improve while the subject remained on doripenem therapy and returned to normal levels (88.4 µmol/L) on Day 6. Only one other adverse event was reported: hypomagnesemia on Day 4 that was also considered mild and not related to study medication and resolved in 2 days. No concomitant antibiotic medications were reported. No potentially nephrotoxic concomitant non-antibiotic medication was administered before the adverse event of renal impairment was reported. The serum creatinine level remained within normal limits for the duration of doripenem treatment and through the end of the study. The subject completed the study per protocol through the late follow-up visit.

FDA Medical Officer Comments: The patient had an abnormal serum creatinine at baseline, which increased by Day 3 and then resolved while continuing to receive study drug. The improvement in renal function despite ongoing doripenem treatment suggests that the event was unrelated to doripenem administration.

DORI-05 Subject 30704002 (Doripenem 500 mg IV infusion q8h): This 82-year-old Hispanic woman entered the study with a diagnosis of symptomatic complicated lower urinary tract infection (UTI). The subject had a history of multiple medical problems including cardiac failure, hypertension, and viral pericarditis. The subject received doripenem 500 mg as a 60-minute IV infusion q12h for 5 days (Days 1 to 5) followed by oral levofloxacin tablets (250 mg once daily) for 7 days (Days 5 to 11). No concomitant antibiotic medications were reported. The subject received furosemide (IV, three times daily) as concomitant therapy on Days –1 and Day 1. No other potentially nephrotoxic concomitant non-antibiotic medication was administered before the adverse event of worsening renal impairment was reported. At baseline, the subject's creatinine level was more than twice the upper limit of normal (ULN) (194.48 µmol/L; ULN=79.56 µmol/L). The subject's creatinine levels remained below the baseline level while receiving IV study medication: 159.12 µmol/L on Day 3 and 123.76 µmol/L on Day 5 (end of IV therapy). At the test of cure visit on Day 11 (6 days after the subject's last administration of doripenem), her creatinine level had increased to 459.68 µmol/L (more than 5 times the ULN) and worsening renal impairment was reported on the same day. The renal impairment was judged by the investigator as mild in severity and not related to study treatment; it resolved in 11 days (Day 21). Her creatinine level had decreased to 114.92 µmol/L on Day 28 and had returned to within normal limits by Day 45 at the late follow-up visit. The subject completed the study per protocol.

FDA Medical Officer Comments: The patient had an abnormal serum creatinine at baseline, had a decrease in serum creatinine while receiving doripenem (but not to normal range), and then had an increase in creatinine over the seven days that oral levofloxacin had been administered. The serum creatinine eventually returned to normal range about three weeks after oral levofloxacin therapy had been completed. The underlying etiology for the renal impairment is unclear from the narrative summary, although the improvement in serum creatinine while receiving doripenem would suggest that the event was not related to exposure to that drug.

DORI-06 Subject 63300108 (Doripenem 500 mg IV infusion q8h):
This 61-year-old Caucasian man entered the study with a diagnosis of complicated pyelonephritis. The subject had a history of multiple medical problems including peripheral vascular disease, spina bifida, tachycardia, type 2 diabetes, and decubitus ulcer. Doripenem 250 or 500 mg was administered as a 60-minute IV infusion q8h for 15 days. At baseline, the subject's creatinine level was more than 1.5 times the upper limit of normal (ULN) (185.64 µmol/L; ULN=114.92 µmol/L). The subject received oral furosemide as concomitant medication on an unreported start day and ended on Day 2. On Day 2, increased creatinine was reported as an adverse event and judged by the investigator to be moderate in severity and possibly related to study medication (note that creatinine values were not reported on Day 2). On Day 3, the subject's creatinine value was reported as 300.56 µmol/L. Acute renal failure (ARF) was reported as an adverse event on Day 4 and was judged as moderate in severity and possibly related to study medication. Vancomycin was administered IV on Days 7 and 8 (no other concomitant antibiotic treatments were administered until Day 22, when levofloxacin was given for 2 days). Despite the report of possibly related ARF, IV study medication was not discontinued. Both the increased creatinine and acute renal failure had fully resolved by Day 12. No further creatinine values were reported until Day 15 (end of IV therapy), when his creatinine level had returned to within normal limits (97.24 µmol/L). At the test of cure visit on Day 22 (1 week after discontinuing doripenem), the subject's creatinine level had increased to 141.44 µmol/L. By Day 50 (late follow-up visit), the creatinine level had returned to normal limits (114.92 µmol/L). The subject completed the study per protocol through the late follow-up visit.

FDA Medical Officer Comments: The patient had an abnormal serum creatinine at baseline, had a increase in serum creatinine while receiving doripenem (but the drug was not discontinued), and then the serum creatinine returned to normal and his renal failure resolved. The underlying etiology for the renal impairment is unclear from the narrative summary, although it may be multifactorial (underlying diabetes mellitus, exposure to nephrotoxic drugs). The improvement noted in his renal function while receiving doripenem would suggest that the event was not primarily related to exposure to that drug.

DORI-06 Subject 63300210 (Doripenem 500 mg IV infusion q8h:
This 62-year-old Caucasian woman entered the study with a diagnosis of uncomplicated pyelonephritis. She had a history of multiple medical problems including tachycardia, loose stools, vomiting, and generalized weakness. Doripenem 250 mg was administered as a 60-minute IV infusion q8h or q12h for 12 days. At baseline, the subject's creatinine level was elevated (123.76 µmol/L; ULN=106.08 µmol/L). Promethazine (a compound known to cause changes in blood pressure) was administered concomitantly for nausea from Day 1 to Day 10. The subject also received medication for back pain on Day 1 (pethidine), Day 2 (Vicodin [acetaminophen and hydrocodone]), and Days 3 through 7 (morphine). On Day 1, the subject experienced tremor (reported term: uncontrollable shaking) and sedation (reported term: oversedation). The sedation was treated with naloxone and the subject recovered in 1 day. Other than headache reported on Day 2, no other adverse events were reported between Days 1 and 3. On

Day 3, her creatinine level had more than doubled to 371.28 µmol/L and acute renal failure was reported as an adverse event on the same day. The acute renal failure was considered severe in intensity and of unlikely relationship to study medication. It resolved in 7 days (Day 9). Furosemide was administered intravenously as concomitant medication on Day 4 for 1 day and again on Day 6 for 3 days. The subject was anemic and was also given packed red blood cells on Day 4 for 2 days and epoetin alpha on Day 6 for 6 days. The only concomitant antibiotic medications administered during the trial were metronidazole on Day 7 for 13 days and levofloxacin on Day 28 (no end date reported). The subject's creatinine level had returned to her baseline level on Day 12 (end of IV therapy)(123.76 µmol/L). At the test of cure visit on Day 20 (8 days after discontinuing doripenem), her creatinine level (114.92 µmol/L) was lower than that reported at baseline and returned to normal (88.4 µmol/L) by Day 40 (late follow-up visit). The subject completed the study per protocol through the late follow-up visit.

FDA Medical Officer Comments: The patient had an abnormal serum creatinine at baseline, had a increase in serum creatinine while receiving doripenem on Day 3, and then the serum creatinine returned to normal by end of therapy and the renal failure resolved. The underlying etiology for the renal impairment is unclear from the narrative summary, although she may have had prerenal azotemia due to loose stools and vomiting prior to admission. The improvement noted in her renal function while receiving doripenem would suggest that the event was not primarily related to exposure to that drug.

DORI-07 Subject 04602510 (Doripenem 500 mg IV infusion q8h):
This 61-year-old Caucasian woman entered the study with a diagnosis of intra-abdominal infection (type not specified). Relevant medical history included chronic obstructive pulmonary disorder, congestive heart failure, hypertension, tachycardia, and diabetes. The subject received doripenem 500 mg as a 60-minute IV infusion q8h and meropenem placebo as a 3- to 5-minute IV bolus q8h for 6 days. At baseline, the subject's creatinine level was at the upper limit of normal (ULN) (106.08 µmol/L; ULN=106.08 µmol/L). On Days 3 and 6 (end of IV therapy), her creatinine levels were above the ULN (167.96 and 141.44 µmol/L, respectively). The subject was administered dopamine (for low urinary output), lidocaine (for congestive heart failure), and propofol (for sedation) on Day 1 for 1 day. Morphine (for post-surgical pain) and acetaminophen (for fever) were also started on Day 1 for 3 and 5 days, respectively. No concomitant antibiotic medications were administered before Day 6. The following additional IV antibiotic medications were initiated on Day 6: imipenem (Day 6 for 9 days), levofloxacin (Day 6 for 5 days), amikacin (Day 10 for 2 days), linezolid (Day 11 for 12 days), and piperacillin and tazobactam (Day 17 for 6 days). Other pertinent reported adverse events were low urinary output lasting for 1 day on Day 1, pneumonia reported on Day 6, and sepsis and urinary tract infection reported on Day 10. All of these events were considered not related to study medication. The low urinary output and pneumonia were considered moderate in severity; the sepsis and urinary tract infection were considered severe. On Day 14, the subject experienced pancreatitis, possible myocardial ischemia, and renal failure. These events were considered life threatening and not related to study medication. The subject died due to worsening of

Staphylococcus sepsis that was considered not related to study medication. In the opinion of the sponsor's medical monitor, this was a severely ill patient with multiple medical problems including poor circulatory function and possible ischemic heart disease.

FDA Medical Officer Comments: This subject' death was reviewed earlier in this report. She was a diabetic patient who was treated with six days of study drug for a cUTI. She developed pneumonia on Day 6 followed by an enterococcal UTI, staphylococcal bacteremia, pancreatitis, myocardial ischemia, and renal insufficiency during the eight days following completion of study drug. She died on Day 22 from staphylococcal sepsis. There were several identifiable aggravating factors noted in association with the deterioration of renal function, including sepsis, heart failure, and exposure to potentially nephrotoxic drugs (amikacin). Although unlikely, it is not possible to definitively exclude the study drug as a contributing factor.

DORI-08 Subject 02902030 (Doripenem 500 mg IV infusion q8h):
This 71-year-old Caucasian man entered the study with a diagnosis of intra-abdominal infection (type not specified). Relevant medical history included hypertension, kidney stones, and urinary tract infection. The subject received doripenem 500 mg as a 60-minute IV infusion q8h and meropenem placebo 1000 mg as a 3- to 5-minute IV bolus q8h for 8 days. The subject's creatinine levels were normal throughout the study (the last assessment was on Day 43). On Day 30, 22 days after doripenem was discontinued, the subject experienced acute renal insufficiency and urinary tract infection. The events were considered mild or moderate and not related to study medication; both events resolved by Day 42. On Day 29, the subject received oral amoxicillin for 2 days. Ciprofloxacin and piperacillin/tazobactam were administered IV on Day 30 for 3 days. Oral ciprofloxacin was given starting on Day 32 for 11 days. The subject completed the study per protocol through the late follow-up visit

FDA Medical Officer Comments: The renal abnormalities developed after doripenem had been discontinued. In view of the short half-life of the drug and the lack of a close temporal association with doripenem exposure, it is unlikely that doripenem had a contributory role in the subject's abnormal renal function abnormalities.

DORI-08 Subject 12806502 (Doripenem 500 mg IV infusion q8h):
This 51-year-old Caucasian man entered the study with a diagnosis of intra-abdominal infection (type not specified). He had no
relevant past medical history. The subject received doripenem 250 to 500 mg as a 60-minute IV infusion q8h and meropenem placebo 1000 mg as a 3- to 5-minute IV bolus q8h or q12h for 11 days. The subject received vancomycin on Day 4 for 1 day, Day 7 for 3 days, and Day 14 for 11 days. His creatinine level was elevated at baseline (132.6 µmol/L; upper limit of normal [ULN]=106.08 µmol/L), decreased to 61.88 µmol/L by Day 3 while receiving IV study medication and increased to 165.01 µmol/L on Days 6, 9, and 11. Just prior to the first elevation in creatinine, the subject had received concomitant vancomycin. On Day 7, an adverse event of elevated signs of inflammation was reported. On Day 10, persisting signs of inflammation and renal failure were reported as adverse events. The persisting

inflammation was considered by the investigator as severe in intensity and not related to study medication; it resolved on the same day. The renal failure was considered moderate in severity and of unlikely relationship to study medication; it resolved in 3 days (Day 12). At the early follow-up visit on Day 21 (10 days after discontinuation of doripenem), his creatinine level (123.76 µmol/L) had decreased to below his baseline value. The subject did not complete the study per protocol due to the need for additional antibiotic therapy.

FDA Medical Officer Comments: The patient had an abnormal baseline creatinine, which declined initially, but increased in association with concomitant vancomycin, a potentially nephrotoxic drug. The serum creatinine decreased following completion of therapy with both drugs. Although unlikely, it is not possible to definitively exclude the study drug as a contributing factor.

In order to further assess the extent of underlying factors that could potentially predispose study subjects to pre-renal azotemia, the FDA Medical Officer used MedDRA preferred terms to compile the number of subjects in the four Phase 3 studies who had dehydration, hypovolemia, diarrhea, pre-existing renal failure, and congestive heart failure as part of their medical history. The following table summarizes the data:

Table 96: FDA Medical Officer Summary of subjects in the doripenem Phase 3 clinical trials who had significant risk factors for pre-renal azotemia and pre-existing renal impairment based on Medical History, ITT population

	DORI-05		DORI-06	DORI-07 and -08	
	Doripenem	Levofloxacin	Doripenem	Pooled Doripenem	Pooled Meropenem
Medical History	n (%)	n (%)	n (%)	n (%)	n (%)
Chronic renal failure and renal insufficiency[a]	3 (0.80)	3 (0.81)	3 (0.71)	1 (0.21)	5 (1.06)
Congestive heart failure[b]	6 (1.60)	7 (1.88)	11 (2.60)	7 (1.47)	5 (1.07)
Dehydration[c]	4 (1.06)	13 (3.49)	28 (6.62)	22 (4.61)	24 (5.12)
Diarrhea[d]	9 (2.40)	12 (3.23)	23 (5.44)	41 (8.60)	25 (5.33)
Hypotension[e]	6 (1.60)	5 (1.34)	7 (1.65)	19 (3.98)	15 (3.20)
Vomiting/emesis[f]	3 (0.80)	2 (0.54)	0 (0.0)	7 (1.47)	6 (1.28)
Renal failure/ Insufficiency[g]	4 (1.06)	4 (1.08)	6 (1.42)	6 (1.26)	3 (0.64)
Shock[h]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.21)	0 (0.0)
TOTALS	35 (9.31)	46 (12.37)	78 (18.44)	104 (21.80)	84 (17.91)

[a] includes chronic renal failure and chronic renal insufficiency
[b] includes congestive heart failure, congestive cardiac failure, congestive cardiac insufficiency
[c] includes dehydration, dehydrated, moderate dehydration, dehydration, dehydration ketosis
[d] includes diarrhea, diarrhea, diarrhea intermittent
[e] includes hypotension , hypotension secondary to sepsis or peritonitis, hypotension due to vascular disorder
[f] includes includes nausea & vomiting, nausea + vomiting, nausea and emesis, nausea and vomiting, nausea, emesis
[g] includes renal failure, impairment, ot insufficiency
[h] includes shock, shock (septic)

As depicted above, there were a higher percentage of subjects with various underlying risk factors for pre-renal azotemia and pre-existing renal impairment in the cIAI studies compared to the cUTI studies. In the cIAI studies, there was a higher prevalence of chronic renal failure and insufficiency in the meropenem group, wheras there was a higher percentage of subjects with diarrhea in the doripenem group. Overall, almost 20% of the

subjects in the cIAI studies had significant risk factors for pre-renal azotemia and pre-existing renal impairment based on Medical History. Thus, the relative imbalance in the incidence of renal failure/renal impairment between the doripenem treated groups and the comparator treated groups does not appear to be based primarily on an inherent disparity in the prevalence of those risk factors among the treatment arms in the safety population. The finding that the preponderance of renal failure/renal impairment-related TEAEs affected only doripenem-treated subjects is notable, since the drug is in the same antibacterial class as meropenem. The FDA Medical Officer discussed the 17 patients with a nephrologist in one of the other divisions in the Agency in order to better understand and analyze this patient subgroup. In consideration of the case narratives, laboratory data, and risk factors based on medical history, the FDA Medical Officer suspects that underlying intravascular volume depletion, pre-renal azotemia, and pre-existing renal insufficiency may enhance the subject's susceptibility to develop acute renal failure/renal impairment following exposure to doripenem and that such patients should have their renal function monitored closely while receiving the drug.

Anemia:

The FDA Medical Officer reviewed laboratory data on all study subjects who completed i.v. study drug without receiving the PO switch agent and experienced anemia as a treatment-emergent adverse event. There were 31 doripenem-treated (9 in the cUTI studies and 22 in the cIAI studies), no levofloxacin-treated, and ten meropenem-treated subjects who completed i.v. study drug without receiving the PO switch agent and experienced anemia as a treatment-emergent adverse event in the combined phase 3 clinical trials experience. Graphic patient profiles (including laboratory test results) were examined for each subject. As depicted in the following table, the median duration of i.v. study drug and the median study day of hemoglobin nadir were similar between the doripenem- and meropenem-treated subjects who experienced anemia. The median change in hemoglobin was larger in the meropenem patients with anemia, but more doripenem-treated subjects received blood transfusions and conversions to a positive direct Coombs test were noted only among subjects treated with doripenem.

Table 97: FDA Medical Officer Summary of Subjects who completed i.v. study drug without receiving the PO switch agent and experienced anemia as a treatment-emergent adverse event, doripenem phase 3 clinical studies, ITT population

	Pooled Doripenem	Meropenem	Levofloxacin
Total # of subjects	31	10	0
Anemia* at baseline	19/28[†] (68%)	7/8[†] (88%)	NA
Median duration of i.v. study drug, days (range)	11 (5-16)	12 (7-15)	NA
Median Study Day of HGB nadir, Study Day # (range)	8 (2-42)	8.5 (1-39)	NA
Median change in HGB from baseline to nadir, G/DL (range)	-1.55 (0.0 to -6.5)	-2.35 (0.0 to -4.0)	NA
# of subjects who received blood transfusions	13 (42%)	3 (30%)	NA
# of subjects who developed positive direct Coombs test[†]	2	0	NA

HGB=hemoglobin, NA=not applicable; HGB <12.5 G/DL; [†]missing data for some subjects

It is noteworthy that 19 doripenem-treated subjects (68%) and 7 meropenem-treated subjects (88%) were anemic at baseline. The median duration of i.v.study drug was similar between the pooled doripenem and the meropenem-treated subjects. The median duration of doripenem administration was 11 days (range, 11-12) in the patients in the cUTI studies and 10 days (range, 5-16) in the cIAI study subjects. Thirteen (42%) of the doripenem-

treated and four (40%) of the meropenem-treated subjects experienced their hemoglobin nadir within the first week of i.v. administration of the drug. It is possible that peri-operative blood loss accounted for the treatment-emergent anemias observed in that subset of study subjects, although no actual or estimated perioperative blood loss data were provided by the Sponsor to support this premise. There was a substantial amount of missing data related to direct coombs tests. Both of the doripenem-treated subjects who developed positive direct Coombs tests during study participation had positive results ≥28 days after completing i.v. doripenem therapy and unrelated to the study day of the hemoglobin nadir.

In order to further investigate the underlying pathophysiology of anemia as a treatment-emergent adverse event, the FDA Medical Officer reviewed data on those subjects who converted their direct Coombs test results from negative to positive with the test conversion as an indicator of possible immune-mediated hemolytic anemia. Pertinent data is summarized in the table below.

Table 98: FDA Medical Officer's Table of subjects who converted their Direct Coombs Test result from negative to positive during the study (including followup) in studies DORI-07 and DORI-08 (ITT population).

Study	Subject ID#	Treatment	Age/Sex	ITT	Study Visit with Negative Result	Study Visit with Positive Result	Anemia as a TEAE	Blood transfusion during study	History of Anemia	Pregnant during study
DORI-07	40204056	Doripenem	20/F	yes	Day 5	EFU	No	No	YES	No
	40204507	Doripenem	93/F	yes	EOT (IV)	RP/UNS SFTY	YES	YES	YES	No
	40204512	Doripenem	78/M	yes	EFU	RP/UNS SFTY	YES	YES	YES	NA
	40204013	Meropenem	41/F	yes	Baseline	EOT (IV)	No	No	YES	No
	40204037	Meropenem	42/M	yes	EOT (IV)	RP/UNS SFTY	YES	YES	YES	NA
	40204041	Meropenem	76/M	yes	RP/UNS SFTY	EFU	No	No	YES	NA
	40204062	Meropenem	42/F	yes	EOT (IV)	EFU	No	No	No	No
	40204504	Meropenem	50/F	yes	EOT (IV)	EFU	No	No	No	No
DORI-08	42603024	Doripenem	33/M	yes	Baseline	EFU	No	No	No	NA
	43004507	Doripenem	56/M	yes	TOC	EFU	YES	No	No	NA

EOT (IV)=End of IV Therapy; EFU=Early followup; RP/UNS SFTY=repeat unscheduled safety lab assessment; TOC=Test of Cure; NA=not applicable; TEAE=treatment-emergent adverse event

Direct Coombs tests were not reported for subjects in DORI-5 and DORI-06. Direct Coombs results were reported for 53 subjects in DORI-07 and 74 subjects in DORI-08. The reason for such testing only among select patients in the cIAI studies is uncertain, but may relate to the need for peri-operative type and cross-matching done in the event that blood transfusions were required for some of the surgical patients.

In total, five doripenem-treated subjects and five meropenem-treated subjects with negative direct Coombs tests converted to a positive test during the study or followup periods. Four of the ten subjects had anemia as a TEAE, including three doripenem-treated and one meropenem-treated subject. Six of the ten subjects had a history of anemia. Six were taking concomitant drugs (captopril) and many had received concomitant antibiotics

(cephalosporins, other beta-lactams) that can be associated with hemolytic anemia. Three subjects had received a blood transfusion during the study. There were no pregnancies among the female subjects. Graphic patient profiles were examined for each subject, but there was missing data for time points beyond early follow-up (EFU) for some subjects. In view of the multiple confounding variables (blood transfusions, concomitant antibiotics, concomitant medications, baseline anemia), it is not possible to determine whether the conversions in direct Coombs test were related to doripenem administration.

In summary, the data analyzed above from subjects who completed i.v. study drug without receiving the PO switch agent and from subjects who experienced conversion of their direct Coombs tests from negative to positive did not provide evidence of a clear association between doripenem exposure and the development of hemolytic anemia as an adverse event. Although the data do not directly implicate doripenem as a causative agent for hemolytic anemia in the safety population in the Phase 3 clinical trials, there were significant limitations that hindered the ability to make a meaningful conclusion regarding this issue, including multiple confounding factors and data collection deficiencies.

***C. difficile*-related colitis:**
There were four doripenem-treated patients identified with *C. difficile*-related colitis during the doripenem phase 3 studies of cUTI and cIAI. No levofloxacin-treated subjects in DORI-05 were diagnosed with the disease. Only one meropenem-treated patient in the combined DORI-09 and DORI-10 experience had *C. difficile* toxin detected in a stool specimen. Relevant information is summarized in the following table and in the narratives on the doripenem-treated subjects who experienced *C. difficile*-related colitis:

Table 99: FDA Medical Officer Table of doripenem-treated subjects identified with *C. difficile*-related colitis

Study	Subject ID#	Age/Sex/ Race	Serious event	AE Outcome	Comments
DORI-05	05501010	72/F/W	No	Recovered	Experienced recurrence
DORI-06	64000287	41/F/W	No	Recovered	No additional comments
DORI-07	01312512	86/M/W	No	Recovered	No additional comments
	02002065	62/M/W	No	Recovered	No additional comments

Sponsor Narratives (from Module 2.7.4 Sponsor's Summary of Clinical Safety):

• Subject 05501010 (study DORI-05) received i.v. doripenem 500 mg on Days 1 through 4 followed by oral levofloxacin on Days 5 through 10. She experienced two episodes of moderate *C. difficile*-associated diarrhea on Days 13 and 30 of the study, which were confirmed by the identification of *C. difficile* toxin in her stools. She was initially treated with metronidazole and later received i.v. meropenem for fever and vancomycin. The events resolved and were considered by the investigator to be probably related to treatment with study drug therapy.

• Subject 64000287 (study DORI-06) had mucous enteritis seen on abdominal CT and was diagnosed with moderate *C. difficile* colitis (method of diagnosis not confirmed) on Day 4 of the study after receiving three doses of i.v. doripenem 500 mg. The subject was treated with metronidazole and the event resolved. The event was considered by the investigator

as unlikely to be related to treatment with study drug therapy. The patient also had received empiric cefazolin for one day during study participation.

• Subject 01312512 (DORI-07) experienced moderate *C. difficile* diarrhea on Day 28 of the study (method of diagnosis unknown). The patient had received cefazolin for one day for peg tube placement (Day 8) and ceftazidime for two days for tachypnea (beginning Day 12) during study participation. He was treated with metronidazole, and the event resolved. The event was considered by the investigator to be possibly related to treatment with study drug therapy.

• Subject 02002065 (DORI-07) experienced moderate *C. difficile* colitis on Day 8 of the study. He received several concomitant antimicrobials including ampicillin, vancomycin, amoxicillin/clavulanate, piperacillin/tazobactam, levofloxacin, and ciprofloxacin. The event resolved after a 14-day course of treatment with metronidazole. The event was considered by the investigator to be possibly related to treatment with study drug therapy.

Hypersensitivity reactions:
Twelve subjects had treatment-emergent adverse events (TEAEs) coded to the preferred term of hypersensitivity (or drug hypersensitivity) in the Phase 2 and 3 complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) studies. Nine events occurred in subjects randomized to doripenem therapy and 3 events were reported in subjects randomized to comparators arms (1 in the levofloxacin arm and 2 in the meropenem arm). For 6 reported events in the doripenem arm, the hypersensitivity reaction was related to other drugs administered as concomitant agents (Subjects 03501017, 40106074, 40106087, 40106091, 02102023 and 40004063). The remaining 3 events occurred during i.v. doripenem therapy and were not attributed to concomitant medications by the investigator. One of these 3 events (Subject 45300420) was described as a local allergic reaction in the upper lip and was considered by the investigator to be unrelated to doripenem therapy. Thus, only 2 out of the 9 events in the doripenem arm (Subjects 56-P0219 from DORI-03 and 10109039 from DORI-05) were plausibly related to doripenem therapy. Subject 56-P0219 experienced an allergic reaction, which was a serious adverse event and was considered by the investigator to be related to doripenem. Subject 10109039 reported an allergic reaction on Day 2 of doripenem therapy. This event was not serious and was considered by the investigator to be related to doripenem therapy. The following table summaries salient features of the cases:

Table 100: Summary of Subjects with Treatment-emergent Adverse Events of Hypersensitivity or Drug Hypersensitivity in doripenem Phase 2 and 3 studies, ITT (adapted from Sponsor submission of 8/24/2007)

Study	Subject ID #	Study Drug	Study Drug Duration (days)		AE Term	Study Day of Onset	Action Taken by Investigator
			IV	PO			
DORI-03	56-P0219	Dori 250 mg	2	0	Allergic Reaction	2	This was a serious event. Doripenem was withdrawn and diphenhydramine prescribed on day 2 for 2 weeks. One dose of IV hydrocortisone was also prescribed on day 2, and then 3 times on day 6. The event resolved 1 day after onset.
DORI-05	10109039	Dori	5	6	Allergy	2	Event was non-serious, mild in severity and considered by the investigator to be related to study drug therapy. Study drug was not withdrawn. IV prednisolone was administered TID for 1 day on day 2 for "suspected allergy". Subject completed study through LFU.
	03501017	Dori	4	7	Sulfa drug reaction-urticaria, malaise, and headache	41	Event secondary to Bactrim in the post treatment period. Diphenhydramine was administered for the sulfa drug reaction on day 41 for 2 days. No action was taken in relation to study drug.
	40106074	Dori	3	7	Allergic Reaction	7	Doripenem was given from day 1–3. Event was mild and considered by the investigator to be related to levofloxacin. No medications or other action was taken and subject completed study through LFU.
	40106087	Dori	3	7	Skin allergy (Skin rash due to allergic reaction after taken acetaminophen)		Event related to acetaminophen. No medications were administered for the skin allergy and no action was taken in relation to study drug because event occurred post treatment with study drug.
	40106091	Dori	3	6	Allergic Reaction	4	Allergic reaction occurred on day 4 (while subject was on oral levofloxacin therapy) and lasted for 1 day. The event was non-serious but severe and considered by the investigator to be related to levofloxacin. Epinephrine was given subcutaneously and hydrocortisone given iv, only one dose of both medications was administered on the day of the event. The subject recovered and completed study through LFU.
	40106048	Levo	4	7	Allergic Reaction	5	Event occurred on day 5, and lasted for 39 days. The event was non-serious, moderate in severity and considered by the investigator to be related to study drug. No medication was administered for treatment of the allergic reaction and study drug was continued despite event. The event was reported as resolved.
DORI-06	45300420	Dori	11	0	Superior Lip Allergic Reaction	3	Event occurred on day 3, and lasted for 6 Days and was considered by the investigator to be unrelated to study drug. No action was taken and study drug was continued despite event. Dexchlorpheniramine was administered on day 8 for 1 day.
DORI-07	02102023	Dori	6	0	Drug Reaction Imipenem-Rash		Event secondary to imipenem. No action was taken in relation to study drug because event occurred post treatment with study drug.
	40004063	Dori	3	7	Allergic Reaction to Micropore	5	No action was taken in relation to study drug.
	40204093	Mero	5	10	Allergic Reaction to Ranitidine	1	Study drug was continued. Promethazine hydrochloride IM was given as treatment on day 1 for 1 day. The event was reported as

							resolved. The subject completed study per protocol through LFU visit.
DORI-08	12705000	Mero	1	0	Allergic Reaction	1	The event was non-serious, moderate in severity and considered by the investigator to be related to study drug. Study drug was withdrawn. Clemastine PO/QD was given as treatment on day 1 for 2 days. The event was reported as resolved. The subject did not complete study per protocol due to the adverse event of an allergic reaction.

Valproic acid:
Valproic acid serum levels were not systematically measured in the phase 3 clinical trials. Six subjects had valproic acid, valproate sodium, or divalproex sodium listed as prior or concomitant medications. None of the subjects had a seizure during the study and none had valproic acid or divalproex levels recorded on their CRFs. The Sponsor plans to conduct a Phase 1 study to evaluate changes in plasma valproic acid levels when co-administered with doripenem later this year.

Special Procedures required due to an adverse event:
Three doripenem-treated subjects required special procedures due to an adverse event. The pertinent information is summarized in the table below. None of the adverse events were attributable to doripenem exposure.

Table 101: FDA Medical Officer Summary of subjects who required procedures due to an adverse event, Doripenem phase 3 clinical trials, ITT population

Study	Subject ID#	Procedure	Outcome
DORI-06	45500330	Dialysis for renal failure related to a bladder neoplasm	Fatal
DORI-06	45100077	Pacemaker implant for sick sinus syndrome	Recovered
DORI-07	04602510	Dialysis for renal failure and staph sepsis	Fatal

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the doripenem phase 3 studies, vital signs and phycial examinations were conducted at screening and at various study visits as follows:
In the cUTI studies, vital signs (blood pressure, pulse, and respiration rate) were measured at screening, the EOT(IV) visit, and the TOC visit. Oral temperature (or equivalent) was measured within 4 hours prior to administration of each dose of study drug therapy while the patient was receiving IV study drug therapy. Height and weight were both measured at screening, and weight was measured while the patient was receiving IV study drug therapy at the discretion of the investigator. A full physical examination was performed at screening, and also at the EOT(IV) and TOC visits.

In the cIAI studies, vital signs (oral temperature [or equivalent], blood pressure, pulse, and respiration rate) were measured at screening, daily while the patient was receiving IV study

drug therapy, and at the EOT(IV), EFU, and TOC visits. Height and weight were measured at screening only. A full physical examination was performed at screening and at the EOT(IV), EFU, and TOC visits.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The studies analyzed in this review are the four doripenem phase 3 clinical studies for the proposed indications of cUTI and cIAI.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The tables below provide vital signs data summarizing measures of central tendency (mean, standard deviation, and median) for the each of the phase 3 clinical trials. There were no substantial differences between the doripenem and comparator groups with respect to the measures of central tendency of the vital sign parameters assessed in the tables.

Table 102: FDA Medical Officer Table of comparative vital signs data for subjects in Study DORI-05 (ITT)

Parameter		Doripenem		Levofloxacin	
		Baseline	End of IV Therapy	Baseline	End of IV Therapy
Systolic BP	n	376	370	372	361
	mean	123.18	122.45	123.05	121.61
	SD	19.26	16.82	19.81	15.84
	median	120	120	120	120
Diastolic BP	n	376	370	372	361
	mean	74.13	73.33	73.93	73.31
	SD	12.06	9.93	11.23	9.5
	median	75	70	76.5	70
Pulse	n	376	369	372	359
	mean	84.82	74.61	84.79	76.39
	SD	16.58	8.71	16.85	8.59
	median	80	75	80	76
Oral Temperature	n	375	372	371	361
	mean	37.75	36.68	37.76	36.68
	SD	1.18	0.51	1.15	0.51
	median	37.8	36.7	37.8	36.6
Respiratory Rate	n	366	361	363	352
	mean	17.88	16.4	17.4	16.19
	SD	4.22	3.02	3.69	3.05
	median	17	16	16	16
Height	n	373	NA	370	NA
	mean	165.98	NA	165.71	NA
	SD	9.05	NA	8.98	NA

	median	165.1	NA	165	NA
Weight	n	376	NA	372	NA
	mean	72.25	NA	74.23	NA
	SD	17.29	NA	17.44	NA
	median	71	NA	72	NA

NA=not applicable

As depicted in the table above, the mean and median values for the vital sign parameters were similar between the two treatment arms in DORI-05 at baseline and end of therapy (EOT). There was a slight drop in median pulse, diastolic blood pressure, and oral temperature from baseline to EOT that was of similar magnitude in both treatment groups.

Table 103: FDA Medical Officer table of comparative vital signs data for subjects in Study DORI-06 (ITT) using the Levofloxacin arm of DORI-05 as comparator

Parameter		Doripenem (DORI-06)		Levofloxacin (from DORI-05)	
		Baseline	End of IV Therapy	Baseline	End of IV Therapy
Systolic BP	n	423	416	372	361
	mean	124.29	122.06	123.05	121.61
	SD	20.7	15.98	19.81	15.84
	median	120	120	120	120
Diastolic BP	n	423	416	372	361
	mean	74.53	74.06	73.93	73.31
	SD	12.12	10.71	11.23	9.5
	median	73	75	76.5	70
Pulse	n	423	416	372	359
	mean	88.01	76	84.79	76.39
	SD	17.3	9.77	16.85	8.59
	median	84	76	80	76
Oral Temperature	n	423	417	371	361
	mean	37.79	36.69	37.76	36.68
	SD	1.1	0.52	1.15	0.51
	median	38	36.6	37.8	36.6
Respiratory Rate	n	419	409	363	352
	mean	18.4	17.26	17.4	16.19
	SD	3.48	2.97	3.69	3.05
	median	18	18	16	16
Height	n	415	NA	370	NA
	mean	164.8	NA	165.71	NA
	SD	8.66	NA	8.98	NA
	median	165	NA	165	NA
Weight	n	423	NA	372	NA
	mean	69.86	NA	74.23	NA
	SD	16.85	NA	17.44	NA
	median	65.5	NA	72	NA

NA=not applicable

As depicted in the table above, the mean and median values for the vital sign parameters

were similar between the doripenem treatment arm in DORI-06 and the levofloxacin treatment arm in DORI-05 at baseline and end of therapy (EOT). There was a slight drop in median diastolic blood pressure and oral temperature from baseline to EOT in the DORI-06 study subjects that was of similar magnitude to the changes observed in the levofloxacin group in DORI-05.

Table 104: FDA Medical Officer table of comparative vital signs data for subjects in Study DORI-07 (ITT)

Parameter		Doripenem		Meropenem	
		Baseline	End of IV Therapy	Baseline	End of IV Therapy
Systolic BP	n	235	229	236	223
	mean	122.94	124.39	123.7	125.38
	SD	19.21	16.69	18.4	15.99
	median	120	120	120	120
Diastolic BP	n	235	229	236	223
	mean	71.34	73.28	73.15	76.14
	SD	12.68	10.7	11.68	10.36
	median	70	71	71.5	76
Pulse	n	234	229	236	224
	mean	91.09	79.15	92.66	80.06
	SD	16.3	10.88	18.36	11.14
	median	88	80	89.5	80
Oral Temperature	n	235	223	236	223
	mean	37.37	36.76	37.32	36.69
	SD	0.87	0.53	0.92	0.54
	median	37.2	36.7	37.3	36.6
Respiratory Rate	n	228	219	230	210
	mean	19.5	18.25	19.62	18.01
	SD	4.28	2.95	4.88	3
	median	19.5	18	20	18
Height	n	234	NA	234	NA
	mean	170.39	NA	169.78	NA
	SD	9.52	NA	9.58	NA
	median	170	NA	170	NA
Weight	n	235	NA	236	NA
	mean	76.92	NA	77.74	NA
	SD	17.77	NA	18.64	NA
	median	75	NA	74.9	NA

NA=not applicable

As depicted in the table above, the mean and median values for the vital sign parameters were similar between the two treatment arms of DORI-07 at baseline and end of therapy (EOT). There was a slight drop in median diastolic blood pressure and oral temperature from baseline to EOT that was of similar magnitude in both treatment groups.

Table 105: FDA Medical Officer table of comparative vital signs data for subjects in Study DORI-08 (ITT)

Parameter		Doripenem		Meropenem	
		Baseline	End of IV Therapy	Baseline	End of IV Therapy
Systolic BP	n	242	233	233	220
	mean	121.43	125.81	121.74	123.85
	SD	18.74	18.83	19.26	16.92
	median	120	120	120	120
Diastolic BP	n	242	233	233	220
	mean	71.99	72.96	72.18	76.62
	SD	12.17	11.37	12.36	10.36
	median	70	72	70	75
Pulse	n	242	233	233	220
	mean	89.52	79.56	89.88	79.71
	SD	15.65	12.21	14.89	12.33
	median	84	79	88	79.5
Oral Temperature	n	240	233	233	223
	mean	37.43	36.75	37.45	36.79
	SD	0.92	0.59	0.96	0.63
	median	37.2	36.7	37.5	36.8
Respiratory Rate	n	226	212	224	202
	mean	18.91	180.1	18.73	17.88
	SD	5	3.18	4.13	260
	median	18	18	18	18
Height	n	239	NA	228	NA
	mean	169.86	NA	170.1	NA
	SD	9.28	NA	9.7	NA
	median	170	NA	170	NA
Weight	n	241	NA	232	NA
	mean	75.91	NA	75.32	NA
	SD	18.61	NA	14.95	NA
	median	72	NA	75.4	NA

NA=not applicable

As depicted in the table above, the mean and median values for the vital sign parameters were similar between the two treatment arms of DORI-08 at baseline and end of therapy (EOT). There was a slight drop in median pulse and oral temperature from baseline to EOT that was of similar magnitude in both treatment groups.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The FDA Medical Officer conducted an exploratory analysis of abnormal vital signs in an effort to identify marked outliers. The criteria for identifying marked outliers is provided in the following table:

Table 106: FDA Medical Officer Criteria for abnormal vital signs as marked outliers, ITT population*

			Markedly Abnormal Criteria	
Vital Sign	Age Group	Gender	Less Than	Greater Than
Systolic BP	≥18	Both	90	180
Diastolic BP	≥18	Both	50	105
Pulse	≥18	Both	50	120
Oral Temp (°C)	≥18	Both	35.6	40.5

*Criteria adapted from Sponsor submission

The results of analyzing individual vital sign parameters for marked outliers using the criteria above are summarized in the following four tables:

Table 107: FDA Medical Officer Summary of subjects with Oral Temperature abnormalities as Marked Outliers, ITT population

Temperature (°C)	Study Visit	DORI-05		DORI-06	DORI-07		DORI-08	
		Doripenem	Levofloxacin	Doripenem	Doripenem	Meropneme	Doripenem	Meropenem
>40.5	Baseline	6	2	1	0	0	0	0
<35.6	Baseline	1	0	4	1	4	2	3
	EOT	4	0	4	1	2	1	4
	EFU	3	1	8	1	4	3	1
	LFU	5	3	10	1	4	5	3
TOTAL OUTLIERS		19	6	27	4	14	11	11

In the cUTI studies, there were more subjects with hyperthermia (oral temperature >40.5°C) and hypothermia (oral temperatrure <35.6°C) in the doripenem group compared to the levofloxacin group. All of the hyperthermic episodes were at baseline, whereas most of the hypothermic episodes occurred after the patient had discontinued doripenem.

Table 108: FDA Medical Officer Summary of subjects with Systolic Blood Pressure abnormalities as Marked Outliers, ITT population

mm Hg	Study Visit	DORI-05		DORI-06	DORI-07		DORI-08	
		Doripenem	Levofloxacin	Doripenem	Doripenem	Meropneme	Doripenem	Meropenem
>180	Baseline	3	1	6	2	2	1	3
	Day 2/3	0	0	0	6	3	6	3
	Day 5	0	0	0	2	7	4	5
	Day 8	0	0	0	2	4	2	0
	Day 11	0	0	0	1	0	1	0
	EOT	0	0	1	0	2	2	1
	EFU	0	1	0	0	1	0	2
	LFU	0	0	0	0	1	1	0
<90	Baseline	5	4	2	4	2	6	6
	Day 2/3	0	0	0	8	5	7	7
	Day 5	0	0	0	1	0	0	1
	Day 8	0	0	0	1	0	1	1
	Day 11	0	0	0	0	2	1	2
	Day 14	0	0	0	0	0	1	3
	EOT IV	1	2	1	1	0	2	2
	EFU	1	0	1	2	0	0	2
	LFU	0	0	0	3	0	0	1
TOTAL OUTLIERS		10	8	11	33	29	35	39

There were no apparent differences among treatment arms in either the cUTI or the cIAI studies with respect to marked outliers in terms of systolic blood pressure.

Table 109: FDA Medical Officer Summary of subjects with Diastolic Blood Pressure abnormalities as Marked Outliers, ITT population

mm Hg	Study Visit	DORI-05		DORI-06	DORI-07		DORI-08	
		Doripenem	Levofloxacin	Doripenem	Doripenem	Meropneme	Doripenem	Meropenem
>105	Baseline	2	0	4	0	0	2	1
	Day 2/3	0	0	0	3	5	1	2
	Day 5	0	0	0	4	1	3	3
	Day 8	0	0	0	1	2	0	0
	EOT IV	0	0	3	0	1	2	1
	EFU	2	0	2	0	1	0	1
	LFU	0	0	0	0	0	1	0
<50	Baseline	5	0	4	10	7	8	9
	Day 2/3	0	0	0	21	12	10	10
	Day 5	0	0	0	3	4	4	2
	Day 8	0	0	0	4	7	2	2
	Day 11	0	0	0	4	2	6	3
	Day 14	0	0	0	1	0	3	3
	EOT IV	0	2	1	2	1	4	2
	EFU	1	0	1	2	1	1	1
	LFU	0	0	0	0	0	0	1
TOTAL OUTLIERS		10	2	15	55	44	47	41

In the cUTI studies, there were more subjects with marked outliers in terms of diastolic blood pressure in the doripenem arm compared to the levofloxacin arm. Most of those occurred at baseline and declined in frequency at later study visits, which makes it unlikely that they were study drug-related. In the cIAI studies, there were no obvious differences in the frequencies of marked outliers in diastolic blood pressure. Most of them occurred at baseline or within the first 5 days on therapy with a rapid decline in frequency thereafter. The pattern of decline in the number of subjects experiencing marked outliers later in the

course of the study might indicate that they are due to the underlying infection in the early stages of treatment.

Table 110: FDA Medical Officer Summary of subjects with Pulse abnormalities as Marked Outliers, ITT population

bpm	Study Visit	DORI-05		DORI-06	DORI-07		DORI-08	
		Doripenem	Levofloxacin	Doripenem	Doripenem	Meropenem	Doripenem	Meropenem
>120	Baseline	9	12	20	11	17	9	6
	Day 2/3	0	0	0	21	14	14	14
	Day 5	0	0	0	4	2	6	1
	Day 8	0	0	0	1	4	5	4
	Day 11	0	0	0	0	1	1	5
	Day 14	0	0	0	1	0	3	2
	EOT	0	0	0	0	1	2	2
	EFU	0	0	0	0	0	2	1
	LFU	0	0	0	1	0	0	3
	Unscheduled	0	0	0	0	0	0	1
<50	Baseline	0	0	0	0	0	0	0
	Day 2/3	0	0	0	0	0	1	0
	Day 5	0	0	0	1	0	0	0
	Day 8	0	0	0	1	1	0	1
	EOT IV	3	0	1	1	0	0	0
TOTAL OUTLIERS		12	12	21	42	40	43	40

There were no apparent differences among treatment arms in either the cUTI or the cIAI studies with respect to marked outliers in terms of pulse.

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

Delayed cardiac repolarization is a potential side effect of some non-anti-arrhythmic drugs that can create an electrophysiological condition that favors the development of torsade de pointes (TdP) and other ventricular arrhythmias.[4] Carbapenem antibiotics as a class have not been associated with QTc prolongation. However, several antimicrobials have been reported to induce QTc prolongation, including macrolides, azoles, and fluoroquinolones.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The Sponsor's assessment of the potential cardiotoxicity of doripenem during the development program for the drug was conducted as follows: The potential cardiac toxicity of doripenem was evaluated in pre-clinical studies. Doripenem exhibited no cardiovascular toxicity at doses up to 300 μM in cells expressing human ether-ago-go-related gene channels and on the action potential of dog Purkinje fibers. Likewise, doripenem had no effects on the cardiovascular system or behavior of dogs at single i.v. doses up to 100 mg/kg. Thus, preclinical data would suggest that doripenem should have no cardiac

liability in man. However, to be thorough, a definitive Phase 1 QT/QTc study (DORI-NOS-1001) was conducted in healthy subjects and was designed in accordance with ICH E14.

DORI-NOS-1001 was a Phase 1 thorough QT/QTc study designed in accordance with ICH E14 to assess the effects of doripenem on cardiac electrophysiology at therapeutic (500 mg q8h) and supratherapeutic (1000 mg q8h) doses. This study demonstrated that i.v. administration of doripenem was non-inferior to, or no worse than, that of placebo on QT/QTc prolongation. Doripenem had no effect on heart rate, PR interval, QRS interval, Twave, or U-wave morphology in healthy adults. No relationship between doripenem plasma concentrations and ΔQTcF was observed. No AEs were reported suggestive of proarrhythmic potential as specified in the ICH E14 Guideline. The results of this "negative" thorough QT/QTc study support the cardiac safety of doripenem (500 mg and 1,000 mg every 8 hours) in healthy subjects.

ECG data in other Phase 1 studies are limited due to the small number of subjects in the doripenem groups, the smaller number of subjects in the placebo groups, lack of timematched ECGs obtained at baseline, lack of a positive control for QT/QTc prolongation, and limited number of ECGs during treatment. In DORI-01, no signal of any effect on QTcF duration or cardiac conduction by PR and QRS evaluations was seen with doripenem when administered as a 500-mg dose q12h to 1000 mg q8h over seven days.5 In DORI-04, an 8 to 13 msec increase from baseline on Day 1 but not on Day 7 was seen for the 1,000 mg q8h dose group. Despite similar exposures (20% lower Cmax, equivalent AUC) for the 1,000 mg q12h dose, no such increases from baseline in QTcF were observed. Given the "negative" results of the thorough QT/QTc study DORI-NOS-1001 and the design limitations of DORI-04 described above, these findings in DORI-04 are likely to be spurious, particularly since one would expect that a related increase after prolonged exposure to a drug that does not induce its own clearance, an approximately equal effect might be seen.[5] A formal analysis of ECGs was not performed for DORI-02 in which ECGs were obtained at baseline and the day after a single dose of doripenem was administered. In studies DORI-NOS-1004, DORI-NOS-1005, and DORI-NOS-1006, ECGs were only performed at Screening.

In the double-blind, Phase 2 study DORI-03, 250 mg or 500 mg of doripenem was administered every 8 hours for 7 to 14 days to subjects with cUTI; this study was not placebo-controlled. Electrocardiograms were performed at screening and on Days 1 and 7. A single ECG recording collected on the day of screening and pre-dose on Day 1 were used for baseline assessments. The data showed a specific outlier in the 250 mg q8h group (one subject with >500 msec and >60 msec) and no such cases in the 500 mg q8h group. There were no treatment-emergent abnormal U-waves. The central tendency data showed that at Day 1 there was about a 4 msec increases in QTcF, whereas on Day 7, an 8 to 13 msec effect was seen without any real difference between the 250 mg and 500 mg doses. However, given the "negative" results of the thorough QT/QTc study DORI-NOS-1001 and the design limitations of DORI-03 described above, these findings are most likely spurious. [5]

In the Phase 3 cUTI and cIAI studies, ECG data were collected routinely at the Screening

Visit only; with the exception of the Phase 2 study DORI-03, routine post-randomization ECG data were not available for integrated analysis.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

Please refer to the report of the Interdisciplinary Review Team for QT Studies for details on ECG assessments and the thorough QT study (DORI-NOS-1001).

7.1.9.3.1 Analyses focused on measures of central tendency

Please refer to the report of the Interdisciplinary Review Team for QT Studies for details on ECG assessments and the thorough QT study (DORI-NOS-1001).

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Please refer to the report of the Interdisciplinary Review Team for QT Studies for details on ECG assessments and the thorough QT study (DORI-NOS-1001).

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Please refer to the report of the Interdisciplinary Review Team for QT Studies for details on ECG assessments and the thorough QT study (DORI-NOS-1001).

7.1.9.4 Additional analyses and explorations

In the Phase 3 cUTI and cIAI studies, ECG data were collected routinely at the Screening Visit only; with the exception of the Phase 2 study DORI-03, routine post-randomization ECG data were not available for integrated analysis. However, for completeness, all events of QT prolonged, ventricular arrhythmia, ventricular tachycardia, atrioventricular block, and bradycardia reported as treatment-emergent adverse events in the Phase 2 and 3 studies were summarized below.

TABLE 111: FDA Medical Officer summary table of the number of subjects with selected cardiac adverse events, Doripenem phase 3 clinical studies, ITT Population

Adverse Event	Doripenem 500 mg q8h	Levofloxacin 250 mg q24h	Meropenem 1 gm q8h
Atrioventricular block second degree	0	0	1
Bradycardia	2	0	3
Ventricular arrhythmia	1	0	0
Ventricular tachycardia	1	0	2
QT Prolonged	0	0	1
TOTAL	4	0	7

Seven subjects experienced cardiac adverse events in the combined meropenem treatment groups from DORI-07 and DORI-08. In the phase 3 doripenem experience, only four subjects experienced such events, whereas none were reported in the levofloxacin-treated patients in DORI-05. There were no episodes of QT prolongation among the doripenem-treated subjects in the four phase 3 studies.

The following table summarizes more detailed information on the four doripenem-treated subjects with cardiac events referenced in the previous table:

Table 112: FDA Medical Officer Patient Summary, selected cardiac adverse events, Doripenem phase 3 studies, ITT Population

Study	Subject ID#	Adverse Event	Age/Sex/Race	Outcome
DORI-05	00502002	Bradycardia	87/M/W	Fatal
	01303047	Ventricular tachycardia	70/W/F	Recovered
DORI-06	45000083	Bradycardia	50/W/F	Recovered
	45000084	Ventricular arrhythmia	81/W/M	Fatal

There were two fatalities and two subjects who recovered from their cardiac adverse events. As described in section 7.1.1 of this report, subject 00502002 was an elderly male who developed bradycardia on Day 1 that was not treated (do-not-resuscitate status) and proved to be life threatening. Subject 45000084 was an elderly male with substantial underlying cardiac disease (including Chagas cardiomyopathy, previous myocardial infarction, heart failure, and a pacemeaker) who succumbed to a ventricular arrhythmia. Neither fatality appeared to be related to doripenem administration.

7.1.10 Immunogenicity

Doripenem is not a therapeutic protein. Human immunogenicity was not studied specifically by the Sponsor. Hypersensitivity reactions are summarized in Section 7.1.7.5 of this report.

7.1.11 Human Carcinogenicity

The maximum proposed proposed duration of treatment with doripenem for the indications of cUTI and cIAI is 14 days. As this drug is primarily being developed for intermittent, short-term use, no human carcinogenicity studies were conducted by the Sponsor. Mutagenicity studies involving the Ames test and the Chinese Hamster Ovarian assay were negative. The *in vivo* mouse micronucleus assay was also negative. Please refer to the report of the Pharmacology-Toxicology Reviewer for details about the genotoxicity studies involving this drug.

7.1.12 Special Safety Studies

The Sponsor performed a thorough QT/QTc trial entitled "A Randomized, Double-Blind, Placebo- and Positive-Controlled Crossover Study evaluating Electrocardiogram Intervals in Healthy Adults Receiving Multiple Intravenous Infusions of Doripenem at Therapeutic

and Supratherapeutic Doses". Please refer to the review of the Interdisciplinary Review Team for QT Studies for details.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

According to the Sponsor's Integrated Summary of Safety Report, the pharmacological profile of doripenem indicated that the abuse and dependence potential of doripenem was minimal such that no analyses related to drug abuse were performed. In addition, no analyses of withdrawal or rebound effects were performed by the Sponsor.

7.1.14 Human Reproduction and Pregnancy Data

There were 13 women whose pregnancies occurred during the doripenem phase 3 studies. Seven were pregnant during DORI-05, four during DORI-06, and two during DORI-07. Seven of the pregnancies resulted in first trimester miscarriage or spontaneous abortion, and all of those were considered unrelated or unlikely to be related to study drug by investigators. Two pregnancies were terminated by elective abortion, one was an ectopic pregnancy and terminated surgically, one resulted in a healthy full-term neonate, and the outcomes of two pregnancies were unknown. Eleven of the women had a baseline diagnosis of pyelonephritis, which can be a risk factor for perinatal and maternal complications. The other two women had generalized peritonitis. Patient 45400273 had polycystic ovarian disease and insulin resistance, which can increase the risk for an adverse pregnancy outcome. Subjects 35300205 and 40104066 had diabetes mellitus, which can also predispose to an adverse pregnancy outcome. Pertinent data is summarized in the following table:

Table 113: FDA Medical Officer Summary of Pregnancy-related Adverse Events in the doripenem Phase 3 Clinical Studies

Study	Subject ID#	Age/Race	Baseline Diagnosis	Treatment	Outcome
DORI-05	30306196	24/W	Pyelonephritis	Doripenem	Abortion (elective)
	30406035	28/W	Pyelonephritis	Doripenem	Abortion incomplete
	40106048	20/W	Pyelonephritis	Levofloxacin	Abortion spontaneous
	40106084	24/W	Pyelonephritis	Levofloxacin	Abortion spontaneous
	40106097	18/B	Pyelonephritis	Doripenem	Abortion spontaneous
	40106143	21/B	Pyelonephritis	Doripenem	Abortion spontaneous
	40106144	20/W	Pyelonephritis	Doripenem	Abortion spontaneous
DORI-06	35300205	30/W	Pyelonephritis	Doripenem	Abortion spontaneous
	45400273	21/W	Pyelonephritis	Doripenem	Abortion spontaneous
	64000370	21/W	Pyelonephritis	Doripenem	Ectopic pregnancy
	64100293	30/H	Pyelonephritis	Doripenem	Unknown
DORI-07	37704070	35/W	Peritonitis	Doripenem	Healthy full-term neonate
	40104066	24/W	Peritonitis	Doripenem	Unknown

W=White, B=Black, H=Hispanic

7.1.15 Assessment of Effect on Growth

The phase 3 clinical studies were limited to adults only. Overall, the median height and weight of study subjects at baseline was similar among the treatment groups in the four

phase 3 clinical trials. Serial height and weight measurements were not assessed routinely following the baseline measurements. Please refer to the tables in the section 7.1.8.3.1 of this review for detailed information relevant to height and weight of study subjects.

7.1.16 Overdose Experience

As described in the Sponsor's Integrated Summary of Safety Clinical Summary, the no observed adverse effect level (NOAEL) of doripenem in preclinical studies was substantially greater than equivalent doses administered in the doripenem clinical studies. In addition, other carbapenems are routinely administered at higher doses than those currently being studied for doripenem. Therefore, it was not clear what dose of doripenem should be considered an overdose.

According to the Sponsor's Summary of Clinical Safety, in the Phase 2/3 studies, any dose of doripenem >1 g, or a total daily dose >3 g was considered a potential "overdose." However no subjects received such dosages and thus the effects of doripenem overdose in humans remains unknown. The usual duration of treatment for doripenem should not exceed 14 days. Although treatment courses exceeding this duration do not strictly constitute an overdose, the AE profile of subjects who received more than 15 days of i.v doripenem therapy was evaluated. Only one subject (01302517) from DORI-07, received doripenem 500 mg for 16 days. This subject experienced six TEAEs considered possibly related to treatment with study drug therapy: mild anxiety and mild tachycardia (Day 3); moderate decrease in blood uric acid (Day 5); moderate pyrexia (Days 7 and 22); and moderate increased platelet count (Day 8). All events resolved with the exception of the increased platelet count, which was ongoing at the end of the study. Because of the limited experience with prolonged courses of doripenem therapy, no conclusions can be drawn regarding the effects of prolonged therapy.

7.1.17 Postmarketing Experience

The Sponsor provided a post-marketing data summary in the ISS Report for the cUTI studies. According to that summary, doripenem has been approved for marketing only in Japan. The product was launched there on September 15, 2005 under the trade name Finibax, for the treatment of moderate to severe bacterial infections. As of August 31, 2006, approximately 100,500 patients have been exposed to Finibax since its launch. There were 49 spontaneously reported cases comprising 59 events with doripenem as the suspect or a suspect interacting drug reported from Japan. Of these cases, there were 29 (59%) serious cases, and 20 (41%) non-serious cases. The 49 cases included 30 men and 18 women (sex not reported for one subject), with a mean age of 68 years (range: 18 to 100 years, age unknown for one subject). Three cases were coded to the preferred term "convulsion". There were eight cases reporting 10 hematological AEs coded to the following preferred terms: platelet count decreased (three cases); white blood cell count decreased (two cases); white blood cell count increased (two cases); agranulocytosis (two cases); and neutrophil count decreased (one case). Cases with the following preferred terms suggestive of allergic events were reported: Stevens-Johnson Syndrome (one case); toxic epidermal necrolysis (one case); and urticaria (three cases). Other cutaneous events included rash (six events in five subjects), drug eruption (six events) and toxic skin

eruption (one case). Cases reporting hepatic AEs were coded to the following preferred terms: hepatic function abnormal (four cases); liver disorder (two cases); and hepatic enzyme increased (one case). There were seven events that coded to preferred terms related to abnormal liver function. Cases of renal AEs coded to the following preferred terms: renal failure acute (one case); blood urea increased (one case); nephritis (one case); and hematuria (one case). The cases of pulmonary AEs were coded to the following preferred terms: pneumonia (three cases); interstitial lung disease (two cases); and pneumonia staphylococcal (one case). There was one case each of hypernatremia and hyperkalemia. The remaining AEs were reported once and included the following preferred terms: Clostridium colitis; muscular weakness; bradycardia; multi-organ failure; septic shock; inappropriate antidiuretic hormone secretion; hypoglycemia; nausea; and dizziness. According to the Sponsor, there is sufficient evidence provided from reviewing the 49 spontaneously reported cases of AEs that occurred with doripenem use to conclude that anaphylaxis is an ADR.

Please refer to Section 7.2.2.2 of this report for the FDA Medical Officer's review of the post-marketing experience.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Patient exposure to study drug was assessed through the various phase 1, phase 2, and phase 3 clinical studies submitted in this NDA application. With respect to the phase 3 studies, however, it is important to note that the studies permitted an oral switch (PO) following which both treatment arms would be on the same oral antibiotic. For the cUTI studies, a switch to oral levofloxacin was permitted after a minimum of three days of IV study drug. For the cIAI studies, a switch to oral amoxicillin-clavulanic acid was permitted after a minimum of three days of IV study drug. As a result, the study populations in the four phase 3 trials were quite heterogeneous with respect to duration of exposure to IV study drug (i.e., completed IV therapy or did not complete) and duration of exposure to oral switch agent (i.e, completed PO, did not complete PO, or no PO switch). The following table summarizes the numbers of subjects in relation to their exposure to IV study drug and PO switch drugs in the phase 3 studies in the ITT population:

Table 114: FDA Medical Officer's Summary of Treatment-emergent Adverse Events in Subjects enrolled in the Phase 3 Clinical Trials stratified by IV and PO Switch Regimen, ITT Population

			Completed IV study drug			Did not complete IV study drug			Total subjects
Study	Treatment		Completed PO switch	Did not complete PO switch	No PO Switch	Completed PO switch	Did not complete PO switch	No PO switch	
DORI-05	Doripenem	n, ITT	293	5	36	1	0	41	376
		≥1 AE	194	4	20	1	0	21	240
		Serious AE	16	2	6	0	0	4	28
	Levofloxacin	n, ITT	255	5	42	1	3	66	372
		≥1 AE	160	4	19	1	2	36	222
		Serious AE	8	2	0	1	1	3	15
DORI-06	Doripenem	n, ITT	279	7	72	2	0	63	423
		≥1 AE	217	7	55	2	0	43	324
		Serious AE	12	2	14	1	0	10	39
DORI-07	Doripenem	n, ITT	142	3	78	0	0	12	235
		≥1 AE	119	3	65	0	0	8	195
		Serious AE	11	1	17	0	0	2	31
	Meropenem	n, ITT	142	5	73	0	1	15	236
		≥1 AE	111	3	56	0	1	13	184
		Serious AE	10	0	15	0	1	7	33
DORI-08	Doripenem	n, ITT	159	7	58	1	0	17	242
		≥1 AE	92	7	47	0	0	16	162
		Serious AE	12	4	18	0	0	7	41
	Meropenem	n, ITT	153	5	55	1	0	19	233
		≥1 AE	83	4	37	1	0	17	142
		Serious AE	14	3	14	0	0	12	43

As evidenced from the table above, only 244 (19.12%) of the 1,276 doripenem-treated subjects were treated completely with IV drug without PO switch. It is this subgroup that provides critical information on drug safety that is not confounded by adverse events that could be attributable to the PO switch agents. In addition, there were 133 doripenem-treated subjects (10.4%) who did not complete IV drug therapy and did not receive PO switch. Safety assessments in these two subgroups provide clearer insight into the safety profile of doripenem, since they are unencumbered by adverse events attributable to the PO switch agent. However, definitive conclusions regarding drug safety based on these subpopulations will be very limited, since they are too small (and the overall study is not powered) to derive substantial statistically relevant data regarding rare adverse events following such doripenem exposure and the effect of random patient allocation is lost.

7.2.1.1 Study type and design/patient enumeration

The following table depicts the Sponsor's pooled data on subjects enrolled in the doripenemphase 1 studies. A total of 72 subjects received placebo; 164 subjects received i.v. doripenem, including 138 subjects who received 500 mg and 107 subjects who received 1,000 mg doses,6 as shown in Table 6 (study design details are provided in Table 1). Due to the crossover design of DORI-NOS-1001 and DORI-NOS-1004, subjects may have received doripenem 500 mg, 1,000 mg, and/or placebo, and were therefore counted once in each treatment arm.

Table 115: Sponsor Summary Table of Subjects Included in the Phase 1 Safety Analysis Set by Study and Treatment Arm (Phase 1 Studies – All Healthy Subjects From DORI-01, DORI-02, DORI-04, DORI-NOS-1001, DORI-NOS-1004, DORI-NOS-1005, and DORI-NOS-1006) (from Sponsor Table 6, Module 2.5 – Clinical Overview)

Study	Placebo (dosed)	Doripenem 500 mg (dosed)	Doripenem 1,000 mg (dosed)	Doripenem Total (Distinct subjects)	All Distinct Subjects
DORI-01	8	12	12	24	32
DORI-02	0	8	0	8	8
DORI-04	6	6	12	18	24
NOS-1001	58	58	59	60	60
NOS-1004	0	24	24	24	24
NOS-1005	0	6	0	6	6
NOS-1006	0	24	0	24	24
Total	72	138	107	164	178

According to the Sponsor's summary for the Safety Analysis Sets (Phase 2 and 3 Studies - All Intent-to-Treat Subjects): The overall Safety Analysis Set of 2238 subjects consisted of: 1332 subjects treated with Doripenem 500 mg q8h, 65 subjects treated with Doripenem 250 mg q8h, 372 subjects treated with Levofloxacin 250 mg q24h, and 469 subjects treated with Meropenem 1g q8h. The overall cUTI Analysis Set of 1292 subjects consisted of: 855 subjects treated with Doripenem 500 mg q8h,65 subjects treated with Doripenem 250 mg q8h, and 372 subjects treated with Levofloxacin 250 mg q24h. The overall cIAI Analysis Set of 946 subjects consisted of: 477 treated with Doripenem 500 mg q8h and 469 treated with Meropenem 1g q8h.

The Phase 2 cUTI studies consisted of 121 total subjects including 56 treated with Doripenem 500 mg q8h and 65 treated with Doripenem 250 mg q8h. The Phase 3 cUTI studies consisted of 1171 total subjects, including 799 treated with Doripenem 500 mg q8h and 372 treated with Levofloxacin 250 mg q24h.

7.2.1.2 Demographics

The following table summarizes key demographic data on all subjects enrolled in the single phase 2 study (DORI-03) and the four phase 3 clinical studies. Evaluation of age demographics reveals no substantial differences between the treatment groups in terms of measures of central tendency. There are comparable gender and race characteristics between the treatment arms in DORI-05, DORI-07, and DORI-08.

Table 116: FDA Medical Officer's Analysis of Demographics for Subjects in the doripenem Phase 2 and Phase 3 Clinical Studies, ITT population

		DORI-03	DORI-05		DORI-06	DORI-07		DORI-08	
		Doripenem	Doripenem	Levofloxacin	Doripenem	Doripenem	Meropenem	Doripenem	Meropenem
		N=121	N=376	N=372	N=423	N=235	N=236	N=242	N=233
Age	Mean, yrs	54.11	51.24	51.07	51.61	47.56	47.23	46.08	6.41
	SD	19.23	21.09	20.99	20.63	18.36	17.43	18.12	17.67
	Median, yrs	58	54	53	52	47	46	45.5	46
Gender	Female	67 (55)	233 (62)	227 (61)	247 (58)	87 (37)	94 (40)	91 (38)	87 (37)
	Male	54 (54)	143 (38)	145 (39)	176 (42)	148 (63)	142 (60)	151 (62)	146 (63)
Race	White	104 (86)	303 (81)	290 (78)	215 (51)	166 (70)	157 (67)	190 (79)	194 (83)
	Black	0 (0)	28 (7)	28 (8)	72 (17)	18 (8)	23 (10)	9 (4)	7 (3)
	Hispanic	16 (13)	41 (11)	47 (12)	100 (24)	49 (21)	53 (22)	36 (15)	29 (12)
	Other	1 (1)	4 (1)	7 (2)	36 (8)	2 (1)	3 (1)	7 (2)	3 (2)
Analysis of Age by Gender									
Female	Mean, yrs	45.58	42.52	44.03	43.25	48.09	49.36	50.77	52.7
	SD	19.27	20.22	19.91	20.17	19.29	18	20.23	17.47
	Median, yrs	43	39	39	39	48	49.5	52	54
Male	Mean, yrs	64.68	65.46	62.09	63.35	47.25	45.82	43.26	42.66
	SD	13	13.36	17.7	14.74	17.84	16.96	16.14	16.75
	Median, yrs	65	69	67	65	47	43.5	41	41.5

An analysis of age by gender, however, revealed important differences with respect to the study populations of DORI-03, DORI-05, DORI-06, and DORI-08. In DORI-03, DORI-05, and DORI-06, there was a marked age dichotomy between men and women in that male study subjects were considerably older than female subjects (median ages were 65-69 for men and 39-43 for women). A dichotomy existed in the DORI-08 study population except that the female patients were older than the male patients; the median age of women was 52-54 while the median age of men was 41-41.5.

As a consequence of the marked age dichotomy among female and male patients in the phase 2 and 3 cUTI studies, further analysis was performed involving baseline creatinine clearance and baseline diagnosis by gender in those studies.

Table 117: FDA Medical Officer's Analyses of Baseline Creatinine Clearance and Baseline Diagnosis by Gender for the phase 2 and 3 cUTI Studies. ITT Population

Analysis by Baseline Creatinine Clearance					
		DORI-03	DORI-05		DORI-06
		Doripenem	Doripenem	Levofloxacin	Doripenem
		N=121	N=376	N=372	N=423
Gender	Baseline Creatinine Clearance	n, (gender%)	n, (gender%)	n, (gender%)	n, (gender%)
Female	Normal (≥80 mL/min)	39 (58)	134 (58)	135 (60)	155 (62)
	Mild (>50 to <80 mL/min)	22 (33)	68 (29)	68 (30)	58 (23)
	Moderate (>30 to ≤50 mL/min)	6 (9)	29 (12)	19 (8)	25 (10)
	Severe (≤30 mL/min)	0 (0)	2 (1)	5 (2)	10 (4)
Male	Normal (≥80 mL/min)	19 (35)	58 (41)	64 (44)	75 (42)
	Mild (>50 to <80 mL/min)	28 (52)	60 (42)	61 (42)	66 (37)
	Moderate (>30 to ≤50 mL/min)	7 (13)	22 (15)	15 (10)	34 (19)
	Severe (≤30 mL/min)	0 (0)	3 (2)	5 (4)	2 (1)
Analysis by Baseline Diagnosis					
		DORI-03	DORI-05		DORI-06
Gender	Baseline Diagnosis	Doripenem	Doripenem	Levofloxacin	Doripenem
Female	Asymtpomatic cLUTI	NR	5 (2)	0 (0)	5 (2)
	Symptomatic cLUTI	NR	61 (26)	55 (24)	50 (20)
	cLUTI (Total)	17 (25)	66 (28)	55 (24)	55 (22)
	Uncomplicated Pyelonephritis	NR	161 (69)	158 (70)	165 (67)
	Complicated Pyelonephritis	NR	6 (3)	16 (6)	26 (11)
	Pyelonephritis (Total)	50 (75)	167 (72)	174 (76)	191 (78)
Male	Asymtpomatic cLUTI	NR	10 (7)	15 (10)	13 (7)
	Symptomatic cLUTI	NR	107 (75)	107 (74)	145 (82)
	cLUTI (Total)	38 (70)	117 (82)	122 (84)	158 (90)
	Uncomplicated Pyelonephritis	NR	1 (1)	2 (1)	8 (5)
	Complicated Pyelonephritis	NR	25 (17)	21 (15)	10 (6)
	Pyelonephritis (Total)	16(30)	26 (18)	23 (16)	18 (10)

As evidenced from the above table, female subjects were more likely to have normal baseline creatinine clearance whereas the male subjects were more likely to have mild renal impairment in studies DORI-03, DORI-05, and DORI-06. Analysis by baseline diagnosis revealed that the female subjects predominantly had uncomplicated pyelonephritis whereas most of the male subjects had symptomatic cLUTIs. The trends were consistent in both the doripenem and levofloxacin treatment groups in DORI-05. The advanced age of the male subjects likely accounts for the greater proportion of renal insufficiency in that group compared to the younger females. The dichotomy in baseline diagnoses in which women had pyelonephritis predominantly whereas men had cLUTI likely reflects the inherent differences in pathophysiology of cUTI in men and women. Younger women have the highest frequency of cystitis and pyelonephritis, whereas older men have a propensity for cLUTI as a consequence of underlying prostatism. An analysis of the baseline creatinine

clearance of subjects in the doripenem cIAI studies revealed that the majority of male and female subjects had normal renal function despite the differences in median age between the gender groups. Please refer to the following two tables for details.

Table 118: FDA Medical Officer's Analyses of Baseline Creatinine Clearance stratified by treatment group for the phase 3 cIAI Studies. ITT Population

Baseline Creatinine Clearance Group	Combined Doripenem	Combined Meropenem
Normal (≥80 mL/min)	347 (72.75%)	352 (75.05%)
Mild (>50 to <80 mL/min)	92 (19.29%)	79 (16.84%)
Moderate (>30 to ≤50 mL/min)	27 (5.66%)	30 (6.40%)
Severe (≤30 mL/min)	10 (2.10%)	7 (1.49%)
Missing	1 (0.21%)	1 (0.21%)

Table 119: FDA Medical Officer's Analyses of Baseline Creatinine Clearance by Gender for the phase 3 cIAI Studies. ITT Population

Gender	Baseline Creatinine Clearance	Combined Doripenem	Combined Meropenem
		N=477	N=469
Female	Normal (≥80 mL/min)	117 (66)	113 (62)
	Mild (>50 to <80 mL/min)	43 (24)	42 (23)
	Moderate (>30 to ≤50 mL/min)	13 (7)	23 (13)
	Severe (≤30 mL/min)	5 (13)	3 (2)
Male	Normal (≥80 mL/min)	230 (77)	239 (83)
	Mild (>50 to <80 mL/min)	49 (16)	37 (13)
	Moderate (>30 to ≤50 mL/min)	14 (5)	7 (2)
	Severe (≤30 mL/min)	5 (2)	4 (1)
	Missing	1 (0.3)	1 (0.3)

7.2.1.3 Extent of exposure (dose/duration)

The sponsor provided an analysis of safety data related to study drug exposure.
The Phase 1 integrated safety information provided in the original SCS was updated in the four-month safety update to include data from eight healthy subjects who received 500 mg of 14C-doripenem in study DORI-NOS-1007. As a result, a total of 186 healthy subjects with normal function were included in the safety analyses of the Phase 1 studies DORI-01, DORI-02, DORI-04, DORI-NOS-1001, DORI-NOS-1004, DORI-NOS-1005, DORI-NOS-1006, and DORI-NOS-1007. A total of 72 subjects received placebo; 172 subjects received doripenem,including 146 who received 500 mg (eight subjects received 14C-doripenem 500 mg) and 107 who received 1 g. Eighty-one subjects who received both 500 mg and 1 g were counted only once in doripenem total. Due to the crossover designs of studies DORI-NOS-1001 and DORI-NOS-1004, subjects may have received doripenem 500 mg, 1 g, and/or placebo, and are therefore counted once in each treatment group (see table below).

Table 120: Sponsor Table from 4-month safety update report: Distribution of Subjects Included in the Safety Analysis Set by Study and Treatment Group (Phase 1 Studies – All Healthy Subjects from DORI-01, -02, -04, DORI-NOS-1001, -1004, -1005, -1006, and -1007)

Study	Placebo (dosed)	Doripenem 500 mg (dosed)	Doripenem 1 g (dosed)	Doripenem Total (Distinct subjects)	All Distinct Subjects
DORI-01	8	12	12	24	32
DORI-02	0	8	0	8	8
DORI-04	6	6	12	18	24
NOS-1001	58	58	59	60	60
NOS-1004	0	24	24	24	24
NOS-1005	0	6	0	6	6
NOS-1006	0	24	0	24	24
NOS-1007[a]	0	8	0	8	8
Total	72	146	107	172	186

[a] Subjects received 14C-doripenem 500 mg.
Cross References: Clinical Study Reports, Module 5, Section 5.3.3.1, DORI-01, DORI-04, DORI-NOS-1004, DORI-NOS-1007; Section 5.3.3.3, DORI-02, DORI-NOS-1005, DORI-NOS-1006; Section 5.3.5, DORI-NOS-1001

In the pooled Phase 1 studies DORI-01, -02, -04, DORI-NOS-1001, -1004, -1005, -1006, and -1007, the sponsor's analysis revealed that 40% of subjects in the doripenem 500 mg group received four infusions, followed by 32% and 16% who received one and two infusions, respectively. In the 1 g group, 54% of subjects received four infusions and 22% of subjects received one infusion (see table below). All eight subjects in study DORI-NOS-1007 received a single dose of 14C-doripenem 500 mg administered as a 1-hour i.v. infusion.

Table 121: Sponsor Table from 4-month safety update report: Extent of Exposure to Doripenem (Pooled Phase 1 Studies JNJ-38174942: All Subjects With Normal Renal Function in Studies DORI-01, -02, -04, DORI-NOS-1001, -1004, -1005, -1006, and -1007)

	Doripenem	
	500 mg	1 gm
	N=146	N=1-7
Number of Infusions, n (%)	n, (%)	n, (%)
1	46 (32)	24 (22)
2	24 (16)	0 (0)
3	0 (0)	1 (1)
4	59 (40)	58 (54)
13	6 (4)	6 (6)
15	1 (1)	0 (0)
19	5 (3)	6 (6)
20	0 (0)	6 (6)
30	5 (3)	6 (6)

Note: Percentages were calculated with the number of subjects in each group as the denominator.

The FDA Medical Officer has provided a series of tables below that summarize data related to exposure to various treatment regimens (involving IV study drug and oral switch agents) in the doripenem phase 3 cUTI and cIAI studies. It is important to note that a PO switch was permissible in all of the phase 3 studies, such that the overall clinical experience predominantly involved subjects who received IV study drug followed by a PO switch agent. The experience involving IV study drug alone (complete treatment course without

PO follow-up therapy) was a small but significant subset that is assessed elsewhere in this report.

Table 122: FDA Medical Officer Summary of Exposure Data for the Phase 3 Clinical Trials stratified by treatment regimen, ITT population

Median Duration of Treatment Exposure by regimen (days)	Phase 3 Complicated UTI Studies			Phase 3 Complicated IAI Studies			
	DORI-05		DORI-06	DORI-07		DORI-08	
	Doripenem n=376	Levofloxacin n=372	Doripenem n=423	Doripenem n=235	Meropenem n=236	Doripenem n=242	Meropenem n=233
IV (entire ITT)*	5	4	4	6	6	5	5
PO (entire ITT)**	7	7	7	6	6	5	5
Combined IV followed by PO	10	10	10	10	10	9	9
Completed IV, no PO switch	11	11	11	8	7	8	8
Did not complete IV, no PO	3	3.5	3	2.5	3	4	2
Bacteremia (IV duration)	6.5	6	5	NA	NA	NA	NA
Bacteremia, combined IV + PO	14	11	11	NA	NA	NA	NA

NA=not applicable; *refers to the duration of IV study drug irrespective of whether or not the subject completed IV treatment and irrespective of whether or not the subject received oral switch treatment; ** refers to the duration of PO study drug irrespective of the duration of IV therapy preceeding the switch and irrespective of whether or not the subject completed PO treatment

As depicted above, the median number of days that subjects were treated with combined IV study drug followed by PO switch therapy was similar between the two treatment arms of the cUTI and cIAI studies and ranged from 9 to 10 days. In the subgroup of subjects who completed IV study drug without a follow-up PO switch, the median treatment duration with study drug was 11 days in the cUTI studies compared to 8 days in the cIAI studies. Among subjects with bacteremia at baseline in the cUTI studies, the median duration of IV study drug administration was 6 days with the median combined IV plus PO treatment duration of 11 to 14 days. The following tables provide more detailed treatment duration data for each of the phase 3 clinical trials.

Table 123: FDA Medical Officer Summary of Exposure to Study Drug, Phase 3 cUTI studies, ITT population

Treatment Duration Strata	DORI-05				DORI-06	
	Doripenem		Levofloxacin		Doripenem	
	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)
N (ITT)	376	36	372	42	423	72
1-2 days	17 (4.5)	0 (0)	17 (4.6)	0 (0)	13 (3.1)	0 (0)
3-6 days	26 (6.9)	3 (8.3)	50 (13.4)	2 (4.8)	55 (13.0)	8 (11.1)
7-11 days	250 (66.5)	1 (2.8)	224 (60.2)	4 (9.5)	217 (51.3)	6 (8.3)
11-14 days	78 (20.7)	32 (88.9)	76 (20.4)	34 (80.9)	128 (30.3)	57 (79.2)
>14 days	5 (1.3)	0 (0)	5 (1.3)	2 (4.8)	10 (2.4)	1 (1.4)

Treatment Duration, days	DORI-05				DORI-06	
	Doripenem		Levofloxacin		Doripenem	
	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)
N	376	36	372	42	423	72
Mean (SD)	9.55 (2.56)	10.52 (1.86)	9.07 (2.89)	10.55 (2.15)	9.39 (2.96)	10.28 (2.2)
Median	10	11	10	11	10	11
Range	(1, 15)	(4, 13)	(1, 18)	(4, 15)	(1, 20)	(4, 15)

Overall, 1.8% (15/799) of doripenem-treated patients in the cUTI phase 3 studies received combination IV followed by PO switch therapy for a duration beyond 14 days. Among the subgroup of subjects who completed IV study drug without a follow-up PO switch, 0.92% (1/108) of doripenem-treated patients received therapy for a duration beyond 14 days.

Table 124: FDA Medical Officer Summary of Exposure to Study Drug, Phase 3 cIAI studies, ITT population

Treatment Duration Strata	DORI-07				DORI-08			
	Doripenem		Meropenem		Doripenem		Meropenem	
	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)
N (ITT)	235	78	236	73	242	58	233	55
1-2 days	6 (2.6)	0 (0)	4 (1.7)	0 (0)	6 (2.5)	1 (1.7)	10 (4.3)	0 (0)
3-6 days	34 (14.5)	26 (33.3)	33 (14)	22 (30.1)	29 (12)	16 (27.6)	32 (13.7)	17 (30.9)
7-10 days	84 (35.7)	29 (37.2)	84 (35.6)	34 (46.6)	107 (44.2)	23 (39.7)	97 (41.6)	20 (36.4)
11-14 days	72 (30.6)	13 (16.7)	81 (34.3)	12 (16.4)	74 (30.6)	12 (20.7)	63 (27)	15 (27.3)
>14 days	39 (16.6)	10 (12.8)	34 (14.4)	5 (6.8)	26 (10.7)	6 (10.3)	31 (13.3)	3 (5.5)

Treatment Duration, days	DORI-07				DORI-08			
	Doripenem		Meropenem		Doripenem		Meropenem	
	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)	Combined IV + PO	Completed IV (no PO)
Mean (SD)	10.32 (3.66)	8.92 (3.4)	10.37 (3.92)	8.56 (3.07)	9.54 (3.51)	8.81 (3.55)	9.55 (3.62)	9.07 (3.08)
Median	10	8	10	7	9	8	9	8
Range	(1, 17)	(4, 16)	(2, 34)	(4, 15)	(2, 27)	(2, 15)	(1, 16)	(4, 15)

Overall, 13.6% (65/477) of doripenem-treated patients in the cIAI phase 3 studies received combination IV followed by PO switch therapy for a duration beyond 14 days. Among the subgroup of subjects who completed IV study drug without a follow-up PO switch, 11.8% (16/136) of doripenem-treated patients received therapy for a duration beyond 14 days.

Overall, the treatment exposure studied in the doripenem phase 3 clinical trials supports the durations of treatment proposed for the product label by the Sponsor. However, there is very limited human safety data regarding doripenem administered for a treatment duration beyond 14 days, especially when restricted to the subgroup of subjects treated with IV doripenem without PO switch.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Post-marketing spontaneous adverse event reports and information from articles in the published medical literature were used as secondary sources of clinical data to evaluate drug safety.

7.2.2.1 Other studies

7.2.2.2 Postmarketing experience

The FDA Medical Officer conducted a post-marketing safety analysis using the US Food and Drug Administration Adverse Event Reporting System (AERS) for spontaneous adverse event reports involving doripenem. The results of the review are summarized in the following table:

Table 125: FDA Medical Officer List of all Post-marketing Spontaneous Adverse Event Reports for Doripenem* from the Adverse Event Reporting System (AERS) of the US Food and Drug Administration†

Patient	ISR Number	Supect and Concomitant Drugs	Age (YRS)	Gender	Weight	FDA Rcvd Date	Reactions	Outcome
1	5285324	Mycamine, Doripenem, Teichoplanin	71	Male	50 kg	3/28/2007	Eosinophil count increased	Recovering
2	5295477	Pepcid, Doripenem, Teicoplanin	43	Female	NR	4/12/2007	Drug eruption, liver disorder	Resolved
3	5227699	Klarcid, Doripenem, Cefmetazole, Meropenem, Erythromycin, Doxapram	Elderly	Female	NR	2/2/2007	Hepatic failure, fulminant hepatitis, respiratory failure, depressed level of consciousness	Death
4	5344173	Cellcept, Doripenem, Inovan, Diltiazem, Neo-minophagen C, Acyclovir, Solu-cortef, Alprostadil, Fragmin, Halzion, Vfend, Ciproxan, Rebetol, Urso, Zyvox	18	Male	48	6/4/2007	Abdominal distension, Endotoxic shock	Death
5	5146358	Linezolid, Micafungin, Gabexate mesilate, Doripenem, Teichoplanin, Venoglobulin-IH	55	Male	NR	11/2/2006	Agranulocytosis, Candidiasis, chills, erythema,pyrexia, Respiratory failure, Shock	Recovering
6	5380849	Doripenem, Glovenin, Gasmotin, Zantac, Elaspol, Miraclid, Mucodyne, Neuart, Probitor, Solu-cortef, Inovan, Noradrenaline, Propofol	Elderly	Male	NR	7/6/2007	Liver Disorder, Platelet count decreased, Renal impairment, Respiratory failure, Sepsis	Death
7	5388558	Dalacin S, Cefepime, Doripenem, chemotherapy	75	Male	NR	7/16/2007	Interstitial lung disease	Death
8**	5392296	Cercine, Doripenem, Rohypnol, Flumarin, Polaramine, Myslee, Ubretid, Amoban, Phenobarbital, Takepron, Neo-minophagen C, Voltaren, Selbex, Loxonin, Bayaspirin, Naixan, Tegretol, Solu-medrol, Magmitt, Spelear, Pasil, aminofluid, Laxoberon, Mohrus, Rinderon-VG	70	Male	60 Kg	7/20/2007	Liver disorder, Oculomucocutaneous Syndrome, Sepsis	Death
9**	5392301	Perdipine, Myslee, Sennoside, Humulin R, Albumin, Aminotripa, Bisolvon, Cataclot, Neolamin Multi V, Novo-heparin, Omepral, Pansporin, Radicut, Ropivacaine, Mobic, Takepron, Voltaren, Wakobital, Phenobarbital, Bisolvon, Magnesium oxide, Bayaspirin, Neo-minophagen C, Laxoberon, Ubretid, Rohypnol, Spelear, Flumarin, Mohrus, Loxonin, Rinderon, Doripenem, Pazufloxacin mesilate, Solu-medrol, Amoban, Naixan, Tegretol, Polaramine, Cercine, Selbex, Aminofluid	70	Male	NR	7/20/2007	Stevens-Johnson Syndrome	Death

10**	5397452	Naixan, Rohypnol, Doripenem, Flumarin, Polaramine, Cercine, Myslee, Ubretid, Amoban, Phenobarbital, Neo-minophagen C, Voltaren, Takepron, Selbex, Bayaspirin, Tegretol, Solu-medrol, Loxonin, Aminofluid, Magmitt, Pasil, Spelear, Laxoberon, Mohrus, Rinderon-VG, Sennoside, Humulin-R, Soldem, Aminotripa, Anapeine, Bisolvon, Cataclot, Heparin novo, Human albumin, Low Molecular Dextran, Mobic, Omepral, Pansporin, Perdipine, Potacol-R, Radicut, Wakobital, Bisolvon, Potacol-R, Neolamin Multi V	70	Male	NR	7/26/2007	Liver disorder, Oculomucocutaneous Syndrome, Sepsis	Death

*All cases originate from Japan; ** The reports refer to the same patient; NR=not reported;
†accessed on August 2, 2007

The following brief synopses of each case are derived from the individual AERS reports:
Report # 5285324: The patient was a 71 year old male from Japan who experienced increased eosinophil count during treatment with doripenem, teicoplanin, and micafungin. His medical history included chronic renal failure, ischemic gastroenteritis, psoas abscess, and deep mycosis. He developed an increased eosinophil count of 32% on the second day of such therapy. Three days later, the eosinophil count increased to 72%, and doripenem and teichoplanin were discontinued the next day. Over the subsequent seven days, the eosinophil count decreased to 50%. Five days later, the eosinophil count declined to 24%. The reporting nephrologist commented that doripenem and teicoplanin possibly resulted in the increase in eosinophil count.

FDA Medical Officer Comments: The patient was receiving multiple drugs during the time that the increased eosinophil count developed. Although the report indicates a positive dechallenge response, assessment of causality is confounded by the multiple concomitant medications.

Report #5295477: This was a 43 year old female from Japan with acute promyelocytic leukemia who was treated with teichoplanin and doripenem for acute tonsillitis due to MRSA. Four days after initiation of those drugs, she developed increased serum liver enzymes. Both drugs were discontinued the following day in view of continued rise in the enzyme levels. She developed a rash across her chest and arms three days later. She was treated with Zyrtec and Almeta for the rash. The liver enzyme abnormalities resolved 12 days after discontinuation of the two drugs. The rash resolved afterwards (later in the same month). A drug lymphocyte stimulation test (DLST) and a patch test for doripenem were negative, whereas the the DLST for teichoplanin was positive. The reporting physician considered teichoplanin and doripenem as possible causative agents. Famotidine was another suspect concomitant drug.

FDA Medical Officer Comments: Teichoplanain is the more likely causative drug in view of the positive DLST and positive dechallenge. However, as doripenem was administered concurrently, it is not possible to completely rule-out a contributory role in the development of the adverse events described.

Report #5227699: This elderly female from Japan was treated initially with cefmetazole for pneumonia. Three days later, she was begun on Klaricid for the same indication. Cefmetazole was discontinued, and Meropenem was begun one day later. Erythromycin was begum for the treatment of pneumonia 11 days later, while Klaricid was discontinued. The patient experienced respiratory failure, and she was begun on Doripenem hydrate and Doxapram hydrochloride hydrate. One day later, the patient had a depressed level of consciousness and was diagnosed with fulminant hepatitis. Erythromycin, Meropenem, Doripenem hydrate, and Doxapram hydrochloride hydrate were discontinued. The patient died of fulminant hepatitis, respiratory failure, and hepatic failure according to the report. The reporting physician reported that fulminant hepatitis was probably related to erythromycin for injection, but considered Klaricid, Cefmetazole, Meropenem, Doripenem hydrate, and Doxapram hydrochloride hydrate as suspect drugs.

FDA Medical Officer Comments: In this case, there was a temporal relationship between the onset of hepatic failure/fulminant hepatitis and the administration of doripenem. However, the duration of doripenem use was quite brief, and the report did not provide specific details or laboratory test results.The overall assessment of this case was confounded by various concomitant antibacterial agents that could also be hepatotoxic.

Report #5344173: This 18 year old male from Japan who was developed the sensation of abdominal distension while receiving cellcept as prophylaxis for graft versus host disease. He died of endotoxic shock.

FDA Medical Officer Comments: Few details were provided in the report. Doripenem was a concomitant drug, although details regarding the indication, dosage, duration, and potential relationship to the adverse events was not provided. There was insufficient information to determine a causality assessment for the drug.

Report #5146358: This is a follow-up report for Mfr Report # JP-JNJFOC-20060801543 in the following table of spontaneous reports of agranulocytosis in subjects treated with doripenem. According to this report, the reporting physician felt that doripenem was probably not involved in the development of agranulocytosis and was more concerned about an association of the event with bone marrow depression that has been observed in some patients treated with linezolid.

Report #5380849: This 66 year old male from Japan was treated with doripenem for sepsis. He developed renal impairment, decreased platelets, exacerbation of liver disorder, and respiratory failure beginning the day after initiation of the drug. He received multiple medical interventions, including mechanical ventilation. Doripenem was discontinued six days later due to aggravation of his medical condition. He died three days after doripenem was discontinued; sepsis was considered to be the cause of death. According to the

reporter, the adverse events were most likely related to septic shock, but could not completely rule-out doripenem in relation to the events of renal impairment, decreased platelets, and respiratory failure.

FDA Medical Officer Comments: Sepsis and septic shock are the probable causes of the patient's adverse events, although there is a temporal association with doripenem administration.

Report #5388558: This 75 year old male was treated with doripenem and clindamycin for interstitial pneumonia while receiving chemotherapy for lung cancer. He died at a later date, but no details were provided in the report. The action taken with respect to his antibiotic therapy was not described.

FDA Medical Officer Comments: The limited data does not permit an assessment of causality with respect to administered drugs.

Report #5392296 (reports 5392301 and 5397452 refer to the same patient): This 70 year old male experienced sepsis, liver disorder, and Stevens Johnson Syndrome following a left upper lobectomy for lung cancer. Post-operatively, he developed an acute cerebral infarction, pleural effusion, fever, and liver function test abnormalities. He required parenteral hypereralimentation and oral antibiotics (Flumarin), which the reporter felt may have contributed to the liver enzyme elevations. Doripenem was started approximately 28 days post-operative for a few days for the treatment of fever. The patient was managed in a rehabilitation center intermittently, but deteriorated with fever, rash, bloody stools (hemorrhoids), and respiratory failure. He was treated with levofloxacin, but had worsening rash, decreased platelet counts, and no improvement in fever. He developed a progressive right lung infiltrate and was switched to teichoplanin and oral vancomycin (for MRSA in stools). He experienced respiratory failure, required ventilator support, and eventually had a tracheostomy. MRSA was isolated from his blood cultures 51 days post-op. He developed septic shock and died.

FDA Medical Officer Comments: Although doripenem was a concomitant medication, the duration of treatment was short, and assessment of causality was confounded by multiple concomitant medications and post-operative infective complications.

The FDA Medical Officer reviewed spontaneous adverse event reports of agranulocytosis involving doripenem that were submitted by the Sponsor during the post-marketing phase of the drug development program. The results of the review are summarized in the following table:

Table 126: FDA Medical Officer Summary of Spontaneous Adverse Event Reports of Agranulocytosis in subjects treated with Doripenem:

Mfr Control # Location	Age/Gender	Outcome	Indication Dose	Event	Concomitant Medications
JP-JNJFOC-20060605510 Japan	77/Male	Recovered	Pneumonia 1 gm/day	Agranulocytosis	Vancomycin* Imipenem/cilastatin Meropenem Lansoprazole Oxycodone Amlodipine Morphine Neurotropin Erythromycin Afloqualone Tienam Ecabet Mecobalamin Loxoprofen Magnesium oxide Teprenone Haloperidol Verapamil Loratadine Meloxicam Glimepiride Spironolactone
A 77 year old male patient in Japan who was hospitalized with pain and decreased appetite due to prostate cancer with bone metastases developed a right lung abscess and was treated with ceftriaxone, but did not improve. Subsequently, ceftriaxone was discontinued and he was treated with meropenem. He later developed MRSA in his sputum cultures, and was treated with vancomycin. He was changed from meropenem to doripenem after approximately nine days due to concomitant development of pneumonia in the left lung. He developed agranulocytosis during treatment with doripenem and vancomycin concurrently for pneumonia. Doripenem had been administered for 10 days and vancomycin had been administered for about three weeks prior to onset of the event. His granulocyte count decreased to 0.0 according to the report. His antibiotics (doripenem and vancomycin) were discontinued, and he was changed to imipenem/cilastatin, which was discontinued due to declining neutrophil counts. He was then changed to cefepime. He eventually recovered from the event agranulocytosis following treatment with lenograstim.					
JP-JNJFOC-20060801543 Japan	55/Male	Recovered	Pneumonia 500 mg/day	Agranulocytosis	Linezolid*
A 55 year old male patient in Japan who was treated with doripenem and linezolid for pneumonia following surgery for esophageal cancer was diagnosed with agranulocytosis. The patient's peripheral WBC count decreased to 1,200 with 0% neutrophils. Doripenem and linezolid were discontinued on the fifth day of treatment. He was given granulocyte colony stimulating factor, but no change was reported. His WBC count returned to normal approximately 2½ weeks after discontinuation of the two antibiotics, and the patient gradually recovered. Drug lymphocyte stimulation tests were negative for doripenem and linezolid according to the report. He was not rechallenged with doripenem.					
JP-JNJFOC-20060906570 Japan	53/Male	Recovered	Renal abscess 750 mg/day	Agranulocytosis	Meropenem* Fosfluconazole* Prodif
A 53 year old male patient in Japan with a history of gastric cancer developed agranulocytosis after receiving doripenem, meropenem, and fosfluconazole for sepsis due to a renal abscess. The patient's medical history included *Candida spp* infection and hepatic cirrhosis. He was treated with haloperidol for delirium. Doripenem had been discontinued approximately two weeks prior to the onset of the event. His neutrophil count decreased to as low as 0.5%. He was treated with lenograstim, and the agranulocytosis resolved. The patient was not treated with chemotherapy or radiation for gastric cancer. Bone marrow examination was not performed.					

*co-suspect concomitant drug

In the first two cases, there was a temporal relationship between the onset of agranulocyosis and the administration of doripenem. However, assessment was confounded by concomitant medications and medical illnesses that can have adverse hematologic effects. Data regarding fever or shock was not reported in any of the three cases.

Finally, the FDA Medical Officer reviewed multiple spontaneous post-marketing adverse event reports that were provided by the Sponsor relevant to doripenem over the past two years. The reports involved various entities, including hypotension, seizure/convulsion, renal impairment, abnormal hepatic function, interstitial lung disease, toxic epidermal necrolysis, and Stevens Johnson Syndrome. Causality assessment was difficult in many cases due to underlying or concurrent medical illnesses, ongoing sepsis, and concomitant medications. However, the following spontaneous reports were considered to be medically significant:

Table 127: FDA Medical Officer Summary of Spontaneous Adverse Event Reports for Doripenem

Mfr Control #	Age/Gender	Event	Indication for doripenem	Outcome for event	Concomitant Medications
2006D1000109	80/Male	Stevens Johnson Syndrome	Sepsis	Recovered	Piperacillin
An 80 year old male developed Stevens Johnson Syndrome following treatment with doripenem for sepsis. The patient had been treated with piperacillin initially, but was changed to doripenem due to a high CRP and decreased blood pressure. The drug was administered for three days prior to the onset of exanthema and reddening of the face, oral mucosal erosion, and conjunctivitis. Doripenem was withdrawn and replaced by ampicillin/sulbactam. Subsequently, the event improved. His medical history included multiple cerebral infarcts and myocardial infarction.					
2006D1000103	80/gender not specified	Toxic epidermal necrolysis	Pneumonia	Improved	Teichoplanin, ledermycin
An 80 year old patient developed toxic epidermal necrolysis (TEN) following doripenem treatment for *Pseudomonas aeruginosa* bacteremia and pneumonia. The patient had been hospitalized for injuries and multiple fractures sustained following an automobile accident. Doripenem was administered for six days and then discontinued secondary to improvement, but it was restarted 11 days later due to re-emergence of *P. aeruginosa* in the sputum. Teichoplanin was also administered for methicillin-resistant *S. aureus* in the sputum. Doripenem was re-administered for two days before the onset of the rash. The rash progressed, became exfoliative, bullae formation was noted over the entire body, and there was involvement of the oral mucous membranes. A dermatologist diagnosed a fulminant drug eruption and considered the rash to be suspect for a TEN-type rash. Doripenem was discontinued, and high dose prednisolone was begun with some improvement. A few days later, the patient experienced sepsis and pneumonia due to methicillin-resistant *Staphylococcus aureus* and died. The death was not considered to be related to doripenem. The patient's past medical history included pneumonia, brain contusion, subarachnoid hemorrhage, and pelvic fracture.					
2005D1000297	26/Male	Hypotension	Ventilator-associated pneumonia (VAP)	Recovered	Dexametatomidine, suxamethonium, midazolam, rocuronium, maxalon, ranitidine, insulin, paracetamol, erythromycin, ceftriaxone, vecuronium
A 26 year old male enrolled in study DORI-10 with VAP experienced hypotension five minutes after receiving doripenem. He had been hospitalized with possible viral encephalitis and required mechanical ventilator support. He had no significant past medical history or drug allergies. The hyotension was unresponsive to a 1,000 ml normal saline bolus. Doripenem was discontinued, and inotropic (noradrenaline) treatment was initiated. Ciprofloxacin, gentamicin, and timentin were begun for treatment of pneumonia. According to the investigator, the event was not part of an anaphylactic reaction.					
2006D1000090	54/Male	Interstitial lung disease/pneumonia	Cellulitis	Recovered	Meropenem, kanamycin, lansoprazole, irsodeoxycholic acid, isoleucine/leucine-valine, magnesium oxide, amino acid preparation
A 54 year old male had been treated with doripenem for five days for cellulitis when he developed interstitial pneumonia (characterized by dyspnea, cough, and bilateral ground glass appearance on chest x-ray). He had initially been treated with meropenem, but was changed to doripenem for unclear reasons. Doripenem was discontinued, and he was treated with pulse steroids (methylprednisolone sodium) for three days for the interstitial pneumonia and recovered. His past medical history was remarkable for cellulitis and alcoholic cirrhosis.					
2005D10000284	63/Male	Convulsion	Pneumonia	Recovered	Meropenem, omeprazole, ursodeoxycholic acid, theophylline, isepamicin sulfate
A 63 year old male had been treated with doripenem for five days for pneumonia when he experienced a convulsion. He had a history of alcoholic cirrhosis and diabetes mellitus. He initially had been treated with meropenem and theophylline with isepamicin sulfate added the following day. However, he did not improve and showed evidence of bronchial pneumonia that prompted the change to doripenem. He experienced a generalized convulsion on the fifth day of doripenem treatment. Doripenem was discontinued, and he was treated with diazepam. Phenobarbital, and methylprednisolone, but the seizure was difficult to control. He subsequently developed a gastrointestinal bleed, declined further clinically, and later died. According to the reporting physician, hyperammonemia, hypoxia, hyponatremia, theophylline, and doripenem may have contributed to the onset of the seizure. Death was attributed to the gastrointestinal bleeding.					

The FDA Medical Officer recommends that Stevens Johnson Syndrome, toxic epidermal necrolysis, [redacted] and interstitial pneumonia should be incorporated into the product label for the following reasons: their seriousness and medical significance, their temporal association with doripenem administration, the action taken was withdrawal of the drug in response to the events, the improvement observed in the events (Stevens Johnson, TEN, interstitial pneumonia) following steroid treatment, and their similarity to events considered typical of severe drug-induced adverse reactions associated with other beta-lactam and carbapenem class agents.

The FDA Medical Officer also recommends inclusion of information regarding seizures in the product label and recommends post-marketing surveillance in doripenem- treated

patients. In addition to the patient described in the table above, there were several other post-marketing reports of patients who developed seizures associated with doripenem administration (2005D1000340, 2004D1000081, and 20070804616). However, those subjects had predisposing conditions for seizure (such as subdural hematoma, subarachnoid hemorrhage, and low serum phenytoin concentrations) that made causality assessment difficult.

7.2.2.3 Literature

The carbapenems are a class of parenteral beta-lactam antibiotics that includes three FDA-approved agents, imipenem-cilastatin, meropenem, and ertapenem. Diarrhea (including *Clostridium difficile*-related diarrhea and colitis), nausea, headache, rash, and transient elevations of liver enzymes are adverse reactions reported in various clinical studies involving each of those drugs.[5] Imipenem-cilastatin has a propensity to induce seizures (especially with high doses and in renal impairment) requiring careful monitoring of patients at risk for neurotoxicity. Phlebitis and infusion-site reactions have been reported with ertapenem.[6] Interactions between carbapenems (meropenem and ertapenem) and valproic acid (VPA) resulting in recurrence of seizures have also been described in the medical literature.[7,8] The mechanism underlying the drug-drug interaction is uncertain, although animal data suggests that carbapenems inhibit the hydrolysis of VPA-glucuronide to VPA, resulting in decreased serum VPA levels.[9]

Based upon the phase 3 doripenem experience, the drug appears to share some of the common adverse reactions observed with other carbapenems, including headache, phlebitis, lievr enzyme elevations, and gastrointestinal disorders. However, in animal studies, the drug has not demonstrated the potential to induce convulsions,[10] and no doripenem-treated subjects in the phase 3 clinical studies experienced a seizure. Furtehr studies are needed to assess whether doripenem has the propensity to interact with VPA in a manner similar to the other carbapenems in reducing VPA levels. A phase 1 study is planned by the Sponsor.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience of patients exposed to doripenem, including elderly, hepatic-impaired, and renal-impaired, was adequate. The doses and durations of drug exposure studied were adequate to assess the drug's safety for the intended use in the treatment of cUTI and cIAI. The safety population (ITT) encompassed a total of 216 subjects in multiple pooled phase 1 studies (including 32 with renal impairment and 12 who were hemodialysis-dependent), 121 subjects in a single phase 2 study, and 1,276 subjects in the four phase 3 studies who were treated with doripenem and a combined total of 841 comparator-treated subjects (372 levofloxacin-treated and 469 meropenem-treated). There are sufficient numbers of subjects to assess common adverse events in doripenem-treated subjects compared to comparator-treated subjects. Potential class-related adverse events were assessed, including gastrointestinal disorders, seizure, *C. difficile* diarrhea and colitis, hepatic and renal toxicity.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please refer to the review of Dr. Wendlyn Schmidt for details.

7.2.5 Adequacy of Routine Clinical Testing

In general, routine clinical testing of study subjects appeared adequate in the conduct of the clinical studies. However, additional information (narratives and laboratory data) was requested during the review process with respect to hepatic, hematologic, and renal adverse events.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please refer to the report of the Clinical Pharmacology reviewer for details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Sponsor attempted to adequately evaluate and analyze adverse events of special interest for the carbapenem and β-lactam classes of antibacterial agents, including drug intolerability, allergic (hypersensitivity) reactions, seizure, *C. difficile* diarrhea, and phlebitis. However, as the combined phase 3 clinical study experience was not sized and statistically powered for safety as the primary endpoint, continued post-marketing surveillance for these adverse events is highly recommended.

7.2.8 Assessment of Quality and Completeness of Data

There were multiple difficulties encountered in accessing the Sponsor's Integrated Summary of Safety (ISS) electronic datasets. Some of the ISS laboratory dataset files were of excessive size and would not open or required excessive time to open on government computer equipment such that they were unusable for computational and analysis purposes. Duplicate files appeared to contribute to large file sizes. The laboratory datasets were structured to provide cross-sectional data at specific timepoints, but did not render longitudional data assessment readily. In addition, the lack of CDISC format contributed to incompatibility of the electronic data with the Integrated Review computer-based program used by the Agency in the safety analysis and construct patient profilesw. Some of the ISS laboratory electronic datasets required revision with the assistance of the Sponsor, as FDA statisticians and computer programmers were unsuccessful in rectifying the relevant issues.

7.2.9 Additional Submissions, Including Safety Update

The Sponsor provided a four-month safety update of Module 2.7.4 to provide additional safety data on doripenem in healthy subjects and subjects with cUTI, cIAI, and NP that became available during the period from September 1, 2006 through December 12, 2006.

The Safety Update included the following data:
• Safety data from one completed Phase 1 study (DORI-NOS-1007). DORI-NOS-1007 was an open-label, single-center, single-dose study designed to characterize the routes of

excretion of doripenem and to elucidate the metabolic pathways and structures of predominant metabolites of doripenem in eight healthy men.
• Listings of deaths, discontinuations due to AEs, and SAEs from the two recently completed Phase 3 NP studies DORI-09 and DORI-10.
• Listings and tabulations of data inadvertently omitted from summary tables provided in the original cIAI/cUTI Clinical Study Reports (CSRs) and/or SCS submitted as part of NDA 22-106. As such, the following are being provided at this time:
– Listings and tabulations of AEs that were not included in the summary tables for the CSRs and SCS due to either: 1) onset date 30 days after last dose, 2) missing AE onset date, 3) missing date of last dose; and listings of AEs that were not treatment emergent but were included as such in the CSR listings
– Listings of subjects who received >250 mg doses of levofloxacin during the cUTI studies DORI-05 and DORI-06.
– Updated summaries of the incidence of phlebitis AEs before and after site education and implementation of the new Case Report Form (CRF) worksheet to correct for different sites that were identified using the same number in the database.
– Listings of laboratory test results for 15 subjects that were inadvertently omitted from the original CSRs and SCS due to a baseline misidentification. The 15 subjects included five in DORI-05, nine in DORI-07, and one in DORI-08. In addition, there were 28 subjects inadvertently omitted from the SCS at some time points due to incomplete times of laboratory sample collection. The 28 subjects included 12 in DORI-03, seven in DORI-05, eight in DORI-07, and one in DORI-08. Three of the 28 subjects had normal baseline laboratory values that increased to Grade 3 or 4 during the study, including one levofloxacin-treated subject in DORI-05 and two meropenem-treated subjects in DORI-07.
• An update of the commercial marketing experience and foreign regulatory actions for doripenem covering the period 01 September 2006 through 12 December 2006. Doripenem is currently approved only in Japanand has not been the subject of a marketing application elsewhere. The Sponsor reports that no new safety issues or labeling changes have been identified for the Japanese label.
• An update of all post-marketing events occurring with doripenem, including spontaneous AEs reported in Japan to Shionogi, entered into the Benefit Risk Management worldwide safety database (SCEPTRE) covering the period 01 September 2006 through 12 December 2006. The search of SCEPTRE retrieved 15 new spontaneous, medically confirmed cases with doripenem as a suspect or suspect-interacting drug for the specified reporting period. The cases included agranulocytosis (1), hepatic function abnormal (8), pneumonia chlamydial (1), drug exposure during pregnancy (1), depressed level of consciousness (1), myoclonus (1), abortion spontaneous (1), interstitial lung disease (1), and urticaria (1).
• An update of safety information from published literature covering the period 01 September 2006 through 12 December 2006.

Table 128: Sponsor Summary Table of Studies included in 4-Month Safety Update (adapted from Table 1, 4-Month Safety Update of Module 2.7.4 – Summary of Clinical Safety of Doripenem)

Completed Phase 1 Pharmacokinetic and Safety Study in Healthy Subjects		
DORI-NOS-1007	OL, SD, PK study of the metabolism and excretion of doripenem in healthy men. Safety and tolerability were also assessed. 14C-doripenem 500 mg infused over 1-hour	N=8 healthy subjects All subjects received14C-doripenem: 500 mg over 1h, once
Completed Phase 3 Efficacy and Safety Studies		
DORI-09	Multicenter, OL, randomized, comparison study of safety and efficacy of i.v. doripenem and i.v. piperacillin/tazobactam in non-ventilated subjects with HAP or subjects with early-onset VAP. Doripenem i.v. 500 mg infused over 1 hour q8h or Piperacillin/tazobactam i.v. 4.5 g over 30 min q6h; 7 to 14 days (i.v. or i.v. + oral) with option to switch to oral levofloxacin (750 mg q.d.) after Day 3	N=440 doripenem: n=220 piperacillin/tazobactam: n=220
DORI-10	Multicenter, OL, randomized, comparison study of safety and efficacy of i.v. doripenem and i.v. imipenem in subjects with VAP Doripenem i.v. 500 mg infused over 4 hours q8h or Imipenem i.v. 500 mg over 30 min q6h, or 1 g over 1 hour q8h, 7 to 14 days, (i.v. only)	N=520 doripenem: n=260 imipenem: n=260

Key: h=hour; HAP=hospital-acquired pneumonia; i.v.=intravenous; OL=open-label; PK=pharmacokinetics; q6h=every 6 hours; q8h=every 8 hours; q.d.=once daily; sd=single dose; VAP=ventilator-associated pneumonia
a Deaths, discontinuations due to AEs, and SAEs reported from 01 September 2006 through 12 December 2006 are included in this summary.

Important safety data from the update report included the following:
1. No deaths occurred during the Phase 1 studies. There were no treatment-emergent serious adverse events for subjects with normal renal function in the phase 1 studies.
2. During the period of September 1, 2006 to December 12, 2006, 56 subjects died during the phase 3 doripenem nosocomial pneumonia (NP) studies DORI-09 and DORI-10. Of those patients, 22 were enrolled in DORI-09 and 34 were enrolled in DORI-10 during the reporting period. The treatment arm assignment and patient narratives were not provided in the safety update.
3. During the reporting period, 106 subjects experienced treatment-emergent serious adverse events in studies DORI-09 and DORI-10. In DORI-09, 39 subjects experienced 46 serious adverse events. In DORI-10, 67 subjects experienced 90 serious adverse events. Four events in four subjects in DORI-10 were considered possibly related to study drug by the investigators: liver function test abnormal (1), rash (1), complex partial seizure (1), and status epilepticus (1). The treatment arm assignment was not provided in the safety update.
4. In relation to adverse events leading to discontinuation during the reporting period, 15 subjects discontinued in Study DORI-09 and 12 discontinued from DORI-10. One subject in DORI-09 had moderate diarrhea considered possibly related to study drug by the investigator. Seven of the adverse events in subjects in DORI-10 were considered related or possibly related to study drug, including rash, pyrexia, liver function test abnormal, hepatic enzyme increase, blood disorder and cholestasis.
5. Data related to adverse events of special interest revealed no new information regarding drug intolerability associated with doripenem from the phase 2 and phase 3 studies during the reporting period. There was no new information reported by the sponsor related to possible allergic reactions, seizures associated with doripenem use, and *Clostridium*

difficile colitis.
6. An updated summary of the incidence of phlebitis as a treatment-emergent adverse event during the reporting period was presented for the pooled phase 3 studies. The sponsor provided a summary of the National Institutes of Health guideline for insertion and maintenance of i.v. catheters to all sites participating in the phase 3 studies and a new CRF worksheet was introduced to collect additional information on adverse events reported as phlebitis.

An updated summary of the incidence of TEAEs of phlebitis during the i.v. treatment period before and after 17 May 2005 is presented for the pooled Phase 3 studies in the following table. Prior to 17 May 2005, high-incidence sites reported TEAEs of phlebitis at a rate of 39.1% (a change of +0.1% from the previous SCS). Following 17 May 2005, the incidence of phlebitis decreased to 23.3% (a change of –1.3% from the previous SCS). At sites identified as standard-incidence sites, the rate of TEAEs of phlebitis remained relatively stable. Overall, after 17 May 2005, the rate of AEs reported as phlebitis decreased from 6.2% to 4.4% (no change from the previous SCS).

Table 129: Sponsor's Summary Table of Phlebitis During i.v. Therapy
(Pooled Phase 3 Studies JNJ-38174942-DORI-05, 06, 07, 08: Safety Analysis Set)

	High-Incidence Sites (a) n/N (%)	Standard-Incidence Sites(b) n/N (%)	Enrolled Only Before (c) 17 May 2005 n/N (%)	Enrolled Only After (d) 17 May 2005 n/N (%)	Total n/N (%)
Phlebitis before site education	54/138 (39.1)	21/927 (2.3)	3/185 (1.6)	0	78/1250 (6.2)
Phlebitis after site education	14/60 (23.3)	23/730 (3.2)	0	1/77 (1.3)	38/867 (4.4)
Phlebitis, total	68/198 (34.3)	44/1657 (2.7)	3/185 (1.6)	1/77 (1.3)	116/2117 (5.5)

N: number of subjects treated in each category; n: number of subjects with phlebitis.
(a) Sites with incidence rate of phlebitis during the i.v. treatment period >25% before site education, and enrolled at least one subject both before and after site education.
(b) Sites with incidence rate of phlebitis during the i.v. treatment period ≤25% before site education, and enrolled at least one subject both before and after site education.
(c) Sites that enrolled at least one subject before site education, but did not enroll any subjects after site education.
(d) Sites that enrolled at least one subject after site education, but did not enroll any subjects before site education.
Note: A subject was counted once if the subject reported one or more occurrences of phlebitis with onset during i.v. study drug therapy. Events were coded under MedDRA 9.0 preferred term of 'Phlebitis'.
tae41_tph01.rtf

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The treatment-emergent adverse events that were assessed as related to study drug by investigators are summarized for the comparative clinical trials in the doripenem phase 3 program in section 7.1.5.5 of this report. The FDA Medical Officer selected the following drug-related treatment-emergent adverse events for further discussion due to the high incidence of the events in the doripenem phase 3 safety population, the potential for substantial disability associated with the adverse events, or evidence of worrisome trends in subgroup exploratory analyses that require further post-marketing surveillance and study.

Important limitations of the safety data include the following issues: 1) The subgroup of

patients treated with doripenem without a PO switch was small compared to the overall size of the pooled ITT population in the Phase 3 clinical trials. The small size of this population subgroup limited the ability of the FDA Medical Officers to derive meaningful differences between doripenem and comparator-treated subjects with respect to various aspects of the efficacy and safety evaluation of the drug. 2) There was a lack of systematic collection of information about the quantity of intra-operative and peri-operative blood loss in patients enrolled in the cIAI studies who had abdominal surgery. 3) There was a lack of uniform collection of blood transfusion data. 4) There was a lack of direct Coombs test results on patients enrolled in both of the doripenem phase 3 cUTI studies and in the remainder of the subjects in the cIAI studies.

7.3.1 Rash

In the doripenem phase 3 studies, rashes were reported with greater incidence in the doripenem-treated subjects compared to the comparator patients treated with levofloxacin and meropenem. Study drug was withdrawn in one doripenem-treated patient in DORI-07 (Subject #04702056) who developed a diffuse rash. In general, the rashes appeared a median of 6.5 days from the start of study drug, and they were of mild to moderate severity. Please refer to Section 7.1.4 for additional details.

As drug-induced rash has been reported with other β-lactan and carbapenem antibacterial agents, rash is not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the rashes observed in in some of the treated patients and, thus, recommends that rash be included in the ADVERSE REACTIONS section of the proposed product label.

7.3.2 Hypersensitivity Reactions

Hypersensitivity/allergic reactions were reported in the phase 2 and phase 3 doripenem studies. There was one subject in the phase 2 study, DORI-03, who experienced a serious allergic reaction (laryngeal obstruction) to doripenem. The investigator discontinued the drug and the patient was withdrawn from study participation. The patient was treated with hydrocortisone and diphenhydramine for the event. In the four phase 3 studies, eight doripenem-treated, one levofloxacin-treated, and two meropenem-treated subjects experienced hypersensitivity reactions. None of the doripenem-treated subjects required study drug withdrawal, although study drug was withdrawn in one of the the meropenem-treated subjects. None of the allergic reactions in the phase 3 studies were assessed as serious by the investigators. Please refer to Section 7.1.4 for additional details.

As hypersensitivity reactions have been reported with other β-lactan and carbapenem antibacterial agents, they are not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in in some of the treated patients and, thus, recommends that hypersensitivity reactions be included in the ADVERSE REACTIONS section of the proposed product label.

The Sponsor has included text in the proposed label in the WARNINGS AND PRECAUTIONS Section as follows:

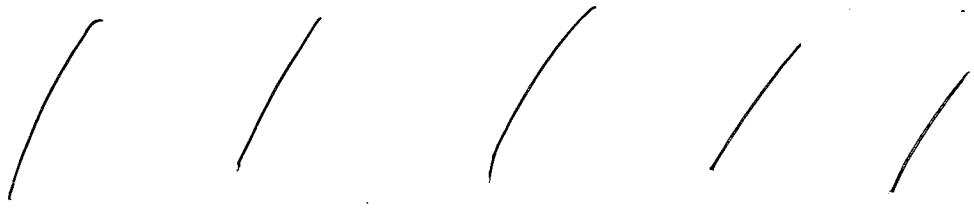
Hypersensitivity Reactions:

> Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with TRADENAME™ is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other carbapenems, cephalosporins, penicillins or other allergens. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross-hyperreactivity among beta-lactam antibiotics has been clearly documented. If an allergic reaction to TRADENAME™ occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

7.3.3 *Clostridium difficile* diarrhea and colitis

Clostridium difficile diarrhea and colitis was not reported in the phase 1 and 2 studies, but the illness was reported in four doripenem-treated, no levofloxacin-treated, and one meropenem-treated subject in the phase 3 studies. None of the adverse events was assessed as serious by investigators, and the affected patients responded to treatment with metronidazole. In three of the four doripenem-related cases, the study subjects had received additional antibacterial agents that may have contributed to the development of the illness. Please refer to Section 7.1.4 for additional details.

As *Clostridium difficile* diarrhea and colitis have been reported with other β-lactan and carbapenem antibacterial agents, they are not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in in some of the treated patients and, thus, recommends that *Clostridium difficile* diarrhea — be included in the ADVERSE REACTIONS section of the proposed product label. The Sponsor has included text in the proposed label in the WARNINGS AND PRECAUTIONS Section as follows:



7.3.4 Oral and vaginal fungal infection-related adverse events

Oral and vaginal fungal infection-related TEAEs were observed in doripenem and comparator treated subjects in the phase 3 studies with the highest incidence in the pooled doripenem experience. In the three comparative phase 3 studies, the incidence of such TEAEs in the combined doripenem groups was 2.23%, which was higher that that reported in the levofloxacin group (0.27%) and the combined meropenem group (1.71%). Oral and vaginal fungal infection-related TEAEs were considered to be drug-related in 30 subjects, including 21 doripenem-treated, one levofloxacin-treated, and eight meropenem-treated patients. All of the drug-related TEAEs were mild to moderate in severity, and none of them were assessed as serious. Please refer to Section 7.1.4 for additional details.

As oral and vaginal fungal infection-related adverse events have been reported with other β-lactan and carbapenem antibacterial agents, they are not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in in some of the treated patients and, thus, recommends

7.3.5 Headache

In the doripenem phase 1, 2, and 3 studies, headache was one of the most commonly reported treatment-emergent and drug-related adverse events. In the pooled doripenem phase 1, 2, and 3 experience, 9.26% (113/1,219) doripenem-treated and 9.27% (78/841) comparator-treated (levofloxacin and meropenem) subjects experienced headache as TEAEs. Headache was considered to be a drug-related adverse event in 2.7% (23/852) in the combined doripenem comparative phase 3 experience (DORI-05, DORI-07, and DORI-08) compared to 1.66% (14/841) in the comparator treated subjects. Similarly, among patients who completed treatment with i.v. study drug without a PO switch, the incidence of headache as a TEAE was highest in the doripenem group; 5.7% (14/244) of the doripenem-treated, 0.0% of the levofloxacin-treated, and 4.7% (6/128) of the comparator-treated subjects reported headache as a TEAE. Please refer to Sections 7.1.5.4 and 7.1.5.5 for details.

As headaches have been reported with other β-lactan and carbapenem antibacterial agents, they are not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in in some of the treated patients and, thus, recommends that headache be included in the ADVERSE REACTIONS section of the proposed product label.

7.3.6 Liver enzyme elevations

In the doripenem pooled comparative phase 3 studies, elevated liver enzymes were reported in 0.94% (8/853) of the doripenem-treated and 1.66% (14/841) of the comparator-treated subjects. Increased ALT was reported in 0.59% (5/853) of the doripenem-treated and 1.31% (11/841) of the comparator-treated subjects. Increased AST was reported in 0.35% (3/853) of the doripenem-treated and 0.48% (4/841) of the comparator-treated subjects. Increased GGT was reported in 2.0% (17/853) of the doripenem-treated and 1.66% (14/841) of the comparator-treated subjects.

Five doripenem-treated and two meropenem-treated subjects fulfilled Hy's Rule for potential drug-induced hepatotoxicity based on maximum number. Two of the doripenem-treated subjects had concurrent elevations of their serum alkaline phophatase levels, which is more suggestive of hepatobiliary disease.

Comparative analyses of patients in the phase 3 studies with shifts in severity grade revealed several instances where doripenem-treated subjects exhibited a pattern of elevations in liver enzymes that suggested a positive dechallenge (Subject #09-P0041, 401/06187, 403/06177355/00169, 01312512, and 01502045). However, in some cases, concomitant medications or illnesses confounded more definitive causality assessments. Please refer to sections 7.1.7.5 and 7.1.7.3.3 for details.

As liver enzyme elevations have been reported with other β-lactan and carbapenem antibacterial agents, they are not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in in some of the treated patients and, thus, recommends that

7.3.6 Nausea

Nausea was one of the most frequently reported TEAEs among doripenem and comparator treated subjects. It was reported in 4.08% (10/245) of doripenem-treated compared to 1.37% (1/72) placebo-treated subjects in the pooled doripenem phase 1 studies. In the phase 3 comparative studies, the incidence of nausea as a TEAE was 8.55% (73/853) in the doripenem-treated, 5.91% (22/372) in the levofloxacin-treated, and 9.38% (44/469) in the meropenem-treated subjects. Nausea was reported as a drug-related adverse event in 2.86% (7/245) of doripenem-treated compared to 1.37% (1/72) placebo-treated subjects in the pooled doripenem phase 1 studies. In the phase 3 comparative studies, the incidence of nausea as a drug-related adverse event was highest [4.22% (36/853)] in the doripenem-treated patients compared to 1.61% (6/372) in the levofloxacin-treated and 1.92% (9/469) in the meropenem-treated subjects. Please refer to Sections 7.1.5.4 and 7.1.5.5 for details.

Among phase 3 study subjects who completed i.v. study drug without a follow-up PO switch, the incidence of nausea was 9.4% (23/244) in the doripenem-treated, 2.4% (1/42) in

the levofloxacin-treated, and 11.7% (15/128) in the meropenem-treated patients. Among subjects who did not complete i.v. study drug and did not receive a PO switch agent, the incidence of nausea was 10% (7/70) in doripenem-treated and 4% (4/100) in pooled comparator treated subjects in the comparative trials. Thus, nausea was a frequently encountered TEAE among doripenem-treated subjects, and may have been a limiting event in a substantial number of subjects unable to complete i.v.study drug who did not receive a followup PO switch.

As nausea has been reported with other β-lactan and carbapenem antibacterial agents, it is not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in in some of the treated patients and, thus, recommends that nausea be included in the ADVERSE REACTIONS section of the proposed product label.

7.3.7 Phlebitis

Phlebitis was reported in both doripenem dosage treatment groups (9.42% in the 500 mg group and 14% in the 1,000 mg group) in the pooled phase 1 studies (combined rate 11.43%) and with a greater incidence than that observed in the placebo group (9.72%). Doripenem-treated subjects had the highest incidence of phlebitis as a TEAE among the subjects in the phase 3 studies. Phlebitis was reported in 6.97%, 4.03%, and 5.54% of subjects in the pooled phase 3 doripenem, levofloxacin, and meropenem treatment groups, respectively. All reports of phlebitis were mild or moderate in severity and did not result in premature discontinuation of study drug therapy, except for one levofloxacin-treated subject. The rates of study drug-related phlebitis were comparable among the three treatment regimens in which the incidences were 2.46% for the pooled doripenem experience, 2.96% for levofloxacin, and 2.13% for meropenem in the phase 3 studies. Injection site- and infusion site-related TEAEs (other than phlebitis) were reported most frequently in the levofloxacin-treated subjects (see section 7.1.3.3) and, collectively, do not appear to represent a separate safety signal for doripenem treatment.

As phlebitis has been reported with other β-lactan and carbapenem antibacterial agents, they are not unexpected adverse events in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in in some of the treated patients and, thus, recommends that phlebitis be included in the ADVERSE REACTIONS section of the proposed product label.

7.3.8 Seizure

No seizures were reported among the doripenem-treated subjects in the phase 1, phase 2, and phase 3 studies. One levofloxacin-treated subject developed a grand mal convulsion, whereas no meropenem-treated subjects experienced a seizure. Convulsions have been described in several post-marketing reports involving doripenem-treated patients. However, causality assessment has been difficult in those cases due to predisposing medical conditions.

Seizures have been reported with other carbapenem and β-lactam antibacterial agents. In preclinical studies, seizures were not observed with administration of doripenem. Although seizures were not reported in doripenem-treated subjects, the cumulative phase 3 experience is of insufficient size and power to establish definitively that patients treated with the drug are not at risk. Additional post-marketing surveillance is recommended with respect to seizures. Thus, the FDA Medical Officer recommends that

In addition, text related to the concomitant use of carbapenems with valprioc acid should be included in the WARNINGS AND PRECAUTIONS section and in the DRUG INTERACTIONS section.

7.3.9 Urinary Tract Infections and Asymptomatic Bacteriuria

Urinary tract infections (UTI) and asymptomatic bacteriuria were both reported with an incidence of greater than 5% in the pooled phase 3 cUTI studies compared to frequencies of 1.61% and 1.08%, respectively, in levoflxacin-treated subjects. They were reported with incidences of 3.35% and 0.0%, respectively, in the pooled doripenem cIAI experience compared to frequencies of 2.35% and 0.0%, respectively, in the pooled meropenem-treated subjects. In addition, there were two doripenem-treated subjects in DORI-05 and six subjects in DORI-06 in which UTI was assessed as a serious adverse event, and there were four doripenem-treated subjects in DORI-05 and one subject in DORI-06 in which pyelonephritis was assessed as a serious adverse event. There were no serious adverse events of UTI and pyelonephritis in the levofloxacin- and meropenem-treated groups. Since the majority of the doripenem-treated patients with UTI and pyelonephritis as serious TEAEs had microbiological outcomes of failure or indeterminate, the FDA Medical Officer agrees with the Sponsor's assertion that the UTI and pyelonephritis TEAEs are more appropriately considered in terms of efficacy outcome measures rather than as adverse safety events.

Asymptomatic bacteriuria was clearly an indication-specific TEAE in the doripenem phase 3 studies, as evidenced by the striking difference in incidence rates between the cUTI and cIAI studies. When the cUTI studies are considered individually, the rate of asymptomatic bacteriuria in the doripenem-treated subjects in DORI-05 was three-fold higher than that observed in the levofloxacin-treated group. In the single arm study DORI-06, the incidence of asymptomatic bacteriuria was 7.09%, which was almost twice the incidence reported in the doripenem-treated group in DORI-05. Although the open-label design of DORI-06 may have introduced bias in adverse event assessment, it was not possible to completely attribute the higher incidence in doripenem-treated compared to levofloxacin-treated subjects in DORI-05 to known predisposing factors for aymptomatic bacteriuria (advanced age, indwelling urinary catheters, significant neurological deficits). Although the Sponsor asserts that asymptomatic bacteriuria does not represent a safety concern, the FDA Medical Officer recommends post-marketing surveillance for cases of asymptomatic bacteriuria in patients treated with doripenem.

7.3.10 Diarrhea

Diarrhea was reported as a TEAE with an incidence of 7.6% for all doripenem-treated subjects in the pooled phase 3 studies compared to 9.95% of levofloxacin-treated and 9.81% of meropene-treated subjects. In terms of drug-related adverse events, diarrhea was reported with an incidence of 3.91% in the pooled doripenem groups compared to 6.18% in the levofloxacin group and 4.48% in the combined meropenem groups. Most of the episodes were mild to moderate in severity. Severe diarrhea was reported in one doripenem, four levofloxacin, and no meropenem-treated subjects; study drug was withdrawn due to the event only for the levofloxacin-treated subjects.

As diarrhea has been reported with other β-lactan and carbapenem antibacterial agents, it is not an unexpected adverse event in doripenem-treated subjects. The FDA Medical Officer believes that doripenem may have caused the adverse events observed in some of the treated patients and, thus, recommends that diarrhea be included in the ADVERSE REACTIONS section of the proposed product label.

7.3.11 Renal Failure and other renal treatment-emergent adverse events

There were 17 patients in the doripenem phase 3 studies who had renal failure or renal impairment reported as treatment-emergent adverse events, including 16 treated with doripenem one treated with meropenem, and no levofloxacin-treated subjects. Of the 17 patients, nine were reported to have had serious adverse events; all of those patients had been treated with doripenem. Approximately half of the 17 subjects had renal impairment at baseline, six had received either vancomycin or aminoglycosides (which are potentially nephrotoxic), and eleven had pre-renal azotemia.

The marked imbalance in the number of subjects with renal failure and other renal treatment-emergent adverse events who were treated with doripenem compared to the two comparator agents is of concern. Five of the 16 doripenem-treated patients had been enrolled in DORI-06, a single-arm, open label study that could have been subject to investigator bias in adverse event assessment. However, the remaining 11 doripenem-treated subjects were derived from the three double-blind, comparative phase 3 studies in which only one comparator-treated subject was reported to have developed renal failure as a TEAE. In relation to doripenem exposure, a review of patient case narratives revealed that seven subjects developed renal failure more than six days after the drug had been discontinued (post-treatment), four had improvement in renal function despite receiving the drug (negative rechallenge), and two had received doripenem for only two days. When the underlying medical history of the subjects in the doripenem and comparator safety poulations was surveyed for risk factotrs for pre-renal azotemia or pre-existing renal insufficiency, there was no difference between the populations. Thus, it is the FDA Medical Officer's contention that underlying intravascular volume depletion, pre-renal azotemia, and pre-existing renal insufficiency may enhance the subject's susceptibility to develop acute renal failure/renal impairment following exposure to doripenem and that such patients should have their renal function monitored while receiving the drug.

Although renal failure has been reported with other antibiotic classes (aminoglycosides and vancomycin), it is not an expected adverse event in patients treated with carbapenems. Thus, it is recommended that there should be continued post-marketing surveillance for renal failure and renal impairment in doripenem-treated subjects. For completeness, monitoring of renal function should be recoimmended for subjects treated with doripenem who have underlying intravascular volume depletion, pre-renal azotemia, and pre-existing renal insufficiency. Applicable text modifications are recommended for the GERIATRIC USE and PATIENTS WITH RENAL IMPAIRMENT Sections of the label until further information is available based on post-marketing experience.

7.3.12 Anemia

During the course of the review, anemia was identified as an indication-specific, treatment-emergent adverse event having an incidence of >5% among doripenem-treated subjects in the cIAI studies. In an exploratory analysis conducted by the FDA Medical Officer of study subjects who completed i.v. study drug but did not receive a followup PO switch antbiotic, anemia was reported most frequently among the pooled doripenem-treated subjects (12.7%) in the phase 3 studies compared to the incidence observed in the pooled meropenem (7.8%) and levofloxacin (0.0%) groups. Many subjects had anemia at baseline, and the nadir in hemoglobin levels was on study Day 8 in the doripenem and meropenem groups. The median change in hemoglobin from baseline to nadir was larger in the meropenm-treated subjects (2.35 gm/dl compared to 1.55 gm/dl in doripenem group). However, blood transfusions were administered to more doripenem-treated subjects.

It is possible that study subjects who completed i.v. study drug but did not receive a followup PO switch antbiotic has a greater severity of illness or had a larger amount of prei-operative blood loss in contrast to subjects who received a PO switch agent to account for the higher anemia rate observed. However, data regarding intra-operative blood loss was not collected in a standardized manner for patients who underwent surgery and data regarding the number of subjects who received blood transfusions may not have been collected in all cases.

An exploratory analysis conducted by the FDA Medical Officer of subjects in the phase 3 studies who converted their Direct Coombs tests from negative at baseline to positive during the study, ten converters were identified in the cIAI studies (five doripenem-treated and five meropenem-treated). Most had a history of anemia, had received concomitant antibiotics, or had received captopril. Blood transfusions were reported for only three of the subjects. There was no direct Coombs data on patients enrolled in the cUTI studies. Overall assessment of these cases was confounded by concomitant medications that could cause anemia and comorbidities (which could suppress bone marrow production of red blood cells).

A Hematology consultataion was obtained to assess anemia as a treatment-emeregent adverse event and to evaluate doripenem as a potential cause for drug-induced hemolytic anemia. The conclusions from the consultation were that there was no clear direct

correlation between doripenem exposure and the adverse event of hemolytic anemia. However, assessment was limited by multiple factors (limited or deficient data collection and concurrent medications and illnesses), such that the possibility of doripenem causing hemolytic anemia could not be fully ruled-out.

Although immune-mediated hemolytic anemia has been reported with other antibiotic classes (cephalosporins and penicillins), it is not an expected adverse event in patients treated with carbapenems. Based on a review of available data, the FDA Medical Officer found no clear evidence to directly implicate doripenem as a causative agent for hemolytic anemia. According to the FDA Pharmacology/Toxicology review, *in vitro* Coombs testing with human blood was negative. However, overall assessment of the clinical cases was problematic and often confounded by various comorbid conditions, baseline anemia, concomitant medications that could cause anemia, lack of systematic data collection regarding direct Coombs tests, lack of quantitation of peri-operative blood loss, and issues about blood transfusion data collection as part of the anemia assessment. In view of the limitations cited above, doripenem cannot be clearly ruled out as a potential cause of hemolytic anemia in the patient population studied. Thus, it is recommended that there should be continued post-marketing surveillance for hemolytic anemia in doripenem-treated subjects. For completeness, anemia should be added to the ADVERSE REACTIONS section of the label (without implicating causality) in a discussion of indication-specific differences in the incidence of treatment-emergent adverse events until further information is available based on post-marketing experience.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Phase 1 studies

In relation to the phase 1 studies, the sponsor's approach to pooled data was as follows: Data from single-dose and multiple-dose studies were pooled by treatment and dosage. Adverse events were summarized by treatment (placebo or doripenem) and doripenem dose (500 mg or 1,000 mg). Adverse events were summarized by system organ class and preferred term for the following four treatment/dose combinations:

- Placebo;
- Doripenem 500 mg;
- Doripenem 1,000 mg; and
- Doripenem total.

All subjects receiving the same treatment/dose were pooled for the analysis regardless of the duration, frequency, or timing of infusions. Subjects from crossover studies (DORI-NOS-1001 and DORI-NOS-1004) who received both 500-mg and 1,000-mg doses were counted only once for doripenem total. Subjects from study DORI-NOS-1004 who received two doses of 500 mg during two separate study periods were counted only once for the 500-mg dose. Adverse events were also tabulated by severity and relationship to the study drug therapy for each treatment/dose. Serious adverse events were summarized separately. Listings of subjects with SAEs, subjects who discontinued due to AEs, and subjects who died during the studies are provided.

Adverse event data from subjects with impaired renal function who participated in DORI-02 and DORI-NOS-1005 were not integrated with safety data from subjects with normal renal function. The safety profile of doripenem in subjects with impaired renal function can be found in the individual CSRs (Module 5, Section 5.3.3.3), but notable findings were discussed in this SCS as appropriate.

Phase 2 and 3 studies

In relation to the phase 2 and 3 studies, the sponsor's approach can be summarized as follows: Treatment-emergent AEs and common (>1% of subjects in any treatment group) TEAEs were summarized separately by system organ class, preferred term, and treatment group for the three study groups. Summaries were provided for the "study drug therapy and follow-up" and "i.v. study drug therapy" phases within each study group.

Treatment-emergent AEs that were considered by the investigator to be possibly or probably related to treatment with study drug therapy were considered related and were summarized in tabular form by system organ class and preferred term for the three study groups. If the relationship of an AE was missing, the AE was considered related to treatment with study drug therapy. The total number of subjects with at least one AE related to treatment with study drug therapy, and the number of subjects with at least one AE related to treatment with study drug therapy under each system organ class and preferred term were tabulated. Summaries are provided for the "study drug therapy and follow-up" and "i.v. study drug therapy" phases within each study group.

Treatment-emergent AEs were summarized by severity (mild, moderate, severe) for the three study groups. Summaries are provided for the "study drug therapy and follow-up" phase within each study group. If the severity of an AE was missing, the severity was reported as "missing". Life-threatening AEs are listed separately. A data listing of all subjects who died and the associated SAE(s) with death as the outcome wer provided in the Sponsor's report.

Serious adverse events were considered study drug related if the investigator assessed the event as "possibly" or "probably" related to treatment with study drug, or the causality assessment was missing. All treatment-emergent SAEs and study drug-related treatment-emergent SAEs were tabulated by treatment group for the three study groups. Summaries are provided for "study drug therapy and follow-up" and "i.v. study drug therapy" phases within each study group. Listings of all SAEs were also provided in the Sponsor's report.

Adverse events and study drug-related AEs considered by the investigator as leading to study drug therapy discontinuation were summarized by treatment group for the three study groups.

Except for AEs of special interest, no formal between group comparisons were planned. For the AEs of special interest (see below), two-sided 95% confidence interval (CI) of the incidence rates are presented for each treatment group. In addition, for the cUTI and cIAI indication, the odds ratio of incidence in the doripenem and comparator arms, and its twosided 95% CI are presented for each AE of special interest.

Adverse events potentially associated with β-lactam antibiotics, including carbapenems (e.g.,seizure, rash, anaphylactic reaction, *Clostridium difficile*-related colitis, and hepatic enzymes increased) were prospectively identified as AEs of special interest and analyzed in more detail. All TEAEs that were coded as follows were analyzed:
• Seizure: coded under the MedDRA high-level group term "seizures (including subtypes)";
• Rash: coded under the MedDRA high-level group terms "epidermal and dermal conditions" and "angioedema and urticaria";
• Anaphylactic reaction: coded under the MedDRA high-level term "anaphylactic responses";
• *C. difficile* colitis: coded under the MedDRA preferred terms "*Clostridium difficile* colitis", "*Clostridium difficile* sepsis", "gastroenteritis clostridial", and "antibiotic-associated diarrhea"; and
• Hepatic enzymes increased: coded under the MedDRA preferred terms "alanine aminotransferase increased", "aspartate aminotransferase increased", and "hepatic enzyme increased".

Treatment-emergent AEs and study drug-related AEs that coded to the above terms were tabulated by treatment group for the three study groups. Summaries are provided for the "study drug therapy and follow-up" phase within each study group.

Subgroup analyses of TEAEs are also presented for the "All Phase 2/3 Studies" group. Subgroups for the AE summaries included:
• Sex: male, female;
• Age: <65 years versus ≥65 years; <75 years versus ≥75 years;
• Race: White, Hispanic, Black, Other;
• Baseline creatinine clearance: <50 mL/min, ≥50 mL/min;
• Hepatic impairment: baseline Child-Pugh total score ≥7. Baseline Child-Pugh scores were not collected in cUTI study group. Therefore, this subgroup analysis was based on the cIAI studies only. Also, for any category (encephalopathy grade, ascites, serum bilirubin, serum albumin, and prothrombin time), if no value was recorded, or the not done (ND) box was checked, it was assumed as normal (with score 1). Child-Pugh criteria are detailed in Table 7 of the Statistical Analysis Plan (SAP) for this SCS (Appendix 1.2);
• Geographic region: North America, South America, Europe (including Russia, Georgia, and Belarus), United States of America (USA); and
• Selected concomitant medications: Subjects who received at least one dose or partial dose of vancomycin, aminoglycosides (amikacin, gentamicin, tobramycin), and valproic acid while on i.v. therapy are summarized separately.

7.4.1.1 Pooled data vs. individual study data

7.4.2 Explorations for Predictive Factors

There were four phase 1 studies that assessed the safety and tolerability of different doses of doripenem: DORI-01, DORI-04, DORI-NOS-1001, and DORI-NOS-1004. There was a

total of 79 subjects enrolled in the four studies. Three of the studies were double-blind, placebo controlled trials, whereas one study (DORI-NOS-1004) was an open-label, crossover design. The following table provides the subject groups by treatment arm for each study:

Table 130: FDA Medical Officer Summary Table of subjects with treatment-emergent adverse events in the doripenem phase 1 studies (DORI-01, DORI-04, DORI-NOS-1001, and DORI-NOS-1004)

Study	Total # of subjects	# of subjects with TEAEs	Doripenem 500 mg	Doripenem 1000 mg	Placebo	Serious adverse events
DORI-01	32	22	9	7	6	0
DORI-04	24	21	6	10	5	0
NOS-1001	60	28	6	15	7	0
NOS-1004	24	6*	5	3	NA	0

TEAE=treatment-emergent adverse event; NA=not applicable

The 79 subjects experienced a total of 182 adverse events. None of the adverse events was considered serious by the investigators. The following table depicts the pooled frequencies of various treatment-emergent adverse events stratified by doripenem dose (500 mg and 1,000 mg).

Table 131: FDA Medical Officer Summary Table of frequency of various treatment-emergent adverse events for the pooled phase 1 experience (DORI-01, DORI-04, DORI-NOS-1001, DORI-NOS-1004) stratified by dosage regimen.

	Doripenem 500-mg n=79	Doripenem 1000-mg n=60
PREFERRED TERM	% of Total	% of Total
Headache	12.66	11.67
Infusion site pain	2.53	8.33
Injection site erythema	6.33	6.67
Injection site swelling	2.53	6.67
Constipation	0.00	5.00
Somnolence	0.00	5.00
Diarrhoea	7.59	3.33
Dysgeusia	3.80	3.33
Influenza like illness	0.00	3.33
Infusion site erythema	1.27	3.33
Nausea	10.13	3.33
Abdominal pain	3.80	1.67
Dizziness	3.80	1.67
Dyspepsia	3.80	1.67
Vomiting	3.80	1.67
Dizziness postural	3.80	0.00
Injection site pain	2.53	0.00
Lethargy	6.33	0.00

n=total number of TEAEs per subgroup

As depicted in the table above, headache was the most frequent treatment-emergent adverse event reported in both dosage groups. Injection/infusion site-related events (pain, erythema, swelling) appeared more frequent in the subjects treated with the higher dose (1,000 mg), whereas gastrointestinal events (nausea, nausea, and vomiting) were reported more commonly at the lower dose (500 mg).

7.4.2.2 Explorations for time dependency for adverse findings

There was one phase 1 clinical study (DORI-NOS-1004) that assessed different doses of doripenem with varying infusion times. A total of 24 subjects were assessed, each of whom received doripenem 500 mg – 1 hour infusion, doripenem 500 mg – 4 hour infusion, and doripenem 1,000 mg – 4 hour infusion. Eight of the subjects (33%) experienced a total of 12 treatment-emergent adverse events; in this small sample, there were no differences in the frequency of specific events across the three treatment regimens. Headache was the most commonly reported event in all three treatment groups followed in frequency by infusion site and gastrointestinal events. The following table summarizes the frequency distribution of treatment-emergent adverse events stratified by drug infusion times for subjects in this study:

Table 132: FDA Medical Officer Summary Table of the frequency distribution of treatment-emergent adverse events stratified by regimen and infusion times, DORI-NOS-1004

PREFERRED TERM	Doripenem 1000 mg IV - 4 Hr	Doripenem 500 mg IV - 1 Hr	Doripenem 500 mg IV - 4 Hr
Dizziness	1	1	1
Dysgeusia	1	1	1
Erythema	1	1	1
Headache	3	3	3
Infusion site erythema	1	1	1
Infusion site pain	1	1	1
Nausea	1	1	1
Somnolence	1	1	1
Syncope	1	1	1
Testicular pain	1	1	1
Vision blurred	1	1	1
Vomiting	1	1	1

7.4.2.3 Explorations for drug-demographic interactions

Please refer to Section 7.1.5.6 of this report for applicable analyses.

7.4.2.4 Explorations for drug-disease interactions

As seizures have been described associated with other drugs in the carbapenem class, the FDA Medical Officer assessed the incidence of seizures as a treatment-emergent adverse events among all study subjects with a medical history of epilepsy, seizure disorder, and convulsions in the four doripenem phase 3 clinical studies.

There were a total of 11 study subjects with a medical history of epilepsy, seizure disorder, and convulsions, including three in DORI-05, three in DORI-06, two in DORI-07, and three in DORI-08 in the ITT population. Of those subjects six had received doripenem, one received levofloxacin, and four received meropenem as study drugs. None of those subjects experienced seizures as a treatment-emergent adverse event during study participation.

However, one levofloxacin-treated subject in DORI-05 (Subject # 03402000) without a seizure history experienced a seizure during study participation.

Although this is a small, statistically underpowered, and non-randomized sample, there was no evidence that patients with a medical history of epilepsy and seizures had an elevated proclivity to experience new onset of seizures during treatment with doripenem. Additional post-marketing surveillance will be necessary to gain additional clinical experience relevant to this issue. In addition, the Sponsor plans to conduct a phase 1 study to assess for changes in plasma valproic acid levels when the drug is co-administered with doripenem.

7.4.2.5 Explorations for drug-drug interactions

The FDA Medical Officer assessed the use of concomitant vancomycin and aminoglycosides (genatmicin, amikacin, and tobramycin) in study subjects. There were 82 subjects co-administered vancomycin (in addition to study drug) in the phase 2 and 3 doripenem clinical trials. The use distribution data for concomitant vancomycin are summarized in the following table:

Table 133: FDA Medical Officer Summary of Administration of concomitant Vancomycin, doripenem phase 2 and 3 studies, ITT population

Clinical Study	Treatment Group	# of subjects administered concomitant vancomycin	# of subjects treated with concomitant vancomycin reported with renal failure or impairment as TEAEs
DORI-03	Doripenem 250 mg	1	0
DORI-05	Doripenem 500 mg	4	0
	Levofloxacin 250 mg	5	0
DORI-06	Doripenem 500 mg	9	2
DORI-07	Doripenem 500 mg	14	0
	Meropenem 1 gm	18	0
DORI-08	Doripenem 500 mg	17	1
	Meropenem 1 gm	14	0

*TEAE=treatment-emergent adverse event

As depicted above, three subjects who were administered concomitant vancomycin along with i.v. doripenem were reported to have renal failure or renal impairment as treatment-emergent adverse events. There were no levofloxacin- or meropenem-treated subjects who received concomitant vancomycin and developed renal failure or renal impairment as treatment-emergent adverse events.

Concomitant aminoglycosides were administered to 171 subjects (in addition to study drug) in the phase 2 and 3 doripenem clinical trials. In terms of specific aminoglycoside agents, gentamicin was administered to 148 subjects, amikacin was administered to 23 subjects, and tobramycin was administered to 6 subjects. The preponderance of gentamicin administration was for a duration of one day (75%, 111/148 subjects).

The use distribution data for concomitant aminoglycosides are summarized in the following table:

Table 134: FDA Medical Officer Summary of Administration of concomitant aminoglycosides, doripenem phase 2 and 3 studies, ITT population

Clinical Study	Treatment Group	# of subjects administered concomitant aminoglycosides	# of subjects treated with concomitant aminoglycosides reported with renal failure or impairment as TEAEs
DORI-03	Doripenem 250 mg	1	0
DORI-05	Doripenem 500 mg	11	0
	Levofloxacin 250 mg	8	0
DORI-06	Doripenem 500 mg	12	1
DORI-07	Doripenem 500 mg	35	1
	Meropenem 1 gm	31	0
DORI-08	Doripenem 500 mg	41	0
	Meropenem 1 gm	32	0

*TEAE=treatment-emergent adverse event

As depicted above, two subjects who were administered concomitant aminoglycosides along with i.v. doripenem were reported to have renal failure or renal impairment as treatment-emergent adverse events. There were no levofloxacin- or meropenem-treated subjects who received concomitant aminoglycosides and developed renal failure or renal impairment as treatment-emergent adverse events.

In assessing the concomitant antibacterial therapy data above, it is noteworthy that none of the subjects administered concomitant vancomycin and only one of the subjects administered concomitant aminoglycosides and reported to have renal failure as a treatment-emergent adverse event had a normal baseline creatinine clearance. Additionally, the concomitant antibacterial agent was administered for more than 3 days in only one subject. Thus, the limited clinical experience described above is insufficient to draw conclusions regarding the potential risk for renal impairment/failure as a consequence of concomitant vancomyicn and aminoglycoside use with doripenem.

7.4.3 Causality Determination

Based on the review of the safety data in this NDA, doripenem appears to cause the following adverse reactions: nausea, diarrhea, vomiting, phlebitis, rash and hypersensitivity, C. difficile colitis, fungal vulvovaginitis, elevations in serum GGT and liver enzymes. Although there were trends suggestive of a possible association between anemia and doripenem exposure, there was insufficient information to establish the existence of a possible causal relationship. The reasons for the relative imbalance in the incidence of renal failure/renal impairment as a TEAE between doripenem- and comparator-treated subjects in the four phase 3 clinical studies appears to be related to underlying intravascular volume depletion, pre-renal azotemia, and pre-existing renal insufficiency that may enhance the subject's susceptibility to develop acute renal failure/renal impairment following exposure to doripenem. Such patients should have their renal function monitored while receiving the drug.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There is sufficient efficacy data to support the Sponsor's proposed dosing regimens for the treatment of cUTIs and cIAIs in adults ≥18 years of age as provided below:

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
cIAI	500 mg	q8h	1	5-14 days*
cUTI,including pyelonephritis	500 mg	q8h	1	10 days*§

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.
§ Duration can be extended up to 14 days for patients with concurrent bacteremia.

In patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 mL/min), the dosage of doripenem should be 250 mg every 8 hours by intravenous infusion over one hour. In patients with severe renal impairment (CrCl > 10 to < 30 mL/min), the dosage of doripenem should be 250 mg every 12 hours by intravenous infusion over one hour.

There is sufficient human safety data from the four phase 3 clincial studies to support the Sponsor's proposed dosing regimens and administration of the drug for the treatment of cUTI and cIAI in which IV doripenem is initiated and then followed by an oral switch antibiotic. However, there is insufficient safety data related to durations of doripenem that extend beyond 14 days.

8.2 Drug-Drug Interactions

Co-administration of doripenem with probenecid decreases the renal clearance of the drug, resulting in increased serum levels of doripenem. Doripenem is not metabolized by the P450 enzyme system; therefore, pharmacokinetic interactions of the drug are not expected with other agents that induce, inhibit or are metabolized by cytochrome P-450 or other liver enzyme systems. Various reports in the medical literature have described an interaction between carbapenem class antibiotics and sodium valproate (valproic acid), in which patients administered both drugs concomitantly experienced an increased risk of seizure. Increased clearance of sodium valproate was recorded in one animal model when doripenem was co-administered. In order to further assess the potential for drug-drug interactions involving doripenem and valproic acid, the Sponsor plans to conduct a Phase 1 clinical study to evaluate changes in plasma valproic acid levels when that drug is co-administered with doripenem.

8.3 Special Populations

Efficacy: cIAI Studies
Two special populations were evaluated for efficacy in the cIAI studies: the elderly

(defined as patients aged ≥ 65 years [106 subjects]; or ≥ 75 years [37 subjects]), and subjects with renal impairment requiring dose adjustments (48 subjects) in the pooled ME at TOC analysis set. Pediatric patients with cIAI were not studied.

Per the sponsor, clinical cure rates at the TOC visit were slightly lower in the elderly, but were similar in the 2 treatment arms of the pooled ME at TOC analysis set. These differences were expected and were likely the result of more co-morbidities and later presentation in the elderly. Furthermore, the difference between the treatment arms for the elderly subgroup aged ≥ 65 years (81.1% [43/53], doripenem; 75.5% [40/53], meropenem) favored doripenem therapy, although the number of subjects was small. Similar clinical cure rates were seen in both treatment arms for subjects aged ≥ 75 years (72.2% [13/18], doripenem; 73.7% [14/19], meropenem) in the pooled ME at TOC analysis set. No dosage adjustments are recommended for elderly subjects with normal age-appropriate renal function.

A total of 48 (7.6%) subjects in the pooled ME at TOC analysis set had renal impairment and required IV study drug dose adjustment. In this subgroup, clinical cure rates were lower compared to subjects with no renal dose adjustment (85.7% versus 72.0% in the doripenem treatment arm, and 86.7% versus 52.2% in the meropenem treatment arm, respectively). Overall, this subgroup had a greater prevalence of high risk factors (e.g., 69% of subjects in this subgroup were aged > 65 years of age compared with 17% overall. Further 46% of subjects in this subgroup had APACHE II scores > 10 compared to 10% overall). Therefore, per the sponsor, the lower clinical cure rates associated with renal failure requiring study drug dose adjustment appear to be related to concurrent risk factors in this population, and not due to a reduced effect of the adjusted study drug dose.

Safety
In adults treated with doripenem, there were no definitive safety issues identified with respect to age, race, renal impairment, or hepatic impairment that would impact dosing and administration. Indication-specific trends that were observed in the phase 3 clinical trials included the following: an increased risk for headache among subjects with low body mass index (BMI) in the phase 3 cUTI studies, an increased risk for asymptomatic bacteriuria in elderly subjects in cUTI studies, and an increased risk for anemia and pyrexia among Black subjects in the cIAI studies. As pediatric populations were not studied, no specific recommendations regarding efficacy and safety in children can be provided.

8.4 Pediatrics

Doripenem has been studied only in adults ≥18 years of age. The Agency granted a deferral of pediatric studies until after approval of doripenem use in adults. The Sponsor has proposed a pediatric development program to satisfy PREA

8.5 Advisory Committee Meeting

No Advisory Committee Meetings were conducted related to this NDA application.

8.6 Literature Review

Please refer to Section 7.2.2.3 of this report for the literature review.

8.7 Postmarketing Risk Management Plan

Please refer to Section 9.3 of this report.

8.8 Other Relevant Materials

A Hematology Consultation was obtained to evaluate the incidence and potential mechanisms for development of anemia in doripenem-treated subjects compared to the comparator agents, and to assess the potential for doripenem to induce immune-mediated hemolytic anemia.

9. OVERALL ASSESSMENT

9.1 Conclusions

Based on evidence from the four opivotal Phase 3 clinical trials supported by various Phase 1 and 2 studies, there is adequate efficacy and safety data to recommend approval of doripenem for the indications of cUTI and cIAI in adults aged 18 years or older. Noteworthy limitations of the studies include a small clinical experience involving patients treated with i.v. doripenem without an oral switch and the small sub-population who received i.v. doripenem for a duration of longer than 10 days.

Based on the review of the electronic datasets, clinical safety reports, and responses to various information requests, doripenem 500 mg every 8 hours appears safe for the intended use in the treatment of cUTI and cIAI for a duration not to exceed 14 days. Please refer to the appropriate reviews for conclusions regarding the efficacy of the drug for the intended indications.

9.2 Recommendation on Regulatory Action

From the clinical perspective, there is adequate efficacy and safety data to recommend approval of this new molecular entity for the treatment of cUTI and cIAI in adults aged 18

years or older. The drug appears safe for its intended use. The data are sufficient to provide adequate directions for use. The route of elimination is via renal excretion, and dose adjustment is necessary for patients with renal impairment.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The FDA Medical Officer recommends that post-marketing surveillance should be conducted with respect to the following issues:

- Anemia
- Renal Failure
- Asymptomatic bacteriuria
- Seizure
- Pregnancy
- Other rare adverse events

9.3.2 Required Phase 4 Commitments

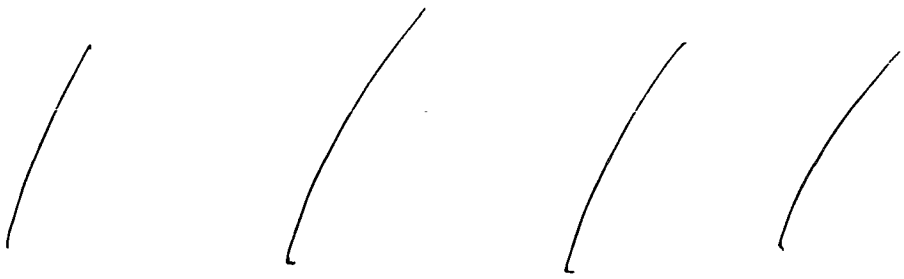
The FDA Medical Officer recommends a study of doripenem in an experimental animal model involving animals with pre-existing renal impairment or pre-renal azotemia to assess the mechanism(s) of renal failure/impairment development following treatment with the drug and to assess for any predictive factors that would be relevant to use of the drug in humans.

The FDA Medical Officer also recommends that the Sponsor conduct a study and analysis of doripenem-treated subjects for the development of hemolytic anemia, renal failure, and seizures, possibly in the form of a post-marketing patient registry.

9.3.3 Other Phase 4 Requests

The FDA Medical Officer has no other phase 4 requests.

9.4 Labeling Review



4 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

9.5 Comments to Applicant

APPEARS THIS WAY
ON ORIGINAL

REFERENCES

1. Hanley J, Lippman-Hand A. If Nothing Goes Wrong, Is Everything All Right? *JAMA* 1983;249(13):1743-45.

2.Division of Microbiology and Infectious Diseases Adult Toxicity Table, May 2001. (http://www.niaid.nih.gov/dmid/clinresearch/dmidadulttoxtable.doc).

3. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Pharmaceutical Research and Manufacturers of America and American Association for the study of Liver Diseases Conference. November 2000;1-13.

4. Sanguinetti M, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. *Nature* 2006;440:463-69.

5. Stein GE. Safety of Newer Parenteral Antibiotics. *Clin Infect Dis* 2005;41:S293-302.

6. Teppler H, Gesser R, Friedland I, et al. Safety and tolerability of ertapenem. *J Antimicrob Chemother* 2004;53(Suppl 2):ii75-ii81.

7. Coves-Orts F, Borras-Blasco J, Navarro-Ruiz A, Murcia-Lopez A, Palacios-Ortega F. Acute Seizures due to a probable interaction between Valproic Acid and Meropenem. *Ann Pharmacother* 2005;39:533-7.

8. Lunde J, Nelson R, Storandt H. Acute Seizures in a Patient receiving Divalproex Sodium after starting Ertapenem Therapy. *Pharmacotherapy* 2007;27(8):1202-1205.

9. Nakajima Y, Mizobuchi M, Nakamura M, et al. Mechanism of the Drug Interaction between Valproic Acid and Carbapenem Antibiotics in Monkeys and Rats. *Drug Metab Dispos* 2004;32:1383-91.

10. Horiuchi M, Kimura M, Tokumura M, Hasebe N, Arai T, Abe K. Absence of convulsive liability of doripenem, a new carbapenem antibiotic, in comparison with β-lactam antibiotics. *Toxicology* 2006;222:114-124.

11. Forer L, Davros W, Goldberg J, et al. Hepatic Cavitation: A Marker of Transient Hepatocellular Injury during Biliary Lithotripsy. *Digestive Diseases and Sciences* 1992;37(10):1510-16.

10 Appendices

10.1 Review of Individual Study Reports

A comprehensive review of individual study reports was not performed as part of the safety assessment of the NDA submission. Both individual study data and pooled study data were used in completing the safety assessment, and those results can be reviewed in Section 7 of this report.

10.2 Line-by-Line Labeling Review

A line-by-line review of labeling relevant to safety is provided below. Underlined text is used for recommended additions and strike-through text is used for recommended deletions.

5 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

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

/s/

Alfred Sorbello
10/4/2007 04:06:11 PM
MEDICAL OFFICER

Sumathi Nambiar
10/4/2007 04:24:51 PM
MEDICAL OFFICER

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: September 20, 2007

From: Andrew Dmytrijuk M.D.
Medical Officer
Division of Medical Imaging and Hematology Drug Products

Through: Kathy Robie-Suh M.D., Ph.D.
Medical Team Leader
Division of Medical Imaging and Hematology Drug Products

Subject: Consult Request regarding
NDA 22-106 (Doripenem)

To: Alfred Sorbello D.O.
Medical Officer
Division of Anti-Infective and Ophthalmology Products

Request:

Consultation requested to obtain assessment of anemia as a treatment emergent adverse event and to rule out drug-induced hemolytic anemia for Doripenem, a drug under review for treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). The PDUFA goal date for the NDA is October 12, 2007. The submission is in the electronic document room (EDR).

Materials reviewed:

- NDA 22-106 submission including but not limited to modules 2.5 and 2.7 of submission 0000; amendments: 0009, 0019, 0020, 0029; and available patient narratives.
- Medical officer review document of anemia as a treatment emergent adverse event (personal communications, e-mails sent August 26, 2007 and September 25, 2007).
- Beutler, E. et al.William's Hematology sixth edition. 2001.
- Literature review (see also References listed below).

Background:

Dr. Alfred Sorbello from the Division of Anti-Infective and Ophthalmology Products requests a consult to obtain assessment of anemia as a treatment emergent adverse event and to rule out drug-induced hemolytic anemia for the carbapenem Doripenem for the NDA 22-106. This NDA contained four phase 3 clinical studies DORI-05, DORI-06, DORI-07 and DORI-08. The study DORI-05 was a double-blind, comparative study of Doripenem compared to Levofloxacin for the treatment of complicated urinary tract infections. DORI-06 was a single arm, open label study of Doripenem for the treatment of complicated urinary tract infections. The studies provided for an oral switch to Levofloxacin after nine doses of intravenous study drug administration. Study DORI-07 and DORI-08 were double-blind, comparative studies of Doripenem compared to Meropenem for the treatment of complicated intra-abdominal infections. These studies provided for an oral switch to amoxicillin-clavulanic acid after day three of intravenous study drug administration.

During his review Dr. Sorbello (personal communications, e-mails sent August 26, 2007 and September 25, 2007) identified anemia as a treatment emergent adverse event in the course of the safety review for this NDA. The preclinical toxicology studies did not indicate a substantial problem with anemia in Doripenem treated animals. In a one month repeat dose toxicity study performed in rats given a 1000mg/kg/day dose of Doripenem, there was a slight increase in lymphocyte count and a mild decrease in neutrophil count observed. Also there was a mild increase in spleen weight in female rats given Doripenem at a 1000mg/kg/day in this study. A hypertrophy of the germinal center white pulp was observed rats given 300-1000mg/kg/day in repeat toxicology studies which was considered to be due to immune response to repeated administration of Doripenem causing weak antigenicity or response to alterations in gut microflora. These