and meropenem dosage adjustments (DORI-07 and DORI-08)

Creatinine Clearance (mL/min)	Doripenem (All Doses Infused over 1 Hour)		Meropenem (All Doses Given as i.v. Bolus over 3 to 5 Minutes)	
	Doripenem Dose (Volume) and Interval	Doripenem Placebo (Volume) and Interval	Meropenem Dose (Volume) and Interval	Meropenem Placebo (Volume) and Interval
> 50	500 mg (100 mL) q8h	(100 mL) q8h	1 g (20 mL) q8h	(20 mL) q8h
30 to 50	250 mg (50 mL) q8h	(50 mL) q8h	1 g (20 mL) q12h	(20 mL) q12h
10 to 29	250 mg (50 mL) q12h	(50 mL) q12h	0.5 g (10 mL) q12h	(10 mL) q12h
< 10	Excluded or removed from study		Excluded or removed from study	

The dosage of amoxicillin/clavulanate was adjusted according to clinical practice in patients with CrCL <30mL/min.

- **Objectives**

The primary objective of the both cIAI studies (DORI-07 and DORI-08) was to compare the safety and to demonstrate equivalent clinical efficacy of doripenem to that of meropenem in the treatment of cIAI. Doripenem was to be considered non-inferior to meropenem if the lower margin of the 95% confidence interval (CI) for the differences between the treatment groups was above 15% for the primary endpoint.

- **Outcomes/endpoints**

The primary efficacy endpoints were clinical cure rate at the test of cure visit (TOC) in the microbiologically evaluable (ME) population at TOC analysis set *and c*linical cure rate at any time up to 60 days after the last dose of study drug therapy in the microbiological modified intent-to-treat (mMITT) analysis set.
Secondary endpoints included clinical cure rate at the TOC in the clinical evaluable (CE) analysis set, microbiological response per patient and per pathogen at early follow-up (EFU) and TOC, clinical response at end of intravenous treatment EOT(IV) and EFU visits and, per blood pathogen microbial outcome.

Clinical response was based on the following criteria:

Clinical Cure: Resolution of signs or symptoms of the index infection, such that no additional antibacterial therapy or surgical or percutaneous intervention was required

Clinical Improvement (only at the EOT(IV) visit): Resolution or significant improvement of signs or symptoms of the index infection. Patients could be switched to oral therapy.

Clinical Failure: Patients were classified as a clinical failure based on:

- Death related to IAI at any time point;
- Persisting or recurrent infection within the abdomen
- Post-surgical wound infection,
- Treatment with additional antibiotics for ongoing symptoms of IAI during the study period.

Indeterminate: Study data were not available for evaluation of efficacy for any reason

Evaluation for microbiological response
Specimens from the site of infection, obtained at study entry and subsequent when clinically indicated, were cultured both aerobically and anaerobically. Microbiological outcome was assessed both per patient (microbiological response) and per pathogen (microbiological outcome), defined as:

Eradication: Absence of causative organism from an appropriately obtained specimen at the site of infection.

Presumed eradication: Absence of material to culture in a patient defined as clinical cure.

Persistence: Presence of the original pathogen in cultures of a specimen from the site of infection.

Persistence acquiring resistance: Continued presence of the original pathogen that was susceptible to study drug therapy pre-treatment but resistant to study drug after treatment.

Presumed persistence: Absence of material to culture in a patient assessed as a clinical failure.

Indeterminate: Entry culture either not obtained or no growth; or assessment not possible because of protocol violation; or any other circumstance making it impossible to define microbiological response.

- **Sample size**

DORI-07: The original total sample size of 346 subjects was based on an evaluability rate of 65%, an expected cure rate of 80% and a power of 80%. In order to increase the power to 90%, this was amended in August 2005 according to Amendment 2 to a total sample size of 472 patients.

DORI-08: The original total sample size of 346 subjects was increased to 472 subjects, for the same reasons as stated for DORI-07.

- **Randomisation**

Eligible patients were randomized to doripenem or meropenem (1:1) by using an interactive voice response system (IVRS). The randomization included stratification by region (North America, South America and Europe) and within each region according to primary sites of infections (complicated localized appendicitis vs. other cIAIs), and APACHE II score ≤10 or >10. Patients with generalized peritonitis, regardless of origin, were stratified to the "other site" infection group.

- **Blinding (masking)**

The assignment to doripenem or meropenem was blinded to study personnel (with the exception of the pharmacist/designee), patients, and the Sponsor. The two study drugs required different administration in terms of volume and duration of infusion. To maintain the blind a double-dummy design approach was implemented with normal saline infusions to match the doripenem and meropenem administration. If unblinding of study drug therapy assignment was considered necessary, the investigator contacted the appropriate regional medical/pharmacovigilance officer to discuss the need for unblinding.

- **Statistical methods**

Data were analysed individually for the two studies and for pooled data in accordance with a Statistical Analysis Plan (SAP), which was finalized before the data were unblinded (one amendment implemented in February 2006). In order to allow inclusion of patients who were otherwise evaluable but had TOC or EFU visits outside the original protocol-defined windows, the windows for the EFU and TOC visits were expanded from 7 to 14 days and 28 to 42 days, to 6 to 20 days and 21 to 60 days, respectively. The primary efficacy analysis was to test the hypothesis that doripenem was non-inferior to meropenem in the treatment of cIAIs. Non-inferiority was to be concluded if the lower bound of the 2-sided 95% CI for the difference (doripenem minus meropenem in the proportion of patients classified as clinical cures at TOC) was greater than or equal to -15%. This CI was obtained using the continuity-adjusted normal approximation to the difference between 2 binomial proportions (Wald method).

Efficacy analyses were performed using the following study populations (DORI-07 and DORI-08):
Intent-to-Treat (ITT): All randomized patients who received any dose of study drug therapy.
Clinical Modified Intent-to-Treat (cMITT): All randomized patients who received any amount of study drug therapy and met the minimal disease definition of IAI.
Microbiological Modified Intent-to-Treat (mMITT): A subset of the cMITT analysis set consisting of patients in the cMITT analysis set who had a baseline bacterial pathogen identified, regardless of susceptibility to study drug therapies.
Clinically Evaluable at Test-of-cure (CE at TOC): A subset of the cMITT analysis set and consisted of all randomized patients who received an adequate course of study drug therapy, who met the protocol-specified disease definition of cIAI, and for whom sufficient information was available to determine the patient's clinical outcome at the TOC visit.
Microbiologically Evaluable at Test-of-cure (ME at TOC): The ME at TOC analysis set was a subset of the CE at TOC analysis set presenting with at least 1 adequate baseline bacterial pathogen, susceptible to both IV study drug therapies. This analysis set was used in the primary analysis.
"Expanded" ME at TOC analysis set: Pathogens form CE patients for whom not all baseline pathogens were susceptible to study drug therapy. These were included for evaluating per-pathogen microbiological outcomes by MIC.
Clinically Evaluable at Early Follow-up (CE at EFU): Similar to the CE at TOC analysis set, but an outcome assessment (other than "indeterminate") was required at the EFU, but not necessarily at TOC visit.
Microbiologically Evaluable at Early Follow-up (ME at EFU): A subset of the CE at EFU analysis set, but with at least one baseline pathogen, susceptible to both i.v. study drug therapies.

Two populations, ME at TOC and mMITT at TOC, were used as primary analysis sets.

Sensitivity analyses of the primary and co-primary endpoints were conducted by adjusting for the effects of the site of infection (complicated localized appendicitis vs diagnosis of other sites of IAI) and the severity of illness (APACHE II score ≤10 or >10) using a continuity-adjusted CMH-type method weighted by the sample sizes.

Results

- Participant flow

Overall, 87% of the subjects completed the studies per protocol through to the "late follow-up visit" in both studies. Reasons for discontinuation were relatively similar in both studies and between treatment arms. Of those subjects who did not complete the studies, the most common reason for discontinuation in Study DORI-07 was loss to follow-up (3%) and in Study DORI-08 the most common reason for discontinuation was adverse event(s) (3%).

The original protocol-defined windows at TOC (28 to 42 days) and EFU (7 to 14 days) after administration of the last dose of study drug were later expanded to 21 to 60 days, and 6 to 20 days after administration of the last dose, respectively.

Study design of DORI-07 and DORI-08 (final visit windows).

SCREENING	TREATMENT	EARLY FOLLOW-UP	TEST-OF-CURE
Day –1 to 0 (24 hours prior to randomization) • Diagnosis of cIAI was established • Stratification by region (North America, South America, Europe), by site of infection (complicated localized appendicitis versus other sites of cIAI), and by disease severity (APACHE II ≤10 versus >10). • Randomization to study drug therapy.	**Day 1 to End of Therapy (5-14 days)** • Doripenem i.v. infusion 500 mg (over 1 hour) q8h or meropenem IV bolus 1 g (over 3 to 5 min) q8h • Optional switch to oral therapy with amoxicillin/clavulanate therapy after at least 9 i.v. doses. • Total study drug therapy (i.v. and oral) was 5 to 14 days. • Vancomycin therapy was added if *Enterococcus* or MRSA infection was suspected or isolated at baseline.	**6 to 20 Days After Final Dose of Study Drug Therapy** Patient returned to study center for assessment of microbiological and clinical response and safety.	**21 to 60 Days After Final Dose of Study Drug Therapy** Patient returned to study center for assessment of microbiological recurrence or clinical relapse and final safety.

The percentages of patients excluded from the ME at TOC analysis set and reasons for exclusion were similar between doripenem and meropenem treated patients in both studies and between studies. The main reason for exclusion from the ME at TOC analysis set in both studies were no IAI culture result at baseline (20%) and absence of a valid TOC visit (9%).

- **Conduct of the studies**

DORI-07 and DORI-08: The original study protocol was dated 04 December 2003. Three amendments were made. Amendment 1 (September 2004) included addition of study centers in South America and Europe as well as several clarifications in the protocol regarding assessment of failure subjects, patients with negative cultures, inclusion and exclusion criteria, dose adjustments for renal impairment and monitoring of severe adverse events. Amendment 2 (August 2005) was implemented to improve the power of the study from 80% to 90% by increasing the sample size. Amendment 3 (October 2005) addressed the addition of a J&JPRD clinical monitor and added a procedure for reporting pregnancies.

- **Recruitment**

DORI-07: A total of 476 patients were randomized in the study, allocated in 46 centers (23 in the United States; 7 in Argentina; 5 in Brazil; 5 in Germany; 5 in Poland; and 1 in Canada).
DORI-08: A total of 486 patients were randomized in the study, allocated in 44 centers (21 in the United States; 10 in Europe, 10 in South America and 3 in Canada.

- **Baseline data**

Baseline demographic characteristics were generally well distributed between the treatment groups and between the two studies.

Baseline disease characteristics did not differ significant between treatment arms. More than 90% of the patients overall had APACHE II scores <10 and the appendix was the source of infection in over 60% of the subjects. Of these subjects, 50% had generalized peritonitis at baseline and were stratified to the "other sites of IAI" group, regardless of the origin of their infection (i.e., even if the infection originated from the appendix).

Baseline disease characteristics for each study and for the pooled data set.

	DORI-07			DORI-08		
	Doripenem (N=163)	**Meropenem** (N=156)	**Total** (N=319)	**Doripenem** (N=162)	**Meropenem** (N=153)	**Total** (N=315)
Stratum, APACHE II Score, n (%)						
N	163	156	319	162	153	315
APACHE II score ≤10	148 (90.8)	143 (91.7)	291 (91.2)	142 (87.7)	140 (91.5)	282 (89.5)
APACHE II score >10	**15 (9.2)**	**13 (8.3)**	**28 (8.8)**	**20 (12.3)**	**13 (8.5)**	**33 (10.5)**
Infection Stratum, n (%)						
Complicated appendicitis with localized peritonitis	55 (33.7)	61 (39.1)	116 (36.4)	57 (35.2)	42 (27.5)	99 (31.4)
Other Sites	108 (66.3)	95 (60.9)	203 (63.6)	105 (64.8)	111 (72.5)	216 (68.6)
Infectious Process, n (%)						
Generalized peritonitis	74 (45.4)	53 (34.0)	127 (39.8)	76 (46.9)	81 (52.9)	157 (49.8)
Localized infection	38 (23.3)	54 (34.6)	92 (28.8)	46 (28.4)	30 (19.6)	76 (24.1)
Single abscess	44 (27.0)	41 (26.3)	85 (26.6)	33 (20.4)	36 (23.5)	69 (21.9)
Multiple abscess	6 (3.7)	7 (4.5)	13 (4.1)	5 (3.1)	4 (2.6)	9 (2.9)
Other	1 (0.6)	1 (0.6)	2 (0.6)	2 (1.2)	2 (1.3)	4 (1.3)
Anatomic Site of Infection, n (%)						
Appendix	**100 (61.3)**	**91 (58.3)**	**191 (59.9)**	**103 (63.6)**	**98 (64.1)**	**201 (63.8)**
Biliary-cholangitis	0	1 (0.6)	1 (0.3)	0	0	0
Biliary-cholecystitis	11 (6.7)	11 (7.1)	22 (6.9)	6 (3.7)	4 (2.6)	10 (3.2)
Colon	32 (19.6)	32 (20.5)	64 (20.1)	33 (20.4)	30 (19.6)	63 (20.0)
Parenchymal (liver)	4 (2.5)	4 (2.6)	8 (2.5)	2 (1.2)	2 (1.3)	4 (1.3)
Parenchymal (spleen)	0	1 0.6)	1 (0.3)	1 (0.6)	0	1 (0.3)
Small Bowel	10 (6.1)	8 (5.1)	18 (5.6)	7 (4.3)	7 (4.6)	14 (4.4)
Stomach/duodenum	3 1.8)	5 (3.2)	8 (2.5)	8 (4.9)	7 (4.6)	15 (4.8)
Other	8 (4.9)	7 4.5)	15 (4.7)	3 (1.9)	8 (5.2)	11 (3.5)
Post-operative Infection, n (%)						
No	142 (87.1)	146 (93.6)	288 (90.3)	152 (93.8)	141 (92.2)	293 (93.0)
Yes	21 (12.9)	10 (6.4)	31 (9.7)	10 (6.2)	12 (7.8)	22 (7.0)
Procedure Type, n (%)						
Laparoscopic	16 (9.8)	14 (9.0)	30 (9.4)	23 (14.2)	15 (9.8)	38 (12.1)
Open	128 (78.5)	127 (81.4)	255 (79.9)	135 (83.3)	129 (84.3)	264 (83.8)
Percutaneous	18 (11.0)	17 (10.9)	35 (11.0)	12 (7.4)	10 (6.5)	22 (7.0)
Other	2 (1.2)	2 (1.3)	4 (1.3)	1 (0.6)	3 (2.0)	4 (1.3)
Bacteremia at Baseline, n (%)						
No	159 (97.5)	148 (94.9)	307 (96.2)	152 (93.8)	138 (90.2)	290 (92.1)
Yes	4 (2.5)	8 (5.1)	12 (3.8)	10 (6.2)	15 (9.8)	25 (7.9)
Baseline Creatinine Clearance (μmol/L) Group, n (%)						
Normal (≥80)	122 (74.8)	124 (79.5)	246 (77.1)	123 (75.9)	109 (71.2)	232 (73.7)
Mild Renal Failure (>50-<80)	34 (20.9)	23 (14.7)	57 (17.9)	24(14.8)	29(19.0)	53(16.8)
Moderate Renal Failure (>30-≤50)	**4 (2.5)**	**8 (5.1)**	**12 (3.8)**	**11(6.8)**	**9 (5.9)**	**20(6.3)**
Severe Renal Failure (≤30)	**3 (1.8)**	**1 (0.6)**	**4 (1.3)**	**4 (2.5)**	**5 (3.3)**	**9 (2.9)**
Missing	0	0	0	0	1 (0.7)	1 (0.3)

Overall, approximately 74% (DORI-07) and 80% (DORI-08) of all patients in the ITT and CE at TOC analysis sets received at least 1 prior antibacterial medication. Nevertheless, these patients were

regarded as evaluable because the prior antibacterial therapy was given for less than 24 hours or, if administered for more than 24 hours, failure of the prior antibacterial therapy (as evident by the isolation of a pathogen at baseline) was documented. The two treatment arms were generally similar in terms of the types of prior antibiotic medications. Overall, the most common specific prior antibacterial medications received by at least 10% of patients in the ITT analysis set included metronidazole, gentamicin, ceftriaxone, cefazolin, ampicillin/sulbactam, piperacillin/tazobactam, and ciprofloxacin.

Approximately 25% of ITT subjects and 14% in the CE at TOC analysis set received at least one concomitant antibacterial drug. Concomitant antibacterial therapy given for treatment of clinical failure did not disqualify patients from the CE at TOC analysis set as described in the SAP. The most common concomitant antibacterial agents received by patients in the ITT analysis set were metronidazole, vancomycin, ciprofloxacin, and piperacillin/tazobactam. Vancomycin treatment was permitted as concomitant medication if enterococci or MRSA was verified or suspected.

The distribution of baseline intra-abdominal pathogens overall was similar between the treatment arms and also between the two studies and are therefore discussed as pooled data from DORI-07 and DORI-08.
The most common pathogens isolated in both the doripenem and meropenem arms included *E. coli* (250 and 226, respectively), *B. fragilis* (77 and 81), *P. aeruginosa* (46 and 35), *B. thetaiotaomicron* (43 and 41), *S. intermedius* (43 and 37), *K. pneumoniae* (41 and 27), *E. faecalis* (33 and 26), *B. caccae* (30 and 21), and *B. uniformis* (23 and 22). Other less common pathogens that were isolated in ≥10 subjects in either the doripenem or meropenem arm included *S. aureus, S. constellatus*, *E. avium*, *E. faecium, S. agalactiae*, *C. perfringens*, *S. anginosis, E. lentum, P. micros, C. freundii*, *E. cloacae*, *K.oxytoca*, *P. mirabilis*, *B. distasonis*, and *B. vulgatus*.

Baseline resistance to doripenem or meropenem was rare among gram-negative organisms, being observed with doripenem for *P. aeruginosa* (1/44), *B. fragilis* (1/71), and *P. bivia* (1/4) and with meropenem for *A. baumannii* (1/3), *S. maltophilia* (1/1), *B. fragilis* (2/72). Overall (i.e. irrespective of treatment group) baseline susceptibility to doripenem and meropenem was 100% for most of the major causative pathogens of cIAI including Enterobacteriaceae, *B. thetaiotaomicron*, *S. intermedius*, *K. pneumoniae*, *B. caccae* and *B. uniformis*. Susceptibility to doripenem and meropenem for *B.fragilis* was 98% and 99%, and for *P. aeruginosa* it was 99% and 97%, respectively. Among the enterococci, none of the *E. faecalis* isolates were resistant to doripenem (10% classified as intermediate susceptible), whereas 45% of *E. faecium* isolates were resistant. Meropenem susceptibility criteria for enterococci are not defined.

- **Outcomes and estimation**

Clinical and microbiological cure rates for primary and selected secondary endpoints in each study and pooled data

	Doripenem			Meropenem				
	N	n	%	N	n	%	Diff (%)	95% CI
Study DORI-07								
Primary endpoints								
Clinical cure								
Microbiologically evaluable at TOC	163	140	**85.9**	156	133	**85.3**	0.6	(-7.7; 9.0)
Microbiological MITT (within 60 days)	195	152	**77.9**	190	150	**78.9**	-1.0	(-9.7; 7.7)
Secondary endpoints								
Clinical cure								
Clinically evaluable at TOC	188	163	**86.7**	186	161	**86.6**	0.1	(-7.3; 7.6)
Microbiologically evaluable at EFU	164	145	**88.4**	152	135	**88.8**	-0.4	(-8.0;7.2)
Clinically evaluable at EFU	188	167	**88.8**	185	166	**89.7**	-0.9	(-7.7; 5.9)
Microbiological cure								
Microbiologically evaluable at TOC	163	139	**85.3**	156	132	**84.6**	0.7	(-7.8; 9.1)
Study DORI-08								
Primary endpoints								
Clinical cure								

Microbiologically evaluable at TOC	162	135	**83.3**	153	127	**83.0**	0.3	(-8.6; 9.2)
Microbiological MITT (within 60 days)	200	149	**74.5**	185	140	**75.7**	-1.2	(-10.3; 8.0)
<u>*Secondary endpoints*</u>								
Clinical cure								
Clinically evaluable at TOC	192	161	**83.9**	192	165	**85.9**	-2.1	(-9.8; 5.6)
Microbiologically evaluable at EFU	158	134	**84.8**	150	133	**88.7**	-3.9	(-12.1; 4.3)
Clinically evaluable at EFU	189	163	**86.2**	186	168	**90.3**	-4.1	(-11.1; 2.9)
Microbiological cure								
Microbiologically evaluable at TOC	162	135	**83.3**	153	129	**84.3**	-1.0	(-9.7; 7.8)
Pooled data (DORI-07 and DORI-08)								
<u>*Primary endpoints*</u>								
Clinical cure								
Microbiologically evaluable at TOC	325	275	**84.6**	309	260	**84.1**	0.5	(-5.5; 6.4)
Microbiological modified ITT	395	301	**76.2**	375	290	**77.3**	-1.1	(-7.4; 5.1)
<u>*Secondary endpoints*</u>								
Clinical cure								
Clinically evaluable at TOC	380	324	**85.3**	378	326	**86.2**	-1.0	(-6.2; 4.3)
Microbiologically evaluable at EFU	322	279	**86.6**	302	268	**88.7**	-2.1	(-7.6; 3.4)
Clinically evaluable at EFU	377	330	**87.5**	371	334	**90.0**	-2.5	(-7.3; 2.3)
Microbiological cure								
Microbiologically evaluable at TOC	325	274	**84.3**	309	261	**84.5**	-0.2	(-6.1; 5.8)

N= number of subjects in each analysis set. n= number of subjects who were cured (clinically or microbiologically)

Clinical response rates (improvement) at the EOT (i.v.) visit in the ME and CE at TOC populations were 92-95% in both studies and in both treatment arms, indicating a high efficacy of the i.v. treatment regimen.

<u>Surgical review panel</u>

The blinded Surgical Review Panel (SRP) reviewed approximately 12% of randomized subjects, primarily subjects deemed as clinical failures, and clinically cured who underwent a second surgical procedure. In general, the SRP agreed with the prior assessment of the patients. In Study DORI-07, 4 subjects (2 from each treatment arm) were changed from evaluable to non-evaluable, and one of these subjects (in the doripenem treatment arm) underwent a second procedure. In addition, the clinical response of one evaluable subject (in the meropenem treatment arm) was changed from clinical cure to failure. In Study DORI-08, two subjects (one from each treatment arm) were changed from evaluable to non-evaluable for efficacy. In addition, the clinical response of 9 evaluable subjects (5 and 4 in the doripenem and meropenem treatment arms, respectively) was changed from clinical cure to failure.

Clinical cure/improvement rates at EOT(IV) in the ME at TOC analysis set were 94% in both treatment arms in DORI-07 and 93% vs. 92% in the doripenem and meropenem arms in DORI-08, respectively, indicating efficacy of the i.v. portion of the treatment regimen.

The clinical cure rates in each of the subgroups (pooled data for studiesDORI-07 and DORI-08) were generally comparable between treatment arms. High-risk patients e.g., patients ≥65 years, patients with impaired renal function, patients with APACHE II scores >10, and those with abscesses, colon perforation and post-operative infections as well as female gender generally had poorer clinical outcomes.

<u>Microbiological outcome</u>

Microbiological outcome is presented as pooled data across studies (DORI-07 and DORI-08)

	Doripenem			**Meropenem**				
	N	n	%	N	n	%	Diff(%)	95% CI
Gram-positive, aerobic	176	150	**85.2**	168	131	**78.0**	7.3	(-1.5; 16.0)
Viridans group streptococci	109	93	85.3	90	71	78.9	6.4	(-5.3; 18.2)
Streptococcus constellatus	10	9	90.0	7	5	71.4	18.6	
Streptococcus intermedius	36	30	83.3	29	21	72.4	10.9	(-12.5; 34.4)
Enterococcus faecalis	20	16	80.0	17	13	76.5	3.5	
Gram-positive, anaerobic	73	61	83.6	82	62	75.6	8.0	(-5.9; 21.8)

Peptostreptococcus micros	13	11	84.6	14	11	78.6	6.0	
Gram negative, aerobic	375	322	**85.9**	316	265	**83.9**	2.0	(-3.7; 7.7)
Enterobacteriaceae	315	271	**86.0**	274	234	**85.4**	0.6	(-5.4; 6.6)
Escherichia coli	216	189	**87.5**	199	168	**84.4**	3.1	(-4.1; 10.3)
Klebsiella pneumoniae	32	25	**78.1**	20	19	**95.0**	-16.9	
Non-fermenters	51	44	**86.3**	39	28	**71.8**	14.5	(-4.8; 33.7)
Pseudomonas aeruginosa	40	34	**85.0**	32	24	**75.0**	10.0	(-11.5; 31.5)
Gram negative, anaerobic	245	209	**85.3**	251	210	**83.7**	1.6	(-5.1; 8.4)
Bacteroides fragilis group	173	152	**87.9**	181	152	**84.0**	3.9	(-3.9; 11.7)
Bacteroides caccae	25	23	92.0	19	18	94.7	-2.7	
Bacteroides fragilis	67	56	83.6	68	54	79.4	4.2	(-10.4; 18.7)
Bacteroides thetaiotaomicron	34	30	88.2	36	32	88.9	-0.7	(-18.4; 17.1)
Bacteroides uniformis	22	19	86.4	18	15	83.3	3.0	
Bacteroides vulgatus	11	11	100.0	8	6	75.0	25.0	

N= number of subjects in each analysis set. n= number of subjects who had a favourable outcome (clinically or microbiologically).

Microbiological failures

The ratio of microorganisms most commonly isolated from treatment failures in doripenem treated patients, in relation to the baseline distribution were *E.coli* (19%/24%), *B. fragilis* (8%/7%), *P. aeruginosa* (4%/4%), *S. intermedius* (4%4%) and *B. thetaiotaomicron* (4%/4%), *Klebsiella pneumoniae* (5%/3%), *E. faecalis* (4%/3%) and *B. caccae* (1%/3%). Similar findings were recorded for meropenem treated patients. Failure could not be predicted from baseline susceptibility data.

Emerging infections

Superinfections, occurring during therapy, were rare in both studies (3 subjects in the pooled doripenem arms and 7 subjects in the pooled meropenem arms). Also new infections, occurring after end of study therapy, were uncommon, being reported for 7 subjects in the pooled doripenem arm and in 11 subjects in the pooled meropenem arms. One doripenem treated patient had a superinfection caused by a resistant organism (*S. aureus*) and one patient in the meropenem arms had a superinfection with a resistant strain (*Acinetobacter baumanii*). Of the organisms that persisted in any of the studies, one doripenem-treated subject had an isolate of *P. aeruginosa* with a 4-fold increase in MIC during the course of study drug treatment.

Nosocomial pneumonia (NP)

Study DORI-09 - Study DORI-10

The clinical development program, aimed to demonstrate the efficacy of doripenem in the treatment of NP in adults includes two phase 3 comparative, open-label multicenter studies, comparing doripenem to piperacillin/tazobactam (DORI-09) and imipenem (DORI-10), respectively.

Methods

- **Study Participants**

In general, populations included in the two studies were similar but different regarding the severity of disease. DORI-09 included non-ventilated patients and ventilated patients with early-onset NP, while DORI-10 included patients with late-onset VAP. Inclusion and exclusion criteria stated below were identical for the two studies unless specifically indicated.

Inclusion criteria for studies DORI-09 and/or DORI-10 included, males or females aged 18 years or older, clinical pulmonary Infection Score (CPIS) of 5 or more (intubated subjects), presence of a new or progressive infiltrate on chest radiograph and at least Fever / hypothermia or elevated total peripheral WBC count or greater than 15% bands or leucopenia.

For study DORI-09 subjects hospitalized ≥ 48 hours or with prior hospital admission of ≥ 48 hours who were discharged within the last 7 days were included. Patients with respiratory failure requiring mechanical ventilation OR at least two of the following: Cough, new onset of purulent sputum production or a change in the character of sputum, auscultatory findings on pulmonary examination, dyspnea, tachypnea, or respiratory rate ≥ 30 per minute or hypoxemia were included. Residents of chronic care facilities admitted with pneumonia were also eligible.
For study DORI-10 subjects who had received mechanical ventilation for more than 24 hours or had been weaned from mechanical ventilation within 72 hours were included.
All subjects who met the clinical and radiographic criteria for VAP had to provide an acceptable specimen of lower respiratory tract (LRT) secretions.

Exclusion criteria included patients to have NP caused by pathogen(s) resistant to meropenem or piperacillin/tazobactam, APACHE II score < 8 and > 25 (**DORI-09**) or < 8 and > 29 (**DORI-10**), considered unlikely to survive the study period, presence of cavitary lung disease, primary lung cancer or another malignancy metastatic to the lungs, Adult Respiratory Distress Syndrome (ARDS), cystic fibrosis, or known or suspected *Pneumocystis carinii* pneumonia, *Legionella* or active tuberculosis, use of systemic antibiotic therapy for 24 or more hours within 72 (**DORI-09**) or 48 (**DORI-10**) hours prior to start of study drug therapy, the need for concomitant systemic antimicrobial agents, requirement for peritoneal dialysis, hemodialysis or hemofiltration, immunocompromising illness or immunosuppressive therapy, clinical laboratory abnormalities, history of moderate or severe hypersensitivity reactions to beta-lactam antibiotics, women who were pregnant, nursing, or if of childbearing potential not using accepted methods of birth control.
For study DORI-09 subjects with mechanical ventilation for ≥ 5 days and presence of known bronchial obstruction or a history of postobstructive pneumonia were excluded.
For study DORI-09 subjects having the need for Xigris® (drotrecogin alpha) and subjects with an order of "no cardiopulmonary resuscitation" in case of cardiac arrest were excluded.

Patients were defined as having completed the study if they had received 7-14 days of study drug therapy (80-120% of postulated doses acceptable) and had attended the TOC and LFU visists as specified in the protocol.

- **Treatments**

In study DORI-09 *Doripenem* was administered as 500 mg infused q8h as a **1-hour** infusion. *Piperacilin/tazobactam (pip/taz)* was given 4.5 g i.v. infused q6h over 30 min.
Subjects could be switched to oral therapy (levofloxacin 750 mg daily) after at least 72 hours of IV study drug therapy. The duration of study drug therapy (i.v. alone or i.v. plus oral) was 7-14 days. Study drug was discontinued during this window (unless clinical failure had occurred sooner) at the discretion of the investigator if the subject had shown signs of improvement such as: decreased WBC counts and body temperature (as specified in the protocol); improvement of pulmonary signs and symptoms manifested at study entry; improvement or lack of progression of findings on chest X-ray; or for subjects with VAP, treatment should have been continued for at least two days after the CPIS has decreased by ≥ 2 points.
In study DORI-10 *Doripenem was administered* 500 mg infused q8h as a **4-hour** infusion. *Imipenem* was given 500mg q6h over 30 min *or* 1000mg q8h over 60 min.
The duration of study drug therapy (i.v. alone) was 7-14 days. Study drug was discontinued during this window at the discretion of the investigator. Study therapy was to be continued for at least 2 days beyond the first day the CPIS score decreased by at least 2 points from baseline (Screening Visit) or until extubated, with a minimum treatment duration of 7 days and a maximum treatment duration of 14 days.
In study DORI-09 and DORI-10 Amicacin and vancomycin (or if needed comparable agents) were accepted as adjunctive therapies for suspected/proven *P. aeruginosa* and MRSA infections, respectively.

For all subjects with renal impairment and for body weight less than 70 kg (imipenem only), appropriate dosage adjustments were made for doripenem and comparators. Subjects who required peritoneal dialysis, hemodialysis, or hemofiltration, and those with oliguria were excluded from the

studies.Levofloxacin and other permitted antimicrobials were adjusted according to national recommendations and clinical practice.

- **Objectives**

The primary objective of both studies (DORI-09 and DORI-10) was to compare the safety and to demonstrate equivalent clinical efficacy of doripenem to that of established comparative therapies (pip/taz or imipenem) in the treatment of nosocomial pneumonia, including non-ventilated patients and ventilated patients with early and late onset nosocomial pneumonia. Secondary objectives included microbiological outcome per patient and per pathogen and to compare emergence of study drug-resistant pathogens between treatment arms.

- **Outcomes/endpoints**

In study **DORI-09** clinical outcome was determined by an external independent blinded evaluation committee (BEC) consisting of 10 authoritative physicians experienced in the diagnosis and management of NP. The primary endpoints included clinical cure rate at the test-of-cure (TOC) visit in the co-primary efficacy analysis sets, i.e. clinical evaluable population (CE) at TOC analysis set and in the clinically modified intention to treat (cMITT) analysis sets.
Key secondary endpoints included, clinical cure rate/improvement in CE population at end of i.v. therapy (EOT(i.v.), clinical relapse rate at LFU, clinical cure rate at TOC in the ME and mMITT analysis sets, clinical cure rate in the VAP-subset At EOT(i.v.), TOC and LFU and microbiological cure rate at TOC and LFU visits per patient and per pathogen.

In study **DORI-10** primary endpoints were clinical response rate at TOC visit in the co-primary efficacy analysis sets, i.e. the CE at TOC analysis set and in the cMITT analysis sets.
Key secondary endpoints included clinical cure rate at the TOC visit in the ME and mMITT analysis set, clinical relapse rate at LFU, microbiological cure rate at TOC and LFU visits per patient and per pathogen, the proportion of subjects with decrease of susceptibility to study drug received in strains of *P. aeruginosa* isolates that were isolated from post-baseline LRT culture specimens, compared with the baseline strain, (analysed in the mMITT analysis set).

The clinical response was determined at the end of i.v. treatment (EOT (i.v.), TOC and LFU visits. Clinical evaluations were based on Clinical Pulmonary Infection Score (CIPS) (points 0-5) in subjects with VAP, clinical examination of the chest, ventilator needs, chest radiographs, oxygenation status and oral temperature.

In DORI-09 the final clinical outcome at TOC in all subjects who had received at least 48 hours of study therapy was determined by an external independent blinded evaluation committee (BEC). In DORI-10 was the assessment performed by the investigator.

Clinical response was based on the following criteria:

Clinical Cure Resolution of signs and symptoms of NP and improvement or lack of progression of all chest x-ray abnormalities, such that no additional antibacterial therapy was required for the treatment of the current infection.

Clinical Improvement (DORI-09 only): Resolution or improvement in the signs and symptoms of NP.

Subjects could be switched to oral study drug therapy (only valid for the EOT(i.v.) visit).

Clinical Failure: Subjects were classified as a clinical failure after at least 48 hours of study drug therapy based on:

• Death due to NP

• Persistence, incomplete resolution or worsening in signs or symptoms of the acute process;

• Development of new signs or symptoms of pulmonary infection requiring antimicrobial therapy other than or in addition to study drug therapy;

• Progression of radiographic findings.

Relapse: Recurrence of signs or symptoms of NP or new radiographic evidence of NP in a subject assessed as cured at the TOC visit.

Indeterminate: Study data were not available for evaluation of efficacy for any reason, including: treatment change (other than allowed adjunctive therapy) in the first 48 hours; death at any time prior to the TOC assessment and the index infection was clearly non-contributory. Subjects with a clinical response of indeterminate were excluded from the per-protocol analysis of clinical response.

Evaluation of microbiological response

Sputum specimens for microbiological analyses in non-intubated subjects were obtained by deep expectoration or by some form of tracheal aspiration. For intubated subjects, the LRT specimen was obtained by endotracheal aspiration or, if bronchoscopy was scheduled for clinical reasons, a specimen was obtained during the procedure, either by BAL or protected-specimen brush.

Blood cultures were obtained at baseline and were repeated at any time during the study in subjects with signs of sepsis or who were assessed as clinical failures.

Identification and susceptibility testing were initially performed in local laboratories, and later confirmed by the central laboratory. Genotyping of baseline and post baseline pathogen pairs from clinical failures was performed in the central laboratory.

Microbiological response was based on the following criteria:

Eradication: Absence of original baseline pathogen from sputum (or other LRT specimen) culture.
Presumed eradication: No source specimen to culture and subject assessed as clinical cure.
Persistence: Continued presence of the original baseline pathogen
Presumed persistence: No source specimen to culture in a subject who was judged to be a clinical failure.
Recurrence: Isolation of the original baseline pathogen from a culture LRT specimen taken after the TOC, and the TOC culture was negative or presumed eradicated.
Indeterminate: Assessment was not possible

Emergent pathogens did not affect the per-subject microbiological response. It was categorized as either superinfection (during therapy) or as a new infection (after therapy).

- **Sample size**

In study DORI-09 the original sample size of 300 was increased to 440 subjects, according to Amendment 3. The expected cure rate of approximately 65% was according to previous studies on pip/taz in patients with NP, and an assumption of that 65% would be clinically evaluable. The sample size calculation was in line with the recently submitted linezolid NP study.
In study DORI-10 the final sample size of 520 subjects (Amendment 2) was based on an expected evaluability rate of 50% and an expected cure rate of 60% in both treatment arms. The latter was in line with previous studies using imipenem in the treatment of NP.
For both studies, these calculated sample size would yield a sample size pf 130 CE subjects per treatment arm and would have approximately 90% power to establish non-inferiority to the comparators.

- **Randomisation**

For both studies subjects were randomly assigned (1:1) to either doripenem i.v. or comparator based on a computer-generated randomization code, using an Interactive Voice Response System (IVRS). The randomization block size was 4 subjects. Prior to randomization, subjects were stratified according to geographic region, ventilation mode and severity of illness.

- **Blinding (masking)**

Both DORI-09 and DORI-10 were performed as open studies.

- **Statistical methods**

Noninferiority of doripenem to comparator was tested in the individual studies and was concluded when the lower bound of the 2-sided 95% CI for the treatment difference (doripenem minus comparator), in the proportion of subjects who were classified as clinically cured, was not less than -20%. The 2-sided 95% CI was obtained in both studies using normal approximation to the difference between 2 binomial distributions with continuity correction.

The following study populations were defined for efficacy evaluation:
Intent-to-Treat (ITT): All randomized patients who received any dose of study drug therapy.
Clinical Modified Intent-to-Treat (cMITT): All randomized patients who received any amount of study drug therapy and met the minimal disease definition of pneumonia.
Microbiological Modified Intent-to-Treat (mMITT): A subset of the cMITT analysis set consisting of patients in the cMITT analysis set who had a baseline bacterial pathogen identified, regardless of susceptibility to study drug therapies.
Clinically Evaluable at Test-of-cure (CE at TOC): A subset of the cMITT analysis set and consisted of all randomized patients who received an adequate course of study drug therapy, who met the protocol-specified disease definition of NP, and for whom sufficient information was available to determine the patient's clinical outcome at the TOC visit.
Microbiologically Evaluable at Test-of-cure (ME at TOC): The ME at TOC analysis set was a subset of the CE at TOC analysis set presenting with at least 1 adequate baseline bacterial pathogen, susceptible to both IV study drug therapies. This analysis set was used in the primary analysis.
"Expanded" ME at TOC analysis set: Pathogens form CE patients for whom not all baseline pathogens were susceptible to at least 1 study drug therapy. These were included for evaluating per-pathogen microbiological outcomes by MIC.
Clinically Evaluable at Late Follow-up (CE at LFU): Subset of the CE at TOC subjects who were clinically cured at TOC and evaluable at LFU.
Microbiologically Evaluable at Late Follow-up (ME at LFU): A subset of the ME at TOC analysis set, with a favourable microbiological response at TOC and evaluable at LFU
VAP Subset (DORI-09): This is the subset of subjects, in any corresponding analysis set, who are diagnosed with early-onset of VAP at baseline.

Two populations, ME at TOC and cMITT at TOC were used as primary analysis sets.

Results

- **Participant flow**

The original protocol defined windows at TOC (7 to 14 days) and LFU (28 to 35 days) after the administration of the last dose of study drug (i.v. or oral) was changed to 6 to 20 days and 21 to 60 days, respectively. The overall designs of the two studies, after amendment concerning broadening of TOC and LFU analysis windows for clinical evaluability were as follows:

Study design DORI-09

SCREENING	TREATMENT	TEST OF CURE	LATE FOLLOW-UP
Day -1 (24 hours prior to randomization) • Established diagnosis of NP • Obtained microbiologic specimen • Stratified by mechanical ventilation association (non- ventilator associated vs. early-onset VAP), and	**Day 1 to end of study drug therapy** • Doripenem i.v. 500 mg q8h (over 1 hour) or piperacillin/ tazobactam i.v. 4.5 g q6h (over 30 min). • Amikacin therapy was added to both groups initially for suspected *P.aeruginosa*.	**6 to 20 days after last dose (IV or oral)** Subject returned to study center for assessment of microbiological and clinical response and safety.	**21 to 60 days after last dose (IV or oral)** Subject returned to study center for assessment of microbiological recurrence or clinical relapse and final safety.

severity of illness (APACHE II ≤15 or > 15), and geographic region (North America, South America and Europe/Other) • Randomized to study drug.	• Vancomycin therapy was added if MRSA infection was suspected or isolated at baseline. • Optional switch to oral levofloxacin therapy (750 mg once daily) after a minimum of 9 i.v. doses of doripenem or 12 i.v. doses of pip/taz. • Total study drug therapy (i.v. alone or i.v. and oral) was 7 to 14 days.		

Study design DORI-10

SCREENING	TREATMENT	TEST OF CURE	LATE FOLLOW-UP
Day -1 (24 hours prior to randomization) • Established diagnosis of VAP • Obtained microbiologic specimen • Stratified by duration of mechanical ventilation (<5 days or > 5 days), and severity of illness (APACHE II ≤15 or > 15), and geographic region (North America, Europe and Other) • Randomized to study drug.	**Day 1 to end of study drug therapy** • Doripenem i.v. 500 mg q8h (over 1h) or imipenem 500 mg 1.v. q6h (over 30 min) or 1000mg i.v. q8h (over 60 min) • Amikacin therapy was added to both groups initially for subjects at risk for *P. aeruginosa*. • Vancomycin therapy was added if MRSA infection was suspected or isolated at baseline. • Total study drug therapy (i.v. alone or i.v. and oral) was 7 to 14 days.	**6 to 20 days after last dose (IV or oral** Subject returned to study center for assessment of microbiological and clinical response and safety.	**21 to 60 days after last dose (IV or oral)** Subject returned to study center for assessment of microbiological recurrence or clinical relapse and final safety.

DORI-09: A total of 448 patients were randomized to the study to receive either doripenem (n=225) or pip/taz (n=223), allocated in 68 centers in North-America, South-America, Europe and Others. Approximately 52% of the subjects were recruited from Europe.

DORI-10: A total of 531 patients were randomized to the study to receive either doripenem (n=264) or imipenem (n=267), allocated in 84 centers in North-America, Europe and Others. Approximately 38% of the subjects were recruited from Europe.

- **Reasons for exclusion and discontinuation**

Reasons for exclusion of subjects from the analysis set differed somewhat between the studies.
A higher percentage of subjects were excluded from the CE at TOC analysis set in DORI-10 than in DORI-09 (53% *vs.* 43%). Exclusion due to negative tracheal aspirate cultures (in ventilated subjects) were between 8% and 6% in DORI-10 while between 2% and 3% in DORI-09, mainly attributed to that more subjects were ventilated in DORI-10 than in DORI-09. Furthermore, concomitant antibacterial therapy violation was higher in DORI-10 (25% vs.10.5% in DORI-09), most probably because of more frequent concurrent infections in ICU subjects. TOC window violation or "indeterminate" clinical outcome assessment at the TOC visit was 21% in DORI-10 *vs.* 15% in DORI-09.

Approximately 67% of patients in both groups completed to the LFU visit per protocol, there were no major differences between the studies or between the treatment groups. Need for additional antibiotic therapy was more common in DORI-10 (14 *vs.* 4 subjects).

- **Conduct of the study**

The original **DORI-09** study protocol was dated 3 March 2004. There were 3 amendments during the study. Amendment 1 (Nov 2004) included among others the institution of a BEC of experts to determine the final clinical outcome. Amendment 2 (Jan 2006) replaced the former ME at TOC with the CE at TOC analysis set as the primary efficacy analysis set. Amendment 3 (April 2006) increased the sample size from 300 to 440 subjects in order to increase the power of the study to 90%.
The original **DORI-10** protocol dated 18 March 2004 underwent two amendments. Amendment 1 (Jan 2005) provided several clarifications and modifications, such as clarification of acceptable pre-therapy microbiological specimens. Amendment 2 (May 2006) increased the power of the study to 90% by increasing the number of subjects from appr. 400 to 520 subjects, and replaced the former ME at TOC with the CE at TOC analysis set as the primary efficacy analysis set.

- **Baseline data**

Demographic and baseline characteristics were generally similar between treatment groups.

Baseline disease characteristics were similar between treatment arms, but differed between the studies.

	DORI-09		DORI-10		Total	
	Doripenem (N=134)	**Pip/ taz** (N=119)	**Doripenem** (N=126)	**Imipenem** (N=122)	**Doripenem** (N=260)	**Comparators** (N=241)
Ventilation Mode, n (%)						
Non-VAP	**105 (78.4)**	**93 (78.2)**	**0**	**0**	**105 (40.4)**	**93 (38.6)**
VAP	**29 (21.6)**	**26 (21.8)**	**126 (100)**	**122 (100)**	**155 (59.6)**	**148 (61.4)**
Early-onset VAP (<5 Days)	**29 (100)**	**26 (100)**	**48 (38.1)**	**49 (40.2)**	**77 (49.7)**	**75 (50.7)**
Late-onset (≥5 Days)	**0**	**0**	**78 (61.9)**	**73 (59.8)**	**78 (50.3)**	**73 (49.3)**
APACHE II Score, n (%)						
< 10	28 (20.9)	31 (26.1)	5 (4.0)	13 (10.7)	33 (12.7)	44 (18.3)
10-15	70 (52.2)	60 (50.4)	54 (42.9)	48 (39.3)	124 (47.7)	108 (44.8)
16-20	29 (21.6)	19 (16.0)	40 (31.7)	35 (28.7)	69 (26.5)	54 (22.4)
21-25	7 (5.2)	9 (7.6)	26 (20.6)	23 (18.9)	33 (12.7)	32 (13.3)
> 25	0	0	1 (0.8)	3 (2.5)	1 (0.4)	3 (1.2)
≤15	99 (73.9)	91 (76.5)	59 (46.8)	61 (50.0)	158 (60.8)	152 (63.1)
>15	**35 (26.1)**	**28 (23.5)**	**67 (53.2)**	**61 (50.0)**	**102 (39.2)**	**89 (36.9)**
Clinical Pulmonary Infection Score, n (%) [c]						
5	7 (24.1)	5 (19.2)	20 (15.9)	23 (18.9)	27 (17.4)	28 (18.9)
6	7 (24.1)	2 (7.7)	29 (23.0)	21 (17.2)	36 (23.2)	23 (15.5)
7	1 (3.4)	7 (26.9)	29 (23.0)	32 (26.2)	30 (19.4)	39 (26.4)
> 7	14 (48.3)	12 (46.2)	48 (38.1)	46 (37.7)	62 (40.0)	58 (39.2)
Baseline Creatinine Clearance Group, n (%)						
Missing	2 (1.5)	5 (4.2)	0	1 (0.8)	2 (0.8)	6 (2.5)
Normal (≥80)	71 (53.0)	70 (58.8)	104 (82.5)	97 (79.5)	175 (67.3)	167 (69.3)
Mild Renal Failure (>50-<80)	35 (26.1)	33 (27.7)	9 (7.1)	16 (13.1)	44 (16.9)	49 (20.3)
Moderate Renal Failure (>30-≤50)	**21 (15.7)**	**9 (7.6)**	**13 (10.3)**	**5 (4.1)**	**34 (13.1)**	**14 (5.8)**
Severe Renal Failure (≤30)	**5 (3.7)**	**2 (1.7)**	**0**	**3 (2.5)**	**5 (1.9)**	**5 (2.1)**
Bacteremia, n (%)						
No	126 (94.0)	102 (85.7)	113 (89.7)	111 (91.0)	239 (91.9)	213 (88.4)
Yes	**8 (6.0)**	**17 (14.3)**	**13 (10.3)**	**11 (9.0)**	**21 (8.1)**	**28 (11.6)**
Pathogen Isolated From Both LRT and Blood, n	2	9	6	7	8	16
Any Adjunctive Therapy, n (%)						
No	25 (18.7)	16 (13.4)	79 (62.7)	74 (60.7)	104 (40.0)	90 (37.3)
Yes	109 (81.3)	103 (86.6)	47 (37.3)	48 (39.3)	156 (60.0)	151 (62.7)
Anti-MRSA Coverage, n (%						

No	117 (87.3)	98 (82.4)	89 (70.6)	88 (72.1)	206 (79.2)	186 (77.2)
Yes	17 (12.7)	21 (17.6)	37 (29.4)	34 (27.9)	54 (20.8)	55 (22.8)
Anti-Pseudomonas Coverage, n (%)						
No	29 (21.6)	18 (15.1)	101 (80.2)	92 (75.4)	130 (50.0)	110 (45.6)
Yes	**105 (78.4)**	**101 (84.9)**	**25 (19.8)**	**30 (24.6)**	**130 (50.0)**	**131 (54.4)**

As all subjects were already hospitalized for reasons other than NP when entering the study, almost all were burdened by a significant medical history. Most subjects had clinically significant cardiovascular (>80%) or respiratory (>60%) history.

The majority, approximately 80%, of the subjects had received prior antibacterial prophylaxis or therapy within four weeks prior to randomization. This is expected in this seriously ill population.

DORI-09: The vast majority (91%) of subjects received at least one concomitant antibacterial medication in the CE at TOC population. Approximately 78% (doripenem arm) and 85% (pip/taz) received protocol defined *P. aeruginosa* therapy. Amikacin for 3 to 5 days was received by 38.8% (doripenem) and 41% (pip/taz) of subjects, while amikacin for > 5 days were received by approximately 33%. Vancomycin for MRSA coverage was given to 13% (doripenem) and 18% (pip/taz), respectively.
DORI-10: At least one concomitant antibacterial medication was received by 81% of subjects in the CE at TOC population, of whom 33% were considered as treatment failures. Approximately 22% received protocol defined *P. aeruginosa* therapy. Among subjects in the doripenem and imipenem arms, respectively, 3.2% and 8.2% of subjects received amikacin for 3 to 5 days while 4% and 3.3% of subjects received amikacin for longer than 5 days. Approximately 28% received MRSA coverage.

Overall, the most frequently isolated baseline organisms were *S. aureus* (266) (161 for methicillin-susceptible *Staphylococcus aureus* [MSSA]), *H. influenzae* (124), *P. aeruginosa* (110), *K pneumoniae* (96), *E. coli* (73), *Enterobacter cloacae* (58), *A. baumanii* (54), and *S. pneumoniae* (50). Other common (isolated in ≥10 subjects) baseline isolates included *Serratia marcescens* (28), *Enterobacter aerogenes* (22), *Enterococcus faecalis* (22), *Proteus mirabilis* (21), *Klebsiella oxytoca* (20), *S. maltophilia* (14), alpha haemolytic *Streptococcus* (12), and *Streptococcus agalactiae* (10). The distribution of pathogen species was similar between the treatment arms within each study.

Although there were some differences in the distribution of pathogens by ventilation mode, in general, the incidence of each pathogen was similar in the 3 ventilation groups.

Organisms isolated in the doripenem arm were considered susceptible **(S),** intermediate **(I)** or resistant **(R)** if the doripenem MIC level was **≤4 µg/mL, =8 µg/mL or ≥16 µg/mL**, respectively. Susceptibility for comparators was defined according to CLSI recommendations. Subjects with baseline pathogens of "intermediate" susceptibility and those with of presence of both "susceptible" and "resistant" pathogens were permitted to remain in the studies and could be included in the CE and ME at TOC analysis sets. Only "resistant" baseline bacterial organisms could not be included in the CE analysis set.

Baseline resistance was not observed to any treatment for MSSA, *H. influenzae*, and *S. pneumoniae*.
None of the baseline Enterobacteriaceae tested, regardless of study group, was resistant to doripenem or imipenem, while 10% were resistant to piperacillin/tazobactam. Most of the resistance to pip/taz among Enterobacteriaceae was due to *K. pneumoniae*, for which 21 of 89 (24%) isolates were resistant. In addition, 5 of 50 (10%) *E. cloacae* isolates tested and 2 of 61 (3%) *E. coli* isolates tested were resistant to pip/taz. Baseline resistance of *P. aeruginosa* to pip/taz (19 of 105 [18%]) and imipenem (15 of 105 [14%]) was greater than it was to doripenem (4 of 105 [4%]). Baseline resistance of *A. baumannii* to pip/taz (18 of 45 [40%]) was greater than it was to doripenem (11 of 45 [24%]) and imipenem (10 of 45, [22%]). All 48 strains of *P. aeruginosa* isolated in the doripenem group and tested were considered susceptible to study drug received, whereas 11 of 32 (34%) in the pip/taz arm and 3 of 25 (12%) in the imipenem arm were resistant to study drug received.

- **Outcomes and estimation**

Doripenem was shown to be non-inferior to the comparators in both studies. The BEC assessment in DORI-09, which was the final, was in agreement with the investigators in 98% of the cases.

Clinical and microbiological cure rates for primary and selected secondary end points.

	Doripenem			Comparators			Diff	
	N	n	(%)	N	n	(%)	(%)	95% CI
Study -DORI-09								
Primary endpoints								
Clinical Cure at TOC/CE at TOC	134	109	**(81.3)**	119	95	**(79.8)**	1.5	**(-9.1; 12.1)**
Clinical Cure/cMITT	213	148	**(69.5)**	209	134	**(64.1)**	5.4	**(-4.1; 14.8)**
Secondary endpoints								
Clinical Cure at TOC/ME at TOC	84	69	**(82.1)**	83	65	**(78.3)**	3.8	(-9.4; 17.1)
Clinical Cure/mMITT	139	94	**(67.6)**	144	97	**(67.4)**	0.3	(-11.4; 11.9)
Clinical cure/improvement at EOT(IV)/CE	134	117	**(87.3)**	119	103	**(86.6)**	0.8	(-8.4; 9.9)
Microbiological Cure at TOC/ME at TOC	84	71	**(84.5)**	83	67	**(80.7)**	3.8	(-8.9; 16.5)
Study -DORI-10								
Primary endpoints								
Clinical Cure at TOC/CE at TOC	126	86	**(68.3)**	122	79	**(64.8)**	3.5	**(-9.1; 16.1)**
Clinical Cure/cMITT[e]	244	144	**(59.0)**	249	144	**(57.8)**	1.2	**(-7.9; 10.3)**
Secondary endpoints								
Clinical Cure at TOC/ME at TOC	116	80	**(69.0)**	110	71	**(64.5)**	4.4	(-8.7; 17.6)
Clinical Cure/mMITT	202	117	**(57.9)**	201	118	**(58.7)**	-0.8	(-10.9; 9.3)
Clinical cure/improvement at EOT(IV)/CE	126	101	**(80.2)**	122	100	**(82.0)**	-1.8	(-12.4; 8.7)
Microbiological Cure at TOC/ME at TOC	116	85	**(73.3)**	110	74	**(67.3)**	6.0	(-6.8; 18.8)
Pooled Data from Studies DORI-09 and DORI-10								
Primary endpoints								
Clinical Cure at TOC/CE at TOC	260	195	(75.0)	241	174	(72.2)	2.8	(-5.3; 10.9)
Clinical Cure/cMITT	457	292	(63.9)	458	278	(60.7)	3.2	(-3.3; 9.7)
Secondary endpoints								
Clinical Cure at TOC/ME at TOC	200	149	(74.5)	193	136	(70.5)	4.0	(-5.3; 13.4)
Clinical Cure/mMITT	341	211	(61.9)	345	215	(62.3)	-0.4	(-8.0; 7.1)
Clinical cure/improvement at EOT(IV)/CE	260	218	(83.8)	241	203	(84.2)	-0.4	(-7.2; 6.4)
Microbiological Cure at TOC/ME at TOC	200	156	(78.0)	193	141	(73.1)	4.9	(-4.1; 13.9)

N= number of subjects in each analysis set. n= number of subjects who had a favourable outcome (clinically or microbiologically).

Low clinical relapse rates of doripenem and the comparator were recorded, 3% and 4% in DORI-09, and 8% in both arms in DORI-10.

In study DORI-10 the median time to CPIS decrease by at least 2 points or extubation was 3 days in both treatment arms. The all cause mortality rate at Day 28 was 10.8% in the doripenem treatment arm and 9.5% in the imipenem treatment arm (95% CI: –4.4%; 7.0%).

The clinical cure rates by different subgroups were generally consistent between the study drugs within each study.

Clinical cure by subgroup in the cMITT and ME at TOC analysis sets were similar to those in the CE at TOC analysis set. Response rates in monomicrobial infections were marginally higher than for polymicrobial infections in both studies.

The microbiological outcome per pathogen was generally consistent between the two studies. The data are presented as pooled data:

Favorable per pathogen clinical and microbiological cure rates at TOC for baseline pathogens isolated in ≥10 subjects in pooled data (DORI-09 and DORI-10 (ME at TOC analysis set)

	Doripenem			Comparator				
	N	n	%	N	n	%	Diff (%)	95% CI
Clinical Cure Rates								
Gram positive, aerobic								
Staphylococcus aureus	37	24	**(64.9)**	38	29	**(76.3)**	-11.5	(-34.6; 11.7)
MSSA	31	20	**(64.5)**	36	27	**(75.0)**	-10.5	(-35.5; 14.5)
Streptococcus pneumoniae	16	10	**(62.5)**	13	12	**(92.3)**	-29.8	
Gram negative, aerobic								
Acinetobacter baumannii	13	11	**(84.6)**	10	7	**(70.0)**	14.6	
Enterobacter cloacae	27	21	**(77.8)**	16	12	**(75.0)**	2.8	
Escherichia coli	21	16	**(76.2)**	25	16	**(64.0)**	12.2	
Klebsiella pneumoniae	29	22	**(75.9)**	21	12	**(57.1)**	18.7	
Haemophilus influenzae	40	29	**(72.5)**	47	33	**(70.2)**	2.3	(-19.1; 23.6)
Pseudomonas aeruginosa	38	31	**(81.6)**	31	17	**(54.8)**	26.7	**(2.4; 51.1)**
Microbiological Cure Rates								
Gram positive, aerobic								
Staphylococcus aureus	37	29	**(78.4)**	38	32	**(84.2)**	-5.8	(-26.1; 14.5)
MSSA	31	25	**(80.6)**	36	30	**(83.3)**	-2.7	(-24.2; 18.8)
Streptococcus pneumoniae	16	14	**(87.5)**	13	12	**(92.3)**	-4.8	
Gram negative, aerobic								
Acinetobacter baumannii	13	11	**(84.6)**	10	7	**(70.0)**	14.6	
Enterobacter cloacae	27	23	**(85.2)**	16	12	**(75.0)**	10.2	
Escherichia coli	21	16	**(76.2)**	25	17	**(68.0)**	8.2	
Klebsiella pneumoniae	29	23	**(79.3)**	21	13	**(61.9)**	17.4	
Haemophilus influenzae	40	33	**(82.5)**	47	38	**(80.9)**	1.6	(-16.9; 20.2)
Pseudomonas aeruginosa	38	28	**(73.7)**	31	17	**(54.8)**	18.8	**(-6.5; 44.2)**

The eradication rate for *P. aeruginosa* for patients that did not receive adjunctive anti-pseudomonas therapy were similar to the overall pseudomonas eradication rate in both treatment arms, 79% (11/14) for doripenem and 57% (4/7) with comparator, respectively. In the pip/taz arm of DORI-09, 8 out of 9 subjects with *P. aeruginosa* infection and 8 of 10 subjects with *K. pneumoniae* infection with MIC ≥128 µg/mL were clinical cures at TOC, implying the beneficial role of adjunctive amikacin administration. In DORI-10 was the clinical cure rate of *P. aeruginosa* infections higher for doripenem (80%) than for imipenem (43%), despite a higher use of anti-pseudomonal adjunctive therapy in the imipenem arm. Thus adjunctive therapy did not seem to enhance the efficacy of imipenem.

The majority of baseline LRT baseline pathogens had very low MICs to both doripenem and comparators, thus no firm conclusions on the predictiveness of high MIC-values can be drawn. In total were 7 of 11 *P.aeruginosa* isolates with MIC ≥1 µg/mL in doripenem treated subjects microbiological cures compared to 5 of 14 isolates from imipenem treated subjects. Six of 11 persistent strains of *P. aeruginosa* isolated post-baseline in subjects treated with doripenem were found to be of intermediate susceptibility (n=2) (MIC=8 µg/mL) or resistant (n=4) (MIC ≥16 µg/mL) to doripenem, whereas all 10 persistent strains of *P. aeruginosa* isolated post-baseline in subjects treated with imipenem were found to be of intermediate susceptibility (n=1) or resistant (n=9) to imipenem (based on the CLSI breakpoints).

In study DORI-09 one *P. aeruginosa* strain in the doripenem arm developed decreased susceptibility, defined as a >4-fold increase in MIC from baseline, and changed from susceptible (S) to intermediate (I). Three isolates in the pip/taz arm developed resistance (R), of which one changed from S to R. In addition, three *K. pneumoniae* isolates in the pip/taz group changed from S to R.

In study DORI 10 a decrease of susceptibility to study drug among *P. aeruginosa* cultured from both baseline and post-baseline specimens in the mMITT analysis set was observed in 10/28 (36%) and 11/25 (44%) strains in the doripenem and imipenem treatment arms, respectively. Baseline and post-baseline susceptibility of these strains are illustrated in the figure below. Most post-baseline *P. aeruginosa* strains with increased MICs were genotypically identical or closely related to the baseline strain. All 11 post-baseline strains with decreased susceptibility in the imipenem arm would be considered intermediate or resistant according to CLSI breakpoints, compared with 5 of 10 in the doripenem arm (tentative resistance breakpoint of 16µg/ml). In addition to the emergence of resistance

on therapy, 3 additional *P. aeruginosa* strains in the imipenem arm were intermediate or resistant to imipenem at baseline. Thus overall, 14/25 (56%) of *P. aeruginosa* isolates in the imipenem arm were either resistant at baseline or became intermediate or resistant on therapy compared with 5/28 (18%) in the doripenem arm.

The rates of emerging infections were generally low in both treatment arms, 5.8% (27/466) in the pooled doripenem group and 8.8% (41/464) in the comparator groups, more frequently occurring in VAP patients. In the doripenem arms were 1.9% (9/466) associated with a non-susceptible pathogen, mainly *P. aureginosa*, compared to 3.4% (16/464) in the comparator groups.

In study DORI-09 superinfections and new infections occurred in 6 and 1 subject in the doripenem arm, and in 10 and 3 subjects in the pip/taz arm, respectively. Superinfections were most common in VAP subjects.

DORI-10. Twenty (8%) and 28 (11%) of subjects in the doripenem arm and imipenem arm, respectively, had emergent infections. Four and 7 of these were caused by study drug-resistant pathogens, respectively. Of the 7 emergent *P. aeruginosa* isolates, one superinfection was of intermediate susceptibility to doripenem and one superinfection was resistant to imipenem.

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant provided analyses across studies which have been presented above by indication.

Clinical studies in special populations

No studies provided in this dossier were conducted in special populations. However, all studies have included elderly subjects and those with renal impairment. The data on these subjects are presented with in each study and commented if needed.

No paediatric subjects were enrolled; the lower age limit was 18 years in all studies. Applicant has submitted PIP to PDCO for the review.

From all studies patients with immunocompromising illnesses (e.g. HIV infection and AIDS, haematological malignancies, patients undergoing BMT) as well those on immunosuppressive therapy (e.g. corticosteroids, chemotherapy) were excluded. The studies excluded also subjects in septic shock or those with very high APACHE scores. The latter varied from study to study.

Supportive study(ies)

No supportive studies are presented in this dossier.

Clinical safety

- Patient exposure

A total of 3,207 subjects, aged 18 years and older, were included in the pooled safety analysis set. This included 1,292 subjects in the cUTI studies, 946 subjects in the cIAI studies and 969 subjects in the NP studies.

- Adverse events

Adverse reactions due to Doribax 500 mg every 8 hours occurred at rate of 32%. Doribax was discontinued because of adverse drug reactions in 0.1% of patients overall. Adverse drug reactions that led to Doribax discontinuation were nausea (0.1%), diarrhoea (0.1%), pruritus (0.1%), vulvomycotic infection (0.1%), hepatic enzyme increased (0.2 %) and rash (0.2%). The most common adverse reactions were headache (10%), diarrhoea (9%) and nausea (8%).

Rates of the majority of AEs, including those most commonly encountered, seen with doripenem in individual studies were generally similar to those for comparators and the same was seen in the pooled analysis. However, several differences between studies in the frequency and severity of AEs have been observed which are most likely due to the varying severity of the condition under study. The applicant specifically evaluated several AE that are though to be associated with the beta-lactam antibiotics and categorised them under adverse drug reactions. The following events have been covered: possible allergic reactions (PAR), rash, hypersensitivity reactions, seizures, *C.difficile* colitis and candidiasis and vaginitis and their distribution in various studies is presented in the table below.

Table. The adverse drug reactions in doripenem clinical programme

ADR Derived Term	NP Dori 500 mg 1- and 4-hour infusion q8h (N=485) n (%)	NP Pip/ Tazo 4.5 g 30-minutes infusion q6h (N=221) n (%)	NP Imip 500 mg/1 g 30-min/1-hour infusion q6h/q8h (N=263) n (%)	cIAI Dori 500 mg 1-hour infusion q8h (N=477) n (%)	cIAI Mero 1g bolus injection q8h (N=469) n (%)	cUTI Dori 500 mg 1-hour infusion q8h (N=376) n (%)	cUTI Levo 250 mg 1-hour infusion q24h (N=372) n (%)
C. difficile colitis	5 (1.0)	2 (0.9)	6 (2.3)	2 (0.4)	0	1 (0.3)	0
Diarrhea	58 (12.0)	24 (10.9)	45 (17.1)	51 (10.7)	52 (11.1)	22 (5.9)	38 (10.2)
Headache	14 (2.9)	5 (2.3)	8 (3.0)	21 (4.4)	24 (5.1)	59 (15.7)	54 (14.5)
Hepatic enzyme increased[a]	9 (3.2)	2 (1.6)	5 (3.2)	2 (0.5)	3 (0.8)	2 (0.6)	1 (0.3)
Hypersensitivity	0	1 (0.5)	0	3 (0.6)	2 (0.4)	7 (1.9)	3 (0.8)
Nausea	33 (6.8)	7 (3.2)	28 (10.6)	57 (11.9)	44 (9.4)	16 (4.3)	22 (5.9)
Oral candidiasis	13 (2.7)	1 (0.5)	6 (2.3)	5 (1.0)	8 (1.7)	4 (1.1)	0
Phlebitis	10 (2.1)	5 (2.3)	2 (0.8)	36 (7.5)	26 (5.5)	15 (4.0)	15 (4.0)
Pruritus	7 (1.4)	1 (0.5)	5 (1.9)	13 (2.7)	9 (1.9)	3 (0.8)	4 (1.1)
Rash[b]	31 (6.4)	7 (3.2)	16 (6.1)	21 (4.4)	11 (2.3)	2 (0.5)	3 (0.8)
Vulvomycotic infection	0	0	1 (0.4)	5 (1.0)	2 (0.4)	6 (1.6)	4 (1.1)

[a] Based on central laboratory data. Percentages calculated using the number of subjects with laboratory values ≤ ULN at baseline and non-missing post-baseline laboratory values.

[b] Includes reactions reported as allergic and bullous dermatitis, erythema, macular/papular eruptions and erythema multiforme

Common side effects of beta-lactam antibiotics are hypersensitivity reactions and skin rash. The applicant has conducted a thorough investigation of all AEs that could be categorized under possible allergic reactions and found that their number in doripenem arm was numerically higher than in any of the comparator arms. However, when only events categorized under rash were analysed it appeared that their frequency was similar to other carbapenems. Not surprisingly it also appeared that the hypersensitivity reaction were more common in NP studies (sicker patients) than in patients with cUTI infections. In the clinical programme no cases of Stevens-Johnson syndrome was reported but there was a case in the post marketing surveillance programme in Japan. Also there have been no cases of anaphylactoid reactions in the clinical development program but there has been one in the post marketing surveillance.

As expected with a beta-lactam antibiotic the AEs associated with gastrointestinal tract such as nausea, vomiting, diarrhoea, constipation were commonly seen in patients treated with doripenem. However, laboratory proven *C.difficile* colitis was rare and seen in less than 1% of patients. Furthermore its frequency was not different of that in the comparator arms. In the post marketing surveillance in Japan only two cases of *C.difficile* have been reported.

Total AEs mapped to the central nervous system (CNS) suggested no major difference between doripenem and comparators; headache was an exception and was seen more often in patients treated with doripenem (especially in those receiving 1-hour infusions) than with comparator agents. However, in the phase 1 studies the frequency of headache in subjects treated with placebo and doripenem was similar. Headache was also more common in women than in men but this might be related to the reporting habits rather than to real gender effect of doripenem.

Carbapenems as other beta-lactam antibiotics are known to be binding to GABA receptor and thus they all have potential to induce seizures. In preclinical programme doripenem was the least potent of all carbapenems in binding to GABA receptor in vitro and did not induce seizures in dogs and rodents.

Also in phase 2/3 convulsion were seen less frequently in patients treated with doripenem than with other beta-lactams except meropenem. However, there may have not been sufficient number of subjects with underlying CNS disorders, who as demonstrated with imipenem meningitis study, might be especially prone to seizures.

The only AE that was reported at rates >1% higher in the doripenem group than any comparator group was asymptomatic bacteriuria which seemed attributed to a lower rate of clinical failure in the doripenem group. In study DORI-02, were 23 TEAEs reported by 14 subjects (44% of the study population) with renal impairment. Nine of these (28%) experienced a total of 11 events that were considered related to treatment. The remaining 12 TEAEs were classified as unrelated or unlikely related to treatment.
In study DORI-NOS-1005 there were no severe TEAE or SAEs. One of the 6 subjects with ESRD (end stage renal disease) who received doripenem prior to hemodialysis experienced three AEs compared with two of 6 healthy subjects who experienced one AE each. None of the six ESRD subjects who received doripenem immediately following a hemodialysis session experienced an AE.

The AE phlebitis (all causality and treatment related) was more common in patients receiving a 1-hour infusion as compared to those receiving the same dose by a 4-hour infusion and it was also more often seen in doripenem than in any of the comparator arms. Furthermore infusion site reactions such as pain and injection site swelling in phase 1 studies were experienced by more subjects receiving 1 g doses of doripenem than by those receiving 500 mg. This all suggests that there is an association between the strength of doripenem dose and/or infusion time and infusion site reaction and/or phlebitis.

The data available suggest that the risk of clinically important QTc prolongation with doripenem is low and no further action is needed.

There is no evidence that gender differences are important in doripenem pharmacokinetics neither do they seem to play a role in its safety profile. The gender differences seen in the clinical programme are most likely associated with the reporting habits not to the gender effect of doripenem.

The applicant has conducted a thorough analysis of TEAE. In general doripenem is safe and well tolerated by patients with cUTI, cIAI and NP including VAP.

- Serious adverse event/deaths/other significant events

The percent of subjects experiencing serious TEAEs were 15.2% in the doripenem group, 4.0% in the levofloxacin group, 16.4% in the meropenem group, 26.2% in the piperacillin/tazobactam group and 27.4% in the imipenem group. Overall, the rates of most serious TEAEs reported in the doripenem group were within the ranges reported for the comparator group. No event occurred at a >2% higher rate in the doripenem group than in all other comparator groups.

Serious AEs were generally more common in the cIAI group and NP group, but within each indication a similar overall incidence was observed among the other treatment groups.
Twenty SAEs pertaining to impaired renal function were reported as renal failure (5), acute renal failure (13), or renal impairment (2). These events occurred in groups receiving doripenem (15) imipenem (4) and piperacillin/tazobactam (1), respectively. No subject in the levofloxacin or meropenem treatment groups experienced of renal failure. Two events in the doripenem group were possibly related to treatment with the study drug.

Death rates in the Phase 2 and 3 studies differed by severity of the indication under study, being highest in the NP studies. Within each indication/ study the mortality rate for the doripenem group was comparable to that of the respective comparator group. The most frequently reported AE leading to death in the doripenem group, which occurred predominantly in the NP group, were pneumonia and respiratory failure.

- Laboratory findings

The applicant has provided a thorough analysis of liver function tests abnormalities showing that with regard to the liver function, doripenem does not present significant concern. Individual and mean

biochemistry data indicate an apparent dose response trend for serum levels of ALT and AST to increase following repeated administration of doripenem. This apparent trend was most pronounced in the high dose cohort. One subject in the doripenem 1g Q8h experienced elevation of transaminases 2.5 times the upper limit of normal. He also had an elevation of bilirubin of unknown etiology nearly twice the upper limit of normal. This dose-response trend appeared to be reversible.

- Safety in special populations

A total of 11 pregnancies were reported in subjects who received doripenem. Only one ended up with the birth of a normal full term baby. Remaining pregnancies were either miscarried, completed in spontaneous abortion or were terminated. In animal studies doripenem had no effect on postnatal development or reproductive performance of offspring (neither was it teratogenic), in the clinical programme, Furthermore in animal studies only a single dose of doripenem was tested and this is most likely not a reflection of clinical practice in where doripenem will be given three times daily for several days. Given the small number of women who were or may have been exposed to doripenem while pregnant, a relationship between doripenem exposure and pregnancy outcome cannot be established. The use of doripenem during pregnancy and breastfeeding are very limited and doripenem should not be used in these circumstances.
No dosage adjustment is required in elderly subjects with normal (age appropriate) renal function. There were no studies on pediatric populations, nor have any age limit for therapeutic use been specified.

- Immunological events

Allergic reactions have been associated with β-lactam antibiotics, including carbapenems. All rash TEAEs from all Phase 2 and 3 studies were summarized and evaluated as possible allergic rash reactions to study drug: and all TEAEs that coded to the MedDRA terms of anaphylactic responses, and to hypersensitivity reactions were evaluated as possible anaphylactic reactions and hypersensitivity to study drug, respectively.

- Safety related to drug-drug interactions and other interactions

Aminoglycosides and vancomycin were permitted in doripenem clinical programme as adjunctive therapies. No significant interferences between aminoglycosides and doripenem regarding the safety profile were observed. However, several TEAEs including those associated with impaired renal function were observed more frequently in patients treated with the combination of doripenem and vancomycin than in those receiving doripenem monotherapy.

Other carbapenem antibiotics are shown to decrease AUC of valproic acid. In experimental studies co-administration of doripenem and valproic acid did not result in the decreased AUC. However, if these agents were given to monkeys a 30% but non-significant decrease in AUC was observed suggesting that interactions between valproic acid and doripenem might be species dependent. In the clinical programme there was no evidence that combination of doripenem and valproic acid has led to the increased frequency of seizures but the blood concentrations of valproic acid were not measured. Applicant recommends during treatment with doripenem measuring valproic acid concentrations and this is appropriately reflected in the SPC.

- Discontinuation due to adverse events

The primary reason for discontinuation from the study was comparable for the doripenem group and the respective comparator groups.

Of the subjects included in the safety analyses from the pooled phase 2 and 3 studies (excluding the doripenem 250 mg group from DORI-03) 78% completed the study per-protocol. Death was the primary reason for discontinuation in the doripenem group 12%, the piperacillin/tazobactam group (14%) and the imipenem group (12%). The rate of discontinuation due to AEs was 2% each for the doripenem and meropenem groups, and 3% each for the levofloxacin, piperacillin/tazobactam, and imipenem groups. Negative pre-treatment cultures (cUTI studies DORI-03, -05 and -06 only)

accounted for 11% (93/855) discontinuations in the doripenem group and 7% in the levofloxacin group. All other reasons for discontinuations were comparable across the treatment groups with the exception of treatment failures.

The table below shows the rate of discontinuation from the pooled Phase 1 studies in the population with normal renal function treated with doripenem 500 mg and 1 g respectively.

Study Completion/Withdrawal Information
(Pooled Phase 1 Studies JNJ38174942: All Subjects With Normal Renal Function in Studies DORI-01, -02, -04, DORI-NOS-1001, -1004, -1005, -1006, and -1007)

		Doripenem		
Number of Subjects	**Placebo (N=74) n (%)**	**500 mg (N=148) n (%)**	**1 g (N=108) n (%)**	**Total (N=172) n (%)**
Randomized	74 (100)	148 (100)	108 (100)	172 (100)
Randomized and dosed	72 (97.3)	146 (98.6)	107 (99.1)	172 (100)
Completed the study	69 (93.2)	142 (95.9)	104 (96.3)	166 (96.5)
Withdrawn	5 (6.8)	6 (4.1)	4 (3.7)	6 (3.5)
Primary reason for discontinuation				
Adverse event	**1 (1.4)**	**1 (0.7)**	**0**	**1 (0.6)**
Subject, investigator, or Sponsor request	2 (2.7)	3 (2.0)	2 (1.9)	3 (1.7)
Other	2 (2.7)	2 (1.4)	2 (1.9)	2 (1.2)

Note: Percentages were calculated with the number of subjects in each group as the denominator. Doripenem total includes all subjects who received at least one dose of doripenem 500 mg or 1 g. Due to crossover designs, the numbers of subjects who received doripenem 500 mg plus doripenem 1 g does not equal doripenem total.

- Post marketing experience

As part of the Shionogi development program, 17 studies were conducted where the safety of doripenem was extensively evaluated in Phase 1, 2 and 3 studies in Japanese subjects. Over 800 Japanese subjects were exposed to at least one dose of doripenem (ranging from 125 mg twice daily bid to 1g bid). More than 60% of the enrolled subjects with a variety of infections received doripenem 250 mg bid and more than 50% received doripenem therapy for at least 7 days. There were 70 spontaneous reports, all from Japan, comprising 84 events with Finibax (doripenem) as the suspect or a suspect interacting drug. Taken together in these studies doripenem was well tolerated and no safety signals were recorded.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
Important identified risks:		
- Anaphylaxis	- Routine pharmacovigilance as outlined in Section 3.1 of the RMP * A Phase 1 study to evaluate a potential drug-drug interaction between doripenem and valproic acid is currently being conducted and results will be available by the end of 2008.	- Information included in the SPC section 4.3, 4.4 and 4.8
- Hypersensitivity reaction		- Information included in the SPC section 4.3, 4.4 and 4.8
- Rash		- The SPC, Section 4.8 identifies rash as common adverse reaction during clinical trials
- Hepatic enzyme increased		- The SPC identifies increased hepatic enzyme as a common adverse increased drug reaction in Section 4.8
- *C. difficile* colitis - Localized fungal overgrowth		- Information included in the SPC section 4.4 and 4.8
- Neutropenia		- Information included in the SPC section 4.4 and 4.8
- Drug interactions*		- Information included in the SPC section 4.4 and 4.8
Important potential risks:		
- Seizure	- Close monitoring of seizures and adverse events in patients with severe renal impairment. Cumulative reviews in future PSURs should be provided - Routine pharmacovigilance as outlined in Section 3.1 of the RMP	Seizures are a known risk with imipenem. Based on the risk assessment, there were 6 reports of seizures in the clinical trial population. Based upon a review of the events of seizures in the clinical trial and post-marketing databases the MAH does not currently feel labelling of this potential risk is warranted.
- Use in patients with severe renal impairment		- Information included in the SPC section 4.2
- Antibiotic Resistance**	** Studies to monitor antibiotic resistance are described in Section 2.2 of the RMP	- Information included in the SPC section 4.4 concerning risk for emergence of resistance and that prolonged use should be avoided to prevent the over-growth of non-susceptible organisms. - Active monitoring of the antimicrobial activity of doripenem (see below)[1]:
Important missing information:		
Use in pediatrics	- Routine pharmacovigilance as outlined in Section 3.1 of the RMP	Information in section 4.2 of the SPC
Use in dialysis patients and patients with severe renal impairment		Information in section 4.2 of the SPC
Use in pregnancy		Information in section 4.6 of the SPC
Use in nursing mothers Use for more than 14 days		Information in section 4.6 of the SPC
Use in severely immunocomprimised patients and in patients receiving immunosuppressive therapy		Information in section 4.4 of the SPC
[1] Concerning surveillance of antibacterial resistance the RMP was amended, section 2.2, with protocols for the JMI European and the British Society for Antimicrobial Chemotherapy (BSAC) surveillance programs;		

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of Doribax is adequately established.

The active substance doripenem monohydrate is a synthetic carbapenem antibiotic structurally related to other β-lactam antibiotics.
Doripenem powder for solution for infusion is provided as single-use vials containing 500 mg (anhydrous basis) of sterile powder. The drug product is manufactured by filling sterilized bulk drug substance powder into clear Type I glass vials with elastomeric stopper. There are no excipients used for this product.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf-life. Furthermore, in-use studies after reconstitution in Sodium chloride or dextrose solution confirm the stability of the product for its administration.

Information on development, manufacture and control of the active substance and the drug product has been presented in a satisfactory manner. The result of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these turn in lead to the conclusion that the product would have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the Risk-Benefit balance of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

Non-clinical pharmacology and toxicology
Taken together, the submitted non-clinical studies with doripenem are found to have addressed major characteristics of the compound in accordance with the relevant guidelines. Issues of importance related to the particular nature of the drug development program have generally been sufficiently addressed. Relevant sections of the SPC dealing with non-clinical data are acceptable. Environmental risk assessment of doripenem will be updated with some additional studies.
No carcinogenicity studies have been conducted. Considering treatment duration and indications as well as results from genotoxicity studies such studies are not required.

Efficacy

The efficacy of doripenem has been demonstrated in phase III active controlled randomized clinical trials to be non-inferior to levofloxacin in complicated urinary tract infections (cUTI) and non-inferior to meropenem in complicated intra-abdominal infections (cIAI). In patients with nosocomial pneumonia (NP) doripenem has shown non inferiority compared to piperacillin/tazobactam and imipenem respectively.

Safety

1.817 adult patients received doripenem and were evaluated for safety in phase 2 and phase 3 clinical trials. Adverse reactions due to doripenem 500 mg every 8 hours occurred at rate of 32%. doripenem was discontinued because of adverse drug reactions in 0.1% of patients overall. Adverse drug reactions that led to doripenem discontinuation were nausea (0.1%), diarrhoea (0.1%), pruritus (0.1%), vulvomycotic infection (0.1%), hepatic enzyme increased (0.2 %) and rash (0.2%). The most common adverse reactions were headache (10%), diarrhoea (9%) and nausea (8%).

Serious adverse events such as hypersensitive reactions were uncommon.

Treatment with doripenem seems associated with similar risk for and pattern of drug-related adverse reactions as meropenem.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Benefits

Doripenem is a new beta-lactam agent of the carbapenem class. The activity and safety of doripenem resembles that of meropenem, which clinical use is well established. Doripenem exerts a broad antibacterial spectrum including recognized "problem organisms", such as ESBL-producing gram-negative bacteria and *Pseudomonas aeruginosa*. Thus this agent has, in line with the older carbapenems, a potential for empiric treatment of severely ill patients and for patients where treatment with other agents had failed or when coverage of multi-resistant bacteria is warranted (with the exception of MRSA). The Applicant has demonstrated non-inferiority of doripenem in the studied populations compared to levofloxacin in cUTIs, compared to meropenem in cIAIs, and compared to piperacillin/tazobactam and imipenem in nosocomial pneumonia.

Although the efficacy of doripenem in levofloxacin resistant strains was not optimal it might be that carbapenems including doripenem are one of the few options for more seriously ill patients with cUTI, especially for those infected with fluoroquinolone resistant microorganisms.

Data also indicate that doripenem might have an improved activity against *P. aeruginosa* compared to the older carbapenems, which may be considered as clinically relevant.

In the NP studies in 55% of the cases doripenem was used in combination with aminoglycosides. Although in the post-hoc analysis there were no differences in outcome between those treated with mono- and combination therapy, the data of using doripenem monotherapy in NP are limited and monotherapy should used with caution.

Risks

According to international guidelines, carbapenems should primarily be considered for high-risk patients, for the treatment of severe infections where alternative agents are proven or suspected to be ineffective. The rational for these recommendations is to preserve the activity of these important agents, since it has been shown that carbapenem treatment is associated with resistance development, in particular in *P. aeruginosa*. This finding was also confirmed in the present studies. Unrestricted use of doripenem may lead to an increased resistance in important target pathogens for which current treatment alternatives are limited. Prolonged use of carbapenems has been identified as a risk factor for pan-resistant *P. aeruginosa*, in the ICU setting.

Most of the reported adverse events were solicited and listed as ADRs. However, anaphylactic reactions, effects on liver function tests other than transaminases should be closely monitored. Furthermore, seizure is a known adverse event observed with the use of imipenem. Some cases of seizures and convulsions have been also reported from the studies with doripenem and these adverse events should similarly be carefully noted and observed. The experience of the dosing regimen 1g q 8 hours is very limited, and doses higher than 1g q8h (2-fold the recommended dose) have not been studied. With the currently suggested dose regimen in subjects with severe renal impairment, an increased exposure of doripenem and M-1 metabolite as compared to patients with normal renal

function is expected. Doripenem should therefore be used with caution in severe renal impairment and should not be used in dialysis patients.

The experience in immunosuppressed patients is limited, since patients with identified significant immunosuppression were excluded from the Phase 3 studies. In clinical practice, carbapenems are primarily used in severe infections and when broad-spectrum coverage is warranted. Hence, the target attainment of 35% T > MIC might not be optimal for all patients since it is calculated for bacteriostatic effect, which may not be sufficient in seriously ill patients with impaired immune defence. As a precaution in this group of seriously ill and often immunocompromised patients a 40-50% T>MIC corresponding to 4 h infusion time would likely be more suitable.

For patients with cUTI infected with fluoroquinolone susceptible strains doripenem may not be the best choice as its microbiological efficacy was ***numerically*** lower than that of levofloxacin. This was especially valid for emergence of new and super-infections – there was a greater number of emergent infections at TOC window in patients treated with doripenem as compared to those treated with levofloxacin.

No formal dose finding studies have been conducted for the dose selection of doripenem for the indications cIAI and NP. The currently applied dose is mainly based on PK/PD approaches. There is an option to prolong the duration of infusion (500mg given over 4 hours) in NP patients in order to cover less susceptible pathogens, such as *P. aeruginosa*. PK/PD data indicate that 1g q8 hours, administered during 4 hours, may further enhance the efficacy for pathogens with decreased susceptibility, although clinical efficacy and safety data for this regimen is currently lacking.

The experience of using Doripenem during pregnancy and breastfeeding is very limited and should occur only if benefits clearly outweigh the risks.

Balance

Doripenem is a new potent antimicrobial agent and is essentially similar to meropenem in terms of clinical efficacy and safety. The activity against *Pseudomonas aeruginosa*, an important nosocomial pathogen, seems to be somewhat enhanced for doripenem compared to older carbapenems, which might be of clinical value in specific patients.
Taking the demonstrated efficacy and the acceptable safety profile into consideration the overall B/R of Doribax for the indications cUTI, cIAI and NP is considered positive.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Doribax in the treatment of

- nosocomial pneumonia, including ventilator-associated pneumonia (VAP),
- complicated intra-abdominal infections and
- complicated urinary tract infections (UTI) including complicated and uncomplicated pyelonephritis and cases with concurrent bacteremia

was favourable and therefore recommended the granting of the marketing authorisation.