CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-106

OFFICE DIRECTOR MEMO

Office Director Memo

Applicant: Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

NDA #: 22-106

Established Name: doripenem

Trade Name: Doribax

Proposed Indication and Usage Section

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX and other antibacterial drugs, DORIBAX should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Complicated Intra-Abdominal Infections

DORIBAX (doripenem for injection) is indicated as a single agent for the treatment of complicated intra-abdominal infections caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides caccae, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Streptococcus intermedius, Streptococcus constellatus* and *Peptostreptococcus micros.*

1.2 Complicated Urinary Tract Infections, Including Pyelonephritis

DORIBAX (doripenem for injection) is indicated as a single agent for the treatment of complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli including cases with concurrent bacteremia, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*, and *Acinetobacter baumannii.*

Proposed Dose: The recommended dose of doripenem is 500 mg every 8 hours by intravenous infusion with dose adjustments for certain levels of renal impairment.

Date of Initial Submission: December 13, 2006 (receipt date)

PDUFA Goal Date: October 13, 2007

Regulatory Action: Approval

Background
Doribax (doripenem) is a carbapenem antimicrobial agent with activity against a number of gram-positive, gram-negative, and anaerobic bacteria. Previously approved antimicrobial agents in the carbapenem class include Primaxin® I.V. (imipenem and cilistatin), Merrem I.V. (meropenem), and Invanz® (ertapenem). This NDA provides data from clinical studies of doripenem in support of indications for complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of doripenem for the treatment of complicated intra-abdominal infections and complicated urinary tract infections. For a detailed discussion of NDA 22-106, the reader is referred to the individual discipline specific reviews. In addition Dr. Nambiar's Team Leader Memorandum and Dr. Laessig's Division Director's Memo summarize key issues in the NDA submission. This memorandum will focus on selected issues from the application.

Chemistry Manufacturing and Controls
The chemistry manufacturing and controls are summarized in Dr. Qi's Chemistry review which recommends approval from the standpoint of CMC for doripenem powder for injection 500 mg vials. Facilities inspections were performed for the drug substance and drug product manufacturing facilities and found to be acceptable. Dr. Metcalfe's Product Quality Microbiology Review also recommends approval.

Pharmacology Toxicology
The recommendation from Dr. Schmidt with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. Her review of the general toxicology studies finds that seizures did not occur in animals at doses up to 2000 mg/kg in single dose rat and dog studies. Other studies in animals did not find a lowering of seizure threshold or seizures with direct intracisternal injection. The target organs of toxicity in animal studies were kidney, gastrointestinal tract, and hematologic cells. Doripenem is labeled as a pregnancy Category B agent.

Microbiology
The microbiologic assessment of doripenem is discussed in Dr. Corderre's microbiologist's review. Doripenem acts by inhibiting bacterial cell wall biosynthesis. Doripenem is active against a number of gram-positive, gram negative, and anaerobic bacteria. Mechanisms of resistance to carbapenems include alterations in penicillin-binding proteins, carbapenemases, AmpC cephalosporinase over-production, altered permeability and efflux. As noted in Dr. Corderre's review it will be important to obtain additional information on development of resistance as a postmarketing commitment to further assess the observation of increases in MIC noted during doripenem therapy. In addition the product labeling includes the statements from 21CFR §201.24 regarding appropriate use and antimicrobial resistance.

Clinical Pharmacology

The clinical pharmacology of doripenem is discussed in Dr. Sarah Robertson's Clinical Pharmacology Review. Doripenem does not undergo CYP450 metabolism. The primary route of excretion is renal and doripenem concentration in the urine considerably exceeds plasma concentrations. Doripenem is excreted mainly unchanged. In animal models of infection T>MIC was the primary pharmacokinetic parameter related to efficacy. Evaluation of effects on the QT interval in Study DORI-NOS-1001 (a randomized, double-blind, placebo- and positive-controlled, double dummy crossover QT study in healthy subjects) did not find a relationship between plasma levels of doripenem and change in QTc from baseline. The study utilized doses of doripenem of 500 mg and 1000 mg IV q 8 hours x 4 doses.

Dose selection for doripenem of 500 mg IV q8 hours is based in part upon simulations targeting a time above MIC of at least 35% for target pathogens with an MIC $\leq$ 2 mcg/mL.

Clinical Efficacy

The results of the clinical trials evaluating the safety and efficacy of doripenem are discussed in detail in the Medical Officers' and Statistical Reviews for the cIAI and cUTI and also in the reviews prepared by Dr. Nambiar and Dr. Laessig. The reader is referred to their reviews for a detailed discussion of safety and efficacy.

For the indication of cIAI the applicant performed two randomized, double blind trials in cIAI versus meropenem. The study designs were the same for both studies. The primary efficacy endpoint for the studies was clinical cure rate at the test of cure visit (28-42 days after completing therapy. The results for the two studies are tabulated below for the microbiologically evaluable (ME) and microbiological modified Intent-to-Treat (MmITT) populations.

Table 1. Clinical Cure Rates for DORI-07 and DORI-08

	Doripenem n/N (%)	**Meropenem n/N (%)**	**Difference (95%CI)**
DORI-07			
Microbiologically Evaluable	140/165 (85.9)	133/156 (85.3)	0.6 (-7.7, 9.0)
Microbiological modified ITT	152/95 (77.9)	150/190 (78.9)	-1.0 (-9.7, 7.7)
DORI-08			
Microbiologically Evaluable	135/162 (83.3)	127/153 (83.0)	0.3 (-8.6, 9.2)
Microbiological modified ITT	149/200 (74.5)	140/185 (75.7)	-1.2 (-10.3, 8.0)

The justification for the margin for cIAI is reviewed in Dr. Nambiar's review. The efficacy results from studies DORI-07 and DORI-08 provide evidence of the efficacy of doripenem in cIAI. Additional analyses of secondary endpoints and sensitivity analyses support the findings for the primary efficacy endpoints.

For the indication of cUTI including pyelonephritis the application provides results from a dose ranging phase 2 study (DORI-3) and two phase 3 clinical trials (DORI-05 and DORI-06) in patients with complicated urinary tract infection. In addition, the levels of doripenem in urine exceeded the levels of doripenem in serum. A study evaluating doripenem levels in serum compared to urine levels found that levels in urine were 600 times higher at 4 hours post dose. DORI-03 examined two doses of doripenem and found the following cure rates; doripenem 250 mg IV q8h, 64.2% (34/53) and doripenem 500 mg IV q8 68.1% (32/47). The 500 mg IV q8h dose was carried forward in the phase 3 studies. DORI-05 was a randomized, double blind trial in patients with cUTI evaluating doripenem 500 mg IV q8 h versus levofloxacin 250 mg IV q24h. The primary efficacy endpoint was microbiologic cure at 6 to 9 days post completion of study therapy. The co-primary analysis populations were the microbiologically evaluable (ME) and microbiological modified intent-to-treat (MmITT) populations. DORI-06 was a phase 3 open-label single arm study of doripenem 500 mg IV q8h in complicated urinary tract infections. The primary efficacy endpoint results for these studies are tabulated in Table 2.

Table 2. Clinical Cure Rates for DORI-05 and DORI-06

	Doripenem n/N (%)	**Levofloxacin n/N (%)**	**Difference (95%CI)**
DORI-05			
Microbiologically Evaluable	230/280 (82.1)	221/265 (83.4)	-1.3% (-8.0%, 5.5%)
Microbiological modified ITT	259/237 (79.2)	251/321 (78.2)	1.0% (-5.6, 7.6)
DORI-06			
Microbiologically Evaluable	209/250 (83.6)		
Microbiological modified ITT	278/337 (82.5)		

The justification for the non-inferiority margin for cUTI is reviewed in Dr. Deng's review. The results from DORI-05 demonstrate non-inferiority to levofloxacin in the treatment of cUTI. The data from DORI-06 show a similar cure rate to what was observed in DORI-06.

The results from studies DORI-05 and DORI-06 provide evidence of the efficacy of doripenem in cUTI along with supportive information from DORI-03 and information on urinary levels attained by doripenem. Additional analyses of secondary endpoints and sensitivity analyses support the findings for the primary efficacy endpoints.

Safety
Over 1500 subjects received doripenem in clinical program. The pooled data from patients receiving doripenem in phase 2 and phase 3 studies constituted data from 1332 patients. A detailed review of safety is provided in Dr. Sorbello's Medical Officer Safety Review. He recommends approval for doripenem.

The most common adverse events reported were headache, nausea, diarrhea, and rash.

Seizures have been associated with carbapenem antimicrobial agents. Data from preclinical studies evaluating seizure potential suggest a reduced risk of seizure from doripenem. No seizures were reported in the phase 1, 2 or 3 studies in patients receiving doripenem. It will be important to monitor postmarketing adverse event reports for seizure events post approval in the U.S. The labeling lists seizure in the postmarketing experience section of the label based upon post approval use of doripenem from outside of the U.S.

As noted in the clinical pharmacology section evaluation of the effects of doripenem on the QT interval did not find a relationship between plasma levels of doripenem and change in QTc from baseline.

In the comparative phase 3 studies in cIAI there were more reports of anemia as an adverse event in the doripenem arms; from the cIAI the rates were 10% vs. 5% and for the cIAI studies the rates were 2% vs. 1%. An explanation for the difference seen in the cIAI study was not apparent. A hematology consult evaluated reports of anemia and noted that from the available data it is difficult to implicate doripenem as the cause of the anemia or as the cause of hemolytic anemia. The consult recommends further evaluation of hemolytic anemia as a postmarketing commitment. A postmarketing commitment for additional monitoring of hemolytic anemia will be included in the action letter.

The labeling includes in the Warnings and Precautions statement class labeling on hypersensitivity reactions with beta lactams. Also included is class labeling on C. difficile colitis, for which there were some cases reported in the safety database. The Warnings and Precautions section includes a statement on interaction with sodium valproate noting that carbapenems may reduce serum valproic acid which may result in a loss of seizure control.

Doripenem is approved in Japan and postmarketing adverse event information is included in the product label noting the following adverse events: Stevens Johnson syndrome, toxic epidermal necrolysis, interstitial pneumonia, seizure.

DSI Inspections / DDMAC / DMETS consults
DMETS and DDMAC have consulted on the proprietary name, we have also met with DMETS to discuss their consult and DMETS does not object to the use of the proprietary

name DORIBAX. Comments from DMETS, DDMAC, and SEALD have also been incorporated into the product labeling.

The Division of Scientific Investigations performed clinical inspections and did not identify any observations that would compromise the integrity of the data. Pediatric studies required under PREA have been deferred as noted in the approval letter.

Advisory Committee
NDA 22-106 was not referred to an advisory committee for review for the following reasons: There are three previously approved antimicrobial agents in the carbapenem class. Evaluation of the safety data did not reveal particular safety issues that were unexpected for the carbapenem class, and the design and results of the efficacy trials did not pose particular concerns. Doripenem is an intravenous agent studied for more serious infections for which there is adequate justification for using an active controlled study designed to show non-inferiority.

Postmarketing Study Commitments

1. Deferred pediatric studies under PREA for the treatment of cUTI and cIAI in pediatric patients ages 0-18 years.

2. Conduct a post-marketing study regarding hemolytic anemia, renal failure/renal impairment, and seizures in doripenem-treated subjects.

3. Conduct a Phase 1 study to assess potential interactions between doripenem and valproic acid.

4. Conduct US surveillance studies for two years from the date of approval to determine if resistance to doripenem has developed in those organisms specific to the indications in the label for complicated urinary tract infection and complicated intra-abdominal infection. The US surveillance studies on *Klebsiella pneumoniae* isolates should include monitoring for the presence of the KPC carbapenemase.

5. Conduct studies to define the mechanism(s) of resistance for isolates identified as being resistant to doripenem during the surveillance period.

Summary
I concur with the assessment of the review team that substantial evidence of safety and efficacy has been provided for doripenem for the indications of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. The product labeling adequately describes the available information on doripenem and the available information on safety and efficacy supports a satisfactory risk to benefit ratio. The approval includes postmarketing commitments for a postmarketing study to

further evaluate hemolytic anemia, renal failure/renal impairment, and seizures in doripenem-treated subjects, an assessment of potential interactions between doripenem and valproic acid, and evaluation of resistance to doripenem.

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/s/

Edward Cox
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MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: October 11, 2007

FROM: Wiley A. Chambers, MD, Acting Division Director, DAIOP

SUBJECT: NDA 22-106, Doribax (doripenem for injection)

TO: Edward Cox, MD, MPH

I concur with Dr. Laessig's summary review memorandum dated October 11, 2007, recommending approval of NDA 22-106, as amended, Doribax (doripenum for injection) for treatment of complicated intra-abdominal (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis, caused by susceptible strains of designated organisms. NDA 22-106, with the labeling revisions agreed upon by our Division and the applicant is recommended for approval by the Division.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
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