CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-106

SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10-11-07

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

TO: Division File

SUBJECT: Division Director's Summary Review Memo for NDA 22-106, doripenem for injection 500 mg (Tradename DORIBAX)

1.0 Background

Doripenem is an injectable, synthetic, carbapenem in the β-lactam class of antibacterial agents. Its mechanism of action is bactericidal via inhibition of cell wall synthesis by binding to penicillin-binding proteins found in the bacterial cell wall of both Gram-positive and Gram-negative bacteria. The applicant, Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), has submitted NDA 22-106 in support of 500 mg injection and proposed a dose of 500 mg IV q 8h. The requested indication is treatment of complicated intra-abdominal (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis, caused by susceptible strains of designated organisms.

The submission includes multiple phase 1 and 2 studies that support 4 phase 3 clinical trials: 2 in cIAI and 2 in cUTI. This memo will summarize elements of all reviews by discipline. Note that the data supporting this application have been reviewed in depth by multiple review disciplines. For detailed discussions of efficacy, safety, clinical pharmacology, microbiology, pharmacology/toxicology, and chemistry and manufacturing, please refer to the respective reviews.

2.0 Summary of Chemistry, Manufacturing, and Controls

Based on the quality assessment by Dr. Lin Qi, the application is recommended for approval. Doripenem for injection is provided as single-use vials containing 500 mg of sterile powder for constitution. The drug product does not contain excipients and a shelf life of 24 months at room temperature based on 24 months of stability data is acceptable. The infusion solution is stable in PVC and Baxter Minibag Plus® infusion bags for → hours at controlled room temperature and — hours at refrigerated temperature in sodium chloride for injection, USP, and 4

hours at controlled room temperature and —hours at refrigerated temperature in dextrose injection, USP, respectively.

This application is also recommended for approval by Dr. John Metcalfe, product quality microbiology reviewer. He expressed concern that the label described room temperature and refrigerated holding periods for product following reconstitution in infusion bags that might allow for growth of contaminating micro-organisms, since the product does not contain a preservative. The applicant declined to conduct microbial growth promotion studies to assess this risk and therefore the label will be revised to include holding periods not longer than 4 hours at room temperature in 5% dextrose, and 8 hours in normal saline.

3.0 Summary of Pharmacology/Toxicology

Based on the review of the nonclinical pharmacology and toxicology by Dr. Wendelyn Schmidt, this application is recommended for approval. Key findings of her review included: 1) absence of seizures in general toxicology or safety pharmacology studies, 2) negative cardiac effects in safety pharmacology studies but changes in QT interval in 1 and 3 month dog studies, 3) major targets of toxicity were kidney, hematologic cells (esp. WBCs), gastrointestinal tract, and possibly liver, 4) not mutagenic or clastogenic, and 5) pregnancy category B-no effect of reproductive toxicity.

4.0 Summary of Clinical Pharmacology

The clinical pharmacology of doripenem is described in Dr. Sarah Robertson's review and the application is recommended for approval from the clinical pharmacology perspective. Animal models of infection established the T>MIC as the primary PK/PD parameter related to efficacy. In a definitive QT study, administration of doripenem at doses of 500 or 100 mg demonstrated no effects on cardiac repolarization. Doripenem is not metabolized and is renally excreted unchanged. It does not affect CYP or UGT enzymes in human hepatocytes or HLM and therefore is not expected to alter metabolism of concomitantly administered medications metabolized via these routes. Because it is excreted renally, patients with renal impairment require dose adjustment, which is included in the package insert. In a study evaluating the effects of age on doripenem PK, elderly subjects had a 33% lower total body clearance than non-elderly subjects resulting in an exposure approximately 1.5 times that of younger subjects. The label will also describe this age-related effect and — to monitor renal function of elderly patients. There were no gender or race related differences in doripenem PK.

5.0 Summary of Clinical Microbiology

This application is recommended for approval by the clinical microbiology reviewer, Dr. Peter Coderre. He recommends that the cUTI indication be granted for the following organisms: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,* and *Acinetobacter baumannii.* For the cIAI indication, he recommends the following organisms for inclusion: *Bacteriodes caccae, Bacteriodes fragilis, Bacteriodes thetaiotamicron, Bacteriodes uniformis, Bacteriodes vulgatus, Peptostreptococcus micron, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus constellatus,* and *Streptococcus intermedius.* The data suggest that the development of resistance to doripenem by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* may be a safety concern and the applicant will be requested to conduct a phase 4 study to examine the development of resistance for these 2 organisms.

6.0 Summary of Efficacy

For the indication of cUTI, the applicant submitted 2 pivotal studies: DORI-05 and DORI-06. DORI-05 was a phase 3, multicenter, prospective, randomized, double-blind, active-controlled, non-inferiority study of doripenem compared to levofloxacin in the treatment of adults with cUTI. DORI-06 was a phase 3, multicenter, prospective, noncomparative, open-label study of doripenem in the treatment of adults with cUTI. Doripenem-treated subjects in this study were compared to levofloxacin-treated subjects in DORI-05.

The coprimary endpoint for both studies was the microbiological response at test-of-cure visit following a 10-day treatment regimen in the microbiologically evaluable (ME) and the microbiologically modified intent-to-treat populations (mMITT). Important secondary endpoints included per subject clinical cure at TOC and per uropathogen microbiological eradication rate at TOC in the ME. The predefined noninferiority margin was 10%. The justification for this margin is based on placebo cure rates for uncomplicated UTI in female subjects and cure rate of levofloxacin for cUTI. The FDA determined that this justification was reasonable.

The results from the FDA analysis for the ME and mMITT populations are summarized in Table 1.

Table 1. ME and mMITT rates from DORI-05 and DORI-06

	DORI-05		**Difference (95% CI)**	**DORI-06**	**Difference (95% CI)**
	Doripenem n/N (%)	Levoflox n/N (%)		Doripenem n/N (%)	
ME	230/280 (82.1)	221/265 (83.4)	-1.3% (-8.0%, 5.5%)	209/250 (83.6)	0.2% (-6.6, 7.0)

mMITT	259/237 (79.2)	251/321 (78.2)	1.0% (-5.6, 7.6)	278/337 (82.5)	4.3% (-2.1,10.7)

The results support the non-inferiority of doripenem to the levofloxacin comparator for the treatment of cUTI.

For the indication of cIAI, the applicant submitted 2 pivotal studies, DORI-07 and DORI-08. The studies were identical, phase 3, prospective, randomized, double-blind, double-dummy, multicenter trials comparing the efficacy of doripenem to meropenem in treating hospitalized patients with cIAI. The primary efficacy analysis was to establish the non-inferiority of doripenem to meropenem at the TOC within a NI margin of 15% for the ME and mMITT co-primary populations. The applicant provided justification of the noninferiority margin based on data of putative placebo cure rates from 6 selected antibiotic prophylaxis trials of meropenem. The estimate of the active control rates of 90 to 98% was based on 7 published studies of cIAI that had similar study designs to DORI-07 and DORI-08. The FDA determined that this justification was adequate.

The results of the FDA analyses for these endpoints are displayed in Table 2.

Table 2. ME and mMITT rates from DORI-07 and DORI-08

	DORI-07			**DORI-08**		
	Dori n/N (%)	**Mero n/N (%)**	**Diff (95%CI)**	**Dori n/N (%)**	**Mero n/N (%)**	**Diff (95% CI)**
ME	140/165 (85.9)	133/156 (85.3)	0.6 (-7.7, 9.0)	135/162 (83.3)	127/153 (83.0)	0.3 (-8.6, 9.2)
mMITT	152/95 (77.9)	150/190 (78.9)	-1.0 (-9.7, 7.7)	149/200 (74.5)	140/185 (75.7)	-1.2 (-10.3, 8.0)

The results of these studies support the non-inferiority of doripenem to meropenem for the treatment of cIAI. The results of these clinical trials have been thoroughly discussed in the clinical and biometrics reviews of Drs. Blank, Crewalk, Deng, and Khedouri.

7.0 Summary of Safety

Dr. Fred Sorbello's medical officer review provides an extensive discussion of the safety of doripenem and concludes that adequate efficacy and safety data have been presented by the applicant to recommend approval of this NME for the indications of cUTI and cIAI in adult patients aged 18 years and greater. For full information, please refer to his review.

The most frequently reported adverse drug reactions in patients receiving doripenem were headache, nausea, diarrhea, rash, and phlebitis. A greater number of subjects in the cIAI trials experienced adverse events of anemia in the

doripenem arm (9.6%) compared to the meropenem arm (5.5%). Anemia was not noted to be a significant event in the cUTI studies. Notably, no remarkable effect of doripenem on hemoglobin/hematocrit was seen in any of the trials. Although the applicant maintained that this difference was attributable to peri-operative blood loss, no data was provided to substantiate this. A hematology consult was obtained and concluded that there was no clear evidence for a drug association between the reported anemia adverse events and exposure to doripenem. There was also an imbalance between the doripenem-treated subjects and comparators with respect to reported rates of renal failure/renal impairment however review of cases and laboratory data revealed other risk factors and comorbidities in the majority of cases that could predispose to renal insufficiency and failure. There were no cases of seizure, severe skin reaction, agranulocytosis or hepatic necrosis among the 1276 doripenem treated subjects in the phase 3 trials.

In the 4 phase 3 studies, there were 18 deaths involving doripenem-treated subjects and 18 deaths among the comparator treated subjects. Based on the medical officer's review, none of the deaths appeared to be due to a drug-related adverse event. Rates of SAEs were similar for the doripenem and comparator treated subjects in all trials.

8.0 Summary of Other Regulatory Issues

DMETS and DDMAC have consulted on the proprietary name and have no objections to the use of DORIBAX. The Division of Scientific Investigations conducted inspections of selected clinical study sites and concluded that the data generated in support of the NDA appear acceptable.

Phase 4 commitments will include pediatric studies required under PREA, studies to evaluate the development of bacterial isolates resistant to doripenem, and surveillance studies to evaluate the association of doripenem use with seizures, renal impairment/failure, and anemia, and a drug-drug interaction with valproic acid.

9.0 Recommendation

I concur with the recommendations of the review team that the applicant has provided substantial evidence of the efficacy and safety of doripenem 500 mg for injection in the treatment of cUTI and cIAI. Therefore, this application should be approved.

Katherine A. Laessig, M.D.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathrine Laessig
10/12/2007 10:18:05 AM
MEDICAL OFFICER

Wiley Chambers
10/12/2007 04:10:47 PM
MEDICAL OFFICER

Edward Cox
10/12/2007 04:12:51 PM
MEDICAL OFFICER