

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-106

PHARMACOLOGY REVIEW(S)

Comments on NDA 22-106 doripenem

From: A Jacobs
10/04/07

There are no pharm/tox approval issues and the pregnancy category B seems appropriate.

Editorial comments have been conveyed to the Pharm/tox reviewer/ Acting TL.

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

/s/

Abby Jacobs
10/5/2007 08:49:08 AM
PHARMACOLOGIST



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-106
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 12/12/06
PRODUCT: **Doripenem**
INTENDED CLINICAL POPULATION: Patients with complicated intra-abdominal infections,
or complicated urinary tract infections including
pyelonephritis.
SPONSOR: Johnson and Johnson, Pharmaceutical Research and
Development, LLC.
DOCUMENTS REVIEWED: **Electronic submission**
REVIEW DIVISION: **Division of Anti-infective and Ophthalmology Drugs**
PHARM/TOX REVIEWER: Wendelyn Schmidt, Ph.D.
PHARM/TOX SECONDARY REVIEWER: Amy Nostrandt, DVM
ACTING DIVISION DIRECTOR: **Wiley Chambers, MD**
PROJECT MANAGER: **Susmita Samatha**

Date of review submission to Division File System (DFS): 9/17/07

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW.....	8
2.6.1 INTRODUCTION AND DRUG HISTORY.....	8
2.6.2 PHARMACOLOGY.....	16
2.6.2.1 Brief summary.....	16
2.6.2.2 Primary pharmacodynamics	16
2.6.2.3 Secondary pharmacodynamics	16
2.6.2.4 Safety pharmacology	16
2.6.2.5 Pharmacodynamic drug interactions.....	21
2.6.3 PHARMACOLOGY TABULATED SUMMARY.....	21
2.6.4 PHARMACOKINETICS/TOXICOKINETICS.....	21
2.6.4.1 Brief summary.....	21
2.6.4.2 Methods of Analysis.....	22
2.6.4.3 Absorption.....	22
2.6.4.4 Distribution.....	28
2.6.4.5 Metabolism.....	29
2.6.4.6 Excretion.....	34
2.6.4.7 Pharmacokinetic drug interactions.....	36
2.6.4.8 Other Pharmacokinetic Studies.....	41
2.6.4.9 Discussion and Conclusions	42
2.6.4.10 Tables and figures to include comparative TK summary	42
2.6.5 PHARMACOKINETICS TABULATED SUMMARY.....	42
2.6.6 TOXICOLOGY.....	43
2.6.6.1 Overall toxicology summary	43
2.6.6.2 Single-dose toxicity	47
2.6.6.3 Repeat-dose toxicity	47
2.6.6.4 Genetic toxicology.....	50
2.6.6.5 Carcinogenicity.....	51
2.6.6.6 Reproductive and developmental toxicology.....	51
2.6.6.7 Local tolerance	52
2.6.6.8 Special toxicology studies	52
2.6.6.9 Discussion and Conclusions	55
2.6.6.10 Tables and Figures.....	55
2.6.7 TOXICOLOGY TABULATED SUMMARY	55
OVERALL CONCLUSIONS AND RECOMMENDATIONS.....	55
APPENDIX/ATTACHMENTS	ERROR! BOOKMARK NOT DEFINED.

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: There are no pharmacology/toxicology objections to the approval of doripenem.

B. Recommendation for nonclinical studies: No new studies are needed at this time.

C. Recommendations on labeling:

The entire " _____ " section should be deleted.

The ratios obtained for the animal vs. human AUC exposure are also somewhat different between the FDA and sponsor. The recommended human AUC for 500 mg dose was 36.3 ug.h/mL. There was no adequate exposure data for a pregnant rat dose of 1000 mg/kg (300 mg/kg was the highest dose investigated). No data at 1000 mg/kg in males was presented either, _____

1
2
3

Thus, the pregnancy section of the label should read:

Category B: Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1000 mg/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least _____ times the exposure to humans dosed at 500 mg q8h, respectively). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The Nursing Mothers section can continue to read as currently written. The amount of doripenem in the entire fetus is 1/77 that of the maternal plasma.

The fertility section should read: Intravenous injection of doripenem had no adverse effects on general fertility of treated male and female rats or on postnatal development and reproductive performance of the offspring at doses as high as 1 g/kg/day (based on AUC, _____ times the exposure to humans at the dose of 500 mg q8h).

II. Summary of nonclinical findings

Doripenem is a carbapenem class intravenous drug. It is active against both Gram positive and negative bacteria by inhibiting bacterial cell wall synthesis via inactivation of penicillin binding proteins. Other approved drugs in this class include ertapenem, imipenem and meropenem.

One of the class effects of the penems is the increase in seizures. With doripenem, no seizures or convulsions were noted during the general toxicology studies with doses up to 2000 mg/kg in the single dose rat and dog. In the safety pharmacology studies, lower doses were used in combination with electroshock or pentylenetetrazol without a change in incidence or threshold of seizure. Even direct injection intracisternally did not result in seizure. This is particularly striking when compared to other penems, which were tested alongside the doripenem.

The highest dose tested for safety pharmacology in rats and mice, 400 mg/kg, have a HED (human equivalent dose) of 65 mg/kg, more than twice the human total daily dose of 25 mg/kg.

The cardiac effects of doripenem were tested both *in vitro* (hERG, Purkinje fibers) and in the *in vivo* dog. While all of the safety pharmacology studies were negative, the toxicology studies (1 and 3 month dog studies) showed significant changes in the QT interval. It should be noted that the maximum dose in the single dose safety pharmacology study was at 100 mg/kg while the 30 or 90 dose toxicology studies were conducted at 500 and 250 mg/kg. No QT prolongation has been associated with other penems at this time. No effects were noted on respiration with doripenem. Gastrointestinal effects were not investigated.

The pharmacokinetics of doripenem have been investigated in multiple species including mouse, rat, dog, rabbit, and monkey. No gender differences were noted. No accumulation with multiple doses was observed. Exposure was relatively linear with dose. In the pregnant rat, exposures were higher than those seen in the non-pregnant rat (or males). Whether or not this was due to inter-experimental variation could not be determined. The half life was generally less than 1 hour. Similarly, half-life in the human is approximately 1 hour. It should be noted that at the recommended therapeutic dose, 500 mg, the human AUC is 36.3 ug.hr/mL, and the C_{max} 23 ug/mL. This is roughly the same AUC seen at the low dose in the dog (10 mg/kg) and rat (30 mg/kg) DX5 studies. No toxicokinetic data was available for the 1 or 3 month rat or dog studies.

Doripenem is widely distributed in both rat and dog. The majority of drug in both species was found in the kidney, and subsequently, in urine. A secondary site was the bone. Extremely low levels were found in brain and eye suggesting poor passage through the blood brain barrier. Levels of doripenem were at least 40 fold greater in the maternal circulation than in fetal circulation. The highest concentration of doripenem in the fetus was seen in the kidney.

Doripenem has relatively little binding to plasma proteins. In the mouse and rat, 25 and 35% of the drug is protein bound, while in dogs, monkeys, and humans, 10% or less of the drug is bound to plasma proteins. Protein binding of doripenem is approximately 12% in the rabbit.

Doripenem is metabolized in rat and dog to the dicarboxylic acid moiety (D-DC). In the urine of rats, D-DC accounts for approximately 50% of the total dose excreted. D-DC accounts for approximately 15% of the dose excreted in the dog. In the human, the D-DC is approximately 18% of the drug in the plasma, while approximately 15% of the total dose is excreted in the urine as D-DC. Thus, the dog is a better model for investigating doripenem. D-DC is inactive. Doripenem is not a substrate for human P450 enzymes. DHP-1 (dihydropeptidase) is responsible for the breakdown of doripenem to D-DC and the activity is inhibited by cilastatin.

Excretion in the rat, monkey and dog is primarily via the urine. With the exception of a single study in female rats (Sprague Dawley where 88% of the dose was found in the urine), between 90 and 97% of the initial dose is excreted in urine with the majority excreted within the first 2 hours. Fecal excretion accounted for between 0.1% (male rats) and 10% (female rats). As up to 3% of the dose of doripenem can be detected in the bile when only 0.1% is seen in the feces, some enterohepatic recycling may be occurring. These studies did not differentiate between parent and the D-DC metabolite. In the studies where parent versus metabolite were measured in the urine, the metabolite accounted for approximately 30% of the dose, but when cilastatin was added only 5% of the dose was excreted as D-DC. Rats excreted 10% of the total dose as D-DC. Humans also excrete the majority of the doripenem via the urine with 71% as parent drug and 15% as D-DC. Less than 1% of the dose was found in human feces. Renal tubular excretion was partly responsible for doripenem elimination in the rabbit, but not in dog. Glomerular filtration and active tubular excretion were also cited as mechanisms for drug elimination in the human. Doripenem did not affect the pharmacokinetics of valproic acid.

Acute intravenous toxicology studies were conducted in the rat, rabbit, and dog. With doses up to 1 to 2 grams of doripenem, no seizure activity was noted. The major targets of toxicity were kidney, hematologic cells (primarily WBC #), gastrointestinal tract (vomiting in dogs, hemorrhage/erosion), and possibly liver. While the acute toxicity studies seem to emphasize the renal toxicity due to the two rabbit studies, those studies were designed to focus only on the serum chemistry and pathology of the kidney by excluding all other organs from examination.

Subchronic dosing was conducted in the rat and dog. Toxicokinetics were not monitored in these studies. The major targets of toxicity were kidney, gastrointestinal tract and hematologic cells. The changes in WBC and RBC numbers, while usually mild, may possibly be associated with immune responses. This seems likely as splenic hypertrophy was also noted in these studies. An alternate explanation for the RBC decrements would be GI bleeding. Other hematologic changes were variable across studies and species, suggesting that they may be artifacts or not toxicologically relevant. The two 1 month dog studies differed in that lethality occurred at 500 mg/kg in one study, but only at 1000 mg/kg in the other study. QT prolongation was noted in both the 1 month and the 3 month studies in the dogs. Gastrointestinal damage was also noted in both dog studies (hemorrhage and inflammatory cells as well as some vomiting). No new toxicities were noted between 1 month and 3 months in dog or rat. The two week dog study with the new formulation of doripenem did not result in any significant changes in the toxicologic profile. Juvenile dogs actually showed less toxicity than their adult

counterparts. No renal toxicity was noted in the juvenile dogs, nor was there splenic hypertrophy. Direct comparisons of plasma concentrations of drug are not possible as toxicokinetics were not monitored in the adults, although these measurements were part of the juvenile protocol. The major human toxicities have included gastrointestinal and hematologic changes. The table below summarizes the comparison of the NOAEL as an HED in the animal studies as compared to the human dose. The human dose of 500 mg q 8 hour is approximately 1500 mg/day or 25 mg/kg/day.

Species	Schedule	Doses tested (mg/kg)	NOAEL mg/kg	HED (mg/kg) at NOAEL	Margin of Safety
Rat	1X	2000	<2000	<324	<13
	DX14 days	100, 300, 1000	<100 LLD>1000	<16	<1
	DX 1 month	100, 300, 1000	100	16	0.6
	DX 3 months	100, 300, 1000	100	16	0.6
Rabbit	1X	200, 400, 600	200 (renal only)	65	2.6
	1X	250, 400	<250 (renal only)	<81	<3.2
	DX5 days	50, 100, 200	50 (renal only)	16	0.6
Dog	1X	1000, 2000	<1000	<54	<2
	DX 1 month	250, 50, 1000	250	135	5.4
	DX1 month	125, 250, 1000	<125	<68	<3
	DX 3 months	40, 100, 250	<40	<22	<1

**APPEARS THIS WAY
ON ORIGINAL**

The special toxicity studies explored the local effects of doripenem on vascular/muscular tissue, on antigenicity, and on liver function. Renal and cardiac function have already been explored in the safety pharmacology section of the NDA. Intravenous injection daily for 8 days in the rabbit ear vein at up to 2% resulted in damage that was not significantly different from that of a normal saline injection. Similarly, a single intramuscular injection of 1% doripenem did not differ in damage from normal saline. Antigenic effects of doripenem were similar to those of imipenem (weak antigenicity in PCA test, FCA positive in ELISA). Guinea pig also showed positive antigenicity in FCA and PCA test. Minimal cross-reactivity between imipenem and doripenem was noted in the guinea pig, but not in the mouse. An *in vitro* Coombs test with human blood was negative.

The sponsor also explored hepatotoxicity in 2 week studies in rats and dogs; however, the doses used were significantly lower than the NOAELs in the 1 month study. It is not surprising that almost no changes were noted.

Mutagenicity of doripenem was investigated in both bacterial (Ames at up to 5 ug/plate) and mammalian (Chinese Hamster Ovary at up to 5000 ug/mL) cells. Both systems were negative. Doripenem was negative for clastogenicity in the Chinese Hamster Lung cell assay. Doripenem was also negative in the *in vivo* mouse micronucleus assay at 2000 mg/kg. No carcinogenicity studies were required based on the short-term, intermittent use of doripenem.

Studies have been conducted in the rat and rabbit to investigate the potential of doripenem to cause reproductive toxicity. The preliminary dose-ranging studies were conducted at the same doses (up to 1000 mg/kg/day *i.v.*) as the definitive studies and showed no significant effects on the feti or on other reproductive parameters (e.g. maternal toxicity, placental weights, implantation sites, abortions etc). The studies are summarized in the table below, along with the relevant toxicokinetic data from separate studies. Additionally, doripenem did not affect fertility in male or female rats at doses up to 1000 mg/kg/day. Nor did doripenem affect the gestation period, behavior or maturation/reproductive potential of the F1 generation where the dams were administered doripenem through weaning. No data on the pharmacokinetic parameters at 1000 mg/kg/day were collected.

Reproductive Toxicity Studies with Doripenem				
Segment	Species	Doses tested	NOAEL	AUC (dose in mg/kg/day)
Segment I	Rat	0, 100, 300, 1000	1000	---
Segment II	Rat	0, 100, 300, 1000	1000	263 ug.h/mL (300)
Segment II	Rabbit	0, 12.5, 25, 50	50	92.1 ug.h/mL (50)
Segment II/III	Rat	100, 300, 600, 1000	1000	---

Conclusions: The non-clinical toxicology of doripenem has been adequately investigated. The studies were well conducted and the doses were sufficient to delineate the toxic potential of doripenem. There are no pharmacology/toxicology reasons not to approve this drug.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-106

Review number: 1

Sequence number/date/type of submission: 000; December 12, 2006; initial

Information to sponsor: Yes () No (X)

Sponsor and/or agent:

Johnson and Johnson, Pharmaceutical
Research and Development, LLC.
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869

Reviewer name: Wendelyn Schmidt

Division name: Division of Anti-Infective and Ophthalmology Drugs

HFD #: 520

Review completion date: 8/23/07, revised 9/11/07

Drug:

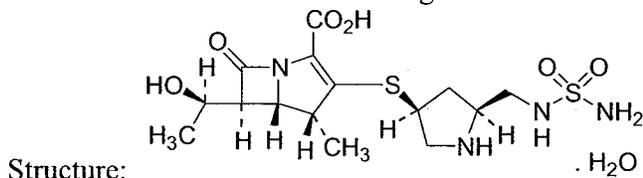
Code Name: S-4661, JNJ-38174942

Trade name: Doripenem

Chemical name: (4*R*,5*S*,6*S*)-3-[[[(3*S*,5*S*)-5-[[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

CAS registry number:

Molecular formula/molecular weight: 438.52



Relevant INDs/NDAs/DMFs: IND 64,416

Drug class: Penem

Intended clinical population: Patients with either complicated intra-abdominal infections, or complicated urinary tract infections including pyelonephritis.

Clinical formulation: Crystallized doripenem.

12. Plasma concentration of S-4661 in safety pharmacology in rats. _____
Shionogi Study # S-4661-TF-564-L. Document ID # EDMS-PSDB-5037727. G
 13. Effects of S-4661 on respiratory system in rats. _____ Shionogi Study #
S-4661-SF-540-L. Document ID # EDMS-PSDB-5037685. G
 14. Effects of S-4661 on cardiovascular system in conscious dogs. _____
Shionogi Study # S-4661-SF-539-L. Document ID # EDMS-PSDB-5037706. G
 15. Plasma concentration of S-4661 in safety pharmacology study in dogs. _____
_____ Shionogi Study # S-4661-TF-565-L. Document ID # EDMS-PSDB-
5037748. G
 16. Interaction of S-4661 and sodium valproate. Shionogi Study # S-4661-B-53-N.
Document ID # EDMS-PSDB-5037773. G
- Pharmacokinetics:
1. Tissue distribution of ¹⁴C-doripenem, as studied by whole-body autoradiography, in the pigmented male rat after single intravenous administration of ¹⁴C-doripenem at 20 mg/kg. Document ID # EDMS-PSDB-5655476. G
 2. Biliary excretion in male rats following single intravenous administration of ¹⁴C-S-4661. Shionogi. Study # S-4661-B-21-N. Document ID # EDMS-PDSB-5296779. G
 3. Studies on the pharmacokinetics of S-4661 in experimental animals:
pharmacokinetic studies of S-4661 in mice. Shionogi. Study # S-4661-B-05-N.
Document ID # EDMS-PSDB-5365061. A
 4. Blood concentration after single intravenous administration of S-4661 to male rats. Shionogi Study # S-4661-B-22-N. Document ID # EDMS-PSDB-5373004. A
 5. Dose-linearity of plasma concentration in rats following single administration of S-4661. Shionogi. Study # S-4661-PB-558-N. Document ID # EDMS-PSDB-5282035. G
 6. Measurement of plasma concentration of S-4661 in rat dose-linearity study. Shionogi. Study # S-4661-PB-560-N. Document ID # EDMS-PSDB-5284164. G
 7. Plasma concentration of S-4661 in safety pharmacology study in rats. _____
_____ Shionogi Study # S-4661-TF-564-L. Document ID # EDMS-
PSDB-5037727. G
 8. Blood concentration after single intravenous administration of S-4661 to female rats. Shionogi Study # S-4661-B-26-N. Document ID # EDMS-PSDB-5374403. A
 9. Studies on the pharmacokinetics of S-4661 in experimental animals:
pharmacokinetic studies of S-4661 in rats. Shionogi. Study # S-4661-B-05-N.
Document ID # EDMS-PSDB-5359369. A
 10. Basic pharmacokinetic studies of S-4661: Quantitative examination for S-4661 and S-4661-DC in plasma and urine after single administration of S-4661 to rats. Shionogi Study # S-4661-B-12-N(9). Document ID # EDMS-PSDB-5327063. G
 11. Plasma concentration in rats following repeated administration of S-4661. Shionogi. Study # S-4661-PB-559-N. Document ID # EDMS-PSDB-5282386. G
 12. Measurement of plasma concentration of S-4661 in rats repeated dosing study. Shionogi. Study # S-4661-PB-561-N. Document ID # EDMS-PSDB-5284363. G

13. Toxicokinetics at 5-day intravenous administration of doripenem hydrate in rats. Study # O-1268. Shionogi Study # S-4661-TF-612-L. Document ID # EDMS-PSDB-5810222. G
14. Toxicokinetics at intravenous administration of doripenem hydrate in pregnant rats. Study # O-1270. Shionogi Study # S-4661-TF-614-L. Document ID # EDMS-PSDB-5810229. G
15. Studies on the pharmacokinetics of S-4661 in experimental animals: pharmacokinetic studies of S-4661 in rabbits. Shionogi Study # S-4661-B-05-N. Document ID # EDMS-PDSB-5357798. A
16. Five-day intravenous nephrotoxicity study S-4661 in rabbits. Shionogi Study # S-4661-TB-569-N. Document ID # EDMS-PSDB-5339205. G
17. Toxicokinetics at intravenous administration of doripenem hydrate in pregnant rabbits. Study # O-1271. Shionogi Study # S-4661-TF-615-L. Document ID # EDMS-PSDB-5810261. G
18. Studies on the pharmacokinetics of S-4661 in experimental animals: pharmacokinetic studies of S-4661 in dogs. Shionogi Study # S-4661-B-05-N. Document ID # EDMS-PSDB-5351405. A
19. Basic pharmacokinetic studies of S-4661: quantitative examination for S-4661 and S-4661-DC in plasma and urine after single administration of S-4661 to dogs. Shionogi Study # S-4661-B-12-N. Document ID # EDMS-PSDB-5324325. G
20. Plasma concentration of S-4661 in safety pharmacology study in dogs. Shionogi Study # S-4661-TF-565-L. Document ID # EDMS-PSDB-5037748. G
21. Pharmacokinetic studies of S-4661 in juvenile dogs. Shionogi Study # S-4661-B-69. Document ID # EDMS-PSDB-5280581. G
22. Basic pharmacokinetic studies of S-4661: plasma concentration, urinary and fecal excretion of radioactivity after single intravenous administration of ^{14}C -S-4661 to dog. Shionogi Study # S-4661-B-12-N(4). Document ID # EDMS-PSDB-5292788. G
23. Toxicokinetics at 5-day intravenous administration of doripenem hydrate in dogs. Study # O-1269. Shionogi study # S-4661-TF-613-L. Document ID # EDMS-PSDB-5810246. G
24. Studies on the pharmacokinetics of S-4661 in experimental animals: pharmacokinetic studies of S-4661 in monkeys. Shionogi Study # S-4661-B-05-N. Document ID # EDMS-PSDB-5353951. A
25. Basic pharmacokinetic study of S-4661: quantitative examination for S-4661 and S-4661-DC in plasma and urine after administration of S-4661 or co-administration of S-4661 with cilastatin to monkey. Shionogi Study # S-4661-B-12-N. Document ID # EDMS-PSDB-5291081. G
26. Tissue distribution after single intravenous administration of S-4661 to rats. Shionogi Study # S-4661-B-23-N. Document ID # EDMS-PSDB-5276428. A
27. Basic pharmacokinetic studies of S-4661: whole body ARG in rats after single intravenous dosing of ^{14}C -S-4661. Shionogi Study # S-4661-B-12-N. Document ID # EDMS-PSDB-5292156. G
28. Tissue distribution after repeated intravenous administration of S-4661 to rats. Shionogi Study # S-4661-B-29-N. Document ID # EDMS-PSDB-5275262. A

29. Whole body ARG in rats after repeated intravenous dosing of ^{14}C -S-4661. Shionogi Study # S-4661-B-27-N. Document ID # EDMS-PSDB-5276044. G
30. Basic pharmacokinetic studies of S-4661: tissue distribution of radioactivity after single intravenous administration of ^{14}C -S-4661 to dog. Shionogi Study # S-4661-B-12-N. Document ID # EDMS-PSDB-5293729. G
31. Studies on the pharmacokinetics of S-4661 in experimental animal: protein binding rats of S-4661 to various animal plasmas. Shionogi Study # S-4661-B-05-N. Document ID # EDMS-PSDB-5347331. A
32. Basic pharmacokinetic studies of S-4661: plasma concentration, urinary and fecal excretion of radioactivity after single intravenous administration of ^{14}C -S-4661 to monkey. Shionogi Study # S-4661-B-12-N(6). Document ID # EDMS-PSDB-5294166. G
33. Fetal transport of radioactivity after dosing of ^{14}C -S-4661 to pregnant rats. Shionogi Study # S-4661-B-37-N. Document ID # EDMS-PSDB-5274565. G
34. Whole body ARG in pregnant rats after single intravenous dosing of ^{14}C -S-4661. Shionogi Study # S-4661-B-36-N. Document ID # EDMS-PSDB-5274835. B
35. Study for the metabolic site of S-4661 in rats. Shionogi Study # S-4661-B-51-N. Document ID # EDMS-PSDB-5299128. G
36. Studies on the stability of S-4661 against DHP-I from various animals. Shionogi study # S-4661-EB-526-N. Document ID # EDMS-PSDB-5342970. G
37. Studies on the stability of S-4661 against human-derived DHP-I. Shionogi Study # S-4661-EB-527-N. Document ID # EDMS-PSDB-5343917. G
38. Urinary and fecal excretion of radioactivity after single intravenous dosing ^{14}C -S-4661 to male rats. Shionogi Study # S-4661-B-20-N. Document ID # EDMS-PSDB-5296493. G
39. Urinary and fecal excretion in female rats following single administration of ^{14}C -S-4661. Shionogi Study # S-4661-B-25-N. Document ID # EDMS-PSDB-5297804. G
40. Basic pharmacokinetic studies of S-4661: biliary excretion in female rats following single intravenous administration of ^{14}C -S-4661. Shionogi Study # S-4661-B-12-N(3). Document ID # EDMS-PSDB-5341706. G
41. Urinary and fecal excretion in rats following repeated intravenous administration of ^{14}C -S-4661. Shionogi Study # S-4661-B-028-N. Document ID # EDMS-PSDB-5342411. G
42. Lactal transport of radioactivity after dosing of ^{14}C -S-4661 to lactating rats. Shionogi Study # S-4661-B-38-N. Document ID # EDMS-PSDB-5321733. G
43. Influence on plasma concentration of VPA after co-administration of VAP with S-4661 or other carbapenems to monkeys. Shionogi Study # S-4661-B-52-N. Document ID # EDMS-PSDB-5302157. G
44. Basic pharmacokinetic studies of S-4661: quantitative examination of S-4661 and S-4661-DC in plasma and urine after co-administration of S-4661 with cilastatin to rats. Shionogi Study # S-4661-B-12-N(10). Document ID # EDMS-PSDB-5296126. G
45. Mechanism of renal excretion of S-4661 in rabbits. Shionogi Study # S-4661-B-45-N. Document ID # EDMS-PSDB-5279160. G

46. Mechanism of renal excretion of S-4661 in dogs. Shionogi Study # S-4661-B-47-N. Document ID # EDMS-PSDB-5289494. G

Toxicology

Acute:

1. Intravenous single administration toxicity study of S-4661 in rats. Shionogi Study # S-4662-B-10-L. Document ID # EDMS-PSDB-5039439. A
2. Intravenous nephrotoxicity study of S-4661 in rabbits. Shionogi Study # S-4661-B-19-L. Document ID # EDMS-PSDB-5039456. A
3. Intravenous nephrotoxicity study of S-4661 in rabbits (part II: comparison to other drugs). Shionogi Study # S-4661-B-41-L. Document ID E EDMS-PSDB-5039470. A
4. Intravenous single dose toxicity study of S-4661 in dogs. Shionogi Study # S-4661-B-09-L. Document ID # EDMS-PSDB-5039425. A
5. Toxicological characterization of effective compound: pre-toxicity study of S-4661 in rats. Shionogi Study # — Y-001. Document ID # EDMS-PSDB-5346257. G
6. Intravenous repeated dose nephrotoxicity study of S-4661 in rabbits for 5 days. Shionogi Study # S-4661-B-40-N. Document ID # EDMS-PSDB-5039404. A
7. Study of nephrotoxicity after five days of repeated intravenous administration of S-4661 to rabbits. Shionogi Study # S-4661-TB-569-N. Document ID # EDMS-PSDB-5333767. A

Sub-Chronic

1. Intravenous one-month toxicity study of S-4661 in rats. Shionogi Study # S-4661-B-13-L. Document ID # EDMS-PSDB-5039347. A
2. Three-month repeated intravenous dose toxicity study in rats. — Study # — 92-RVSA-217. Document ID # EDMS-PSDB-5039269. A
3. Preliminary one-month intravenous toxicity study of S-4661 in dogs. Shionogi Study # S-4661-B-14.Y1.N. Document ID # EDMS-PSDB-5346562. G
4. Intravenous one month toxicity study of S-4661 in dogs. Shionogi Study # S-4661-B-14-L. Document ID # EDMS-PSDB-5039371. A
5. Intravenous three-month toxicity study of S-4661 in dogs. Shionogi Study # S-4661-B-34-L. Document ID # EDMS-PSDB-5039387. A
6. A repeated dose toxicity study of S-4661 administered intravenously to juvenile dogs for 1 month. — Study # SBL35-40. Document ID # EDMS-PSDB-5039248. A

Genotoxicology

1. Reverse mutation test of S-4661 with bacteria. Shionogi Study # S-4661-B-11-L. Document ID # EDMS-PSDB-5418269. A
2. In vitro mammalian cell gene mutation (CHO-HGPRT) test with an independent repeat assay. — Study # AA69YY.782001.BTL (Peninsula Pharmaceutical Study # DORI-T-001). Document ID # EDMS-PSDB-5038753. E
3. CHO HGPRT forward mutation assay of JNJ-38174942 with a confirmatory assay and duplicate cultures (TOX9717). Document ID # EDMS-PSDB-6012746. G
4. Chromosomal aberration test of S-4661 in cultured Chinese hamster cells. Shionogi Study # S-4661-B-35-L. Document ID # EDMS-PSDB-5038777. A

5. Micronucleus test of S-4661 with mouse bone marrow cells. Shionogi Study # S-4661-B-39-L. Document ID # EDMs-PSDB-5038786. A

Reproductive Toxicology

1. Preliminary fertility study in rats treated intravenously with S-4661. Shionogi study # S-4661-F-01.Y1-N. Document ID # EDMS-PSDB-5266077.
2. A teratology study on S-4661 by intravenous administration in rabbits (14 days toxicity study). Shionogi Study # S-4661-B-32.Y1-L. Document ID # EDMs-PSDB-5333767. G
3. Study on intravenous administration of S-4661 prior to and in the early stages of pregnancy in rats. Study # R-443. Shionogi Study # S-4661-F-01-L. Document ID # 5039050. A
4. A teratology study on S-4661 by intravenous administration in rats (preliminary study). Shionogi Study # S-4661-B-31.Y1-L. Document ID # EDMS-PSDB-5332980. G
5. Study on intravenous administration of S-4661 during the period of organogenesis in rats. Shionogi Study # S-4661-B-31-L. Document ID # EDMS-PSDB-5039079. B
6. Study on intravenous administration of S-4661 during the period of organogenesis in rats (supplemental study): effects of S-4661 on nursing performance in dams. Shionogi Study # S-4661-B-43-L. Document ID # EDMs-PSDB-5039122. G
7. Teratology study on S-4661 by intravenous administration in rabbits (preliminary teratology study). Shionogi Study # S-4661-B-32.Y2-L. Document ID # EDMs-PSDB-5337401. G
8. Study on intravenous administration of S-4661 during the period of organogenesis in rabbits. Shionogi Study # S-4661-B-32-L. Document ID # 5039095. B
9. Intravenous study for effects of S-4661 on pre- and post-natal development, including maternal function in rats. Shionogi Study # S-4661-F-05-L. Document ID # EDMS-PSDB-5039034. A

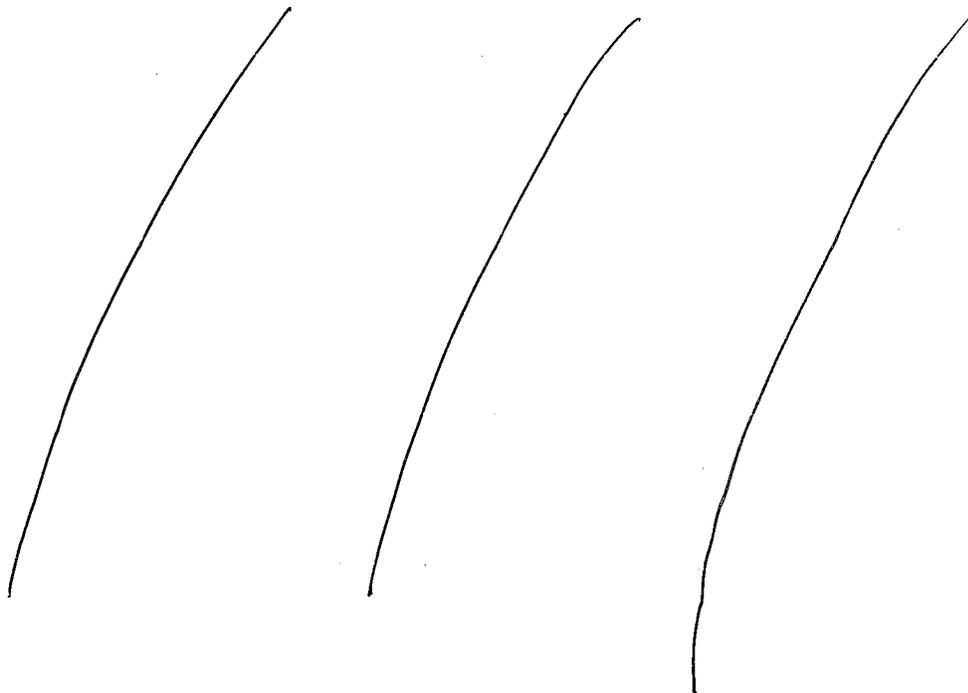
Special Toxicology

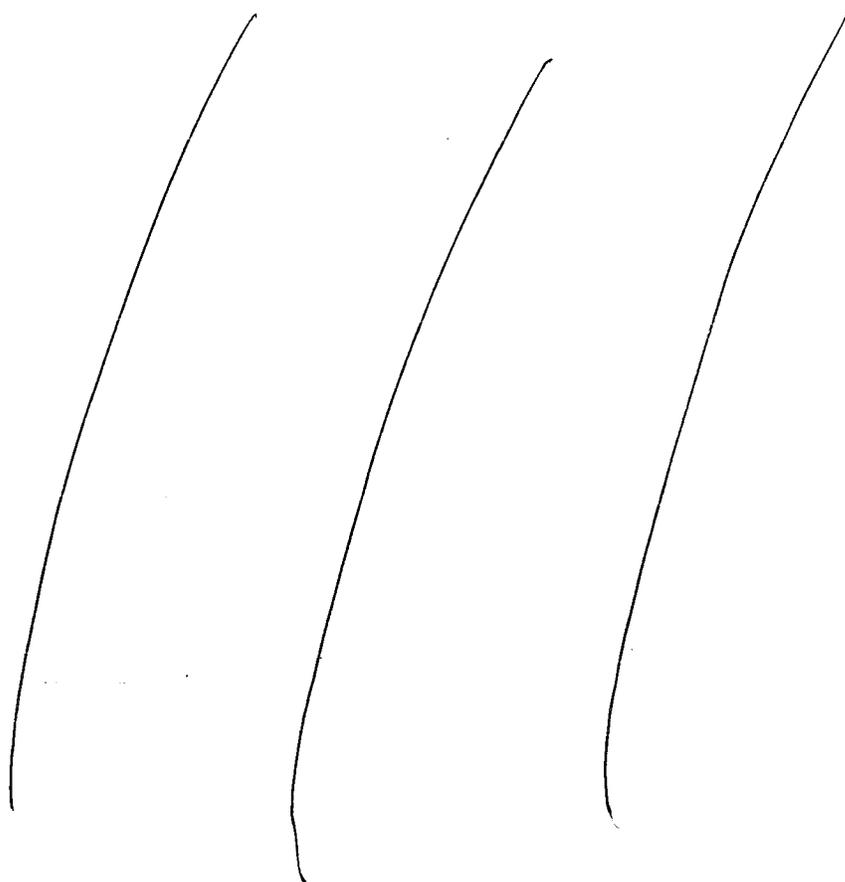
1. Local vascular irritation study of S-4661 in rabbits. Shionogi Study # S-4661-B-18-L. Document ID # EDMS_PSDB-5039561. A
2. Local muscular irritation study of S-4661 in rabbits. Shionogi Study # S-4661-B030-L. Document ID # EDMS_PSDB-5039589. A
3. Antigenicity study of S-4661 (mouse). Study # AG-1110-1. Document ID # EDMS-PSDB-5039487. A
4. Antigenicity study of S-4661 (guinea pig). Study # AG-1110-2. Document ID # EDMS-PSDB-5039501. A
5. In vitro direct Coombs' reaction of S-4661. Shionogi Study # S-4661-B-16-L. Document ID # 5039535. A
6. Intravenous acute tolerance and phototoxicity test of JNJ381749942 (doripenem) in hairless mice (TOX7610). Document ID # EDMS-PSDB-5820805.
7. Hepatotoxicity study of S-4661. Shionogi Study # S-4661-B-49-N. Document ID # EDMS-PSDB-5407595. G

8. Evaluation of hepatic cell injury caused by S-4661 in in-vitro isolated hepatocytes. Shionogi Study # S-4661-B-50-N. Document ID # EDMS-PSDB-5407611. G
9. Hepatotoxicity study of S-4661 in dogs (supplementary study). Shionogi Study # S-4661-B-56-N. Document ID # EDMs-PSDB-5407622. G
10. Study for the influence of S-4661 on hepatic function of mice with a lung infection. Shionogi Study # S-4661-B-68-N. Document ID # EDMS-PSDB-5306517. G
11. Pathological study for the influence of S-4661 on hepatic function of mice with a lung infection: pathological study of the liver in pneumonia model mouse after S-4661 treatment. Shionogi Study # S-4661-B-68.02.N. Document ID # EDMS-PSDB-530-8770. G
12. Measurement of drug concentrations in a study of the influence of S-4661 on hepatic function in a mouse pulmonary infection model. Shionogi Study # S-4661-B-68.01-N. Document ID # EDMS-PSDB-5304208. G

Studies not reviewed within this submission:

The following studies by the inhalation route were not reviewed. An inhalation study conducted outside the United States in normal volunteers was terminated when subjects developed pulmonitis between Day 8 and 10 of dosing. Research by this route was terminated.





2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary (See below.)

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

The mechanistic studies were reviewed in depth by the microbiologist. Doripenem is from the carbapenem class. It is active against both Gram negative and positive bacteria. Doripenem acts by inhibiting bacterial cell wall synthesis by inactivation of penicillin-binding proteins.

Drug activity related to proposed indication: See above.

2.6.2.3 Secondary pharmacodynamics

2.6.2.4 Safety pharmacology

Neurological effects:

- 1. General pharmacology of compound P-11. Shionogi Study # P11-K-13.**

Species tested: Male Scl-ddY mice (5 -6 weeks old, 25-39 g), male and female Beagle dogs (age, weight, not specified).

Drug tested: 104-9261, lot # 104-9261-04.

Vehicle: Physiological saline

Route of administration/Dose: Intravenous or intracisternally (ic) in mice at 0.1 mL/10 g or 50, 250, 500

mg/kg; intracerebroventricularly at 200 uL/dog.

Observations: Gross behavior (i.v. and i.c.), convulsions after electroshock, pentylenetetrazol; EEG (dog only)

Results: Intravenous doses in mice at 50, 250, and 500 mg/kg caused no changes in behavior (with the exception of a slight decrease in abdominal muscle tone 1-2 hours post-dose in ¼ mice at 250 mg/kg) or convulsion frequency after electroshock or pentylenetetrazol (41 mg/kg). Intracisternal administration in mice and dogs resulted in no changes in behavior, convulsions, or EEG (dogs only) at up to 1000 ug/animal.

Conclusions: Doripenem did not cause convulsions in mice or dogs; however, as the neither electroshock nor pentylenetetrazol significantly increased convulsion potential in any group, it is not clear if an adequate dose was used.

2. Interaction of S-4661 and sodium valproate. Shionogi Study # S-4661-B-53-N. Document ID # EDMS-PSDB-5037773.

Species tested: Male Wistar rats, 10-12 weeks, 200-280 g

Drug tested: S-4661, Lot BP6048

Vehicle: Physiological saline

Route of administration/dose/frequency: Intravenous/100, 300, 1000 mg/kg/single dose

Observations: Convulsions following pentylenetetrazol (65 mg/kg), EEG; increase in convulsions with sodium valproate (800 mg/kg) and pentylenetetrazol or bicuculline.

Results: With i.v. administration of up to 1000 mg/kg doripenem, no increase in convulsions, no disturbances of sleep cycles, or EEG were noted. A dose of 800 mg/kg of sodium valproate 35 minutes prior to pentylenetetrazol administration totally ablated the seizure potential (previously 100% incidence, duration of approximately 90 seconds, with an average of 2 seizures/rat). Addition of up to 1000 mg/kg doripenem to the sodium valproate and pentylenetetrazol resulted in convulsions in 10% of the rats. Similar results were seen with bicucullin.

Conclusions: Doripenem did not possess either the potential to cause seizures or the ability to block seizure ablation with valproate (acting via GABA receptors) or bicucullin. Concentrations of pentylenetetrazol were sufficient in this study.

3. Effects of S-461 on electroencephalogram and behavior in dogs. Serial # 038

Conducted at Shionogi, Ltd. In Jan, 2003.

Species: Beagle dogs, 7 months, 9.3-10.8 kg, with implanted EEG electrodes

Route/dose/duration: Intracerebroventricular (icv) at 0 (saline), 100, 300, 1000 ug/dog in volume of 100 uL/dog; single dose

Observations: Clinical signs and EEG signals for 1 hour after dosing.

Results: There were no effects at up to 1000 ug/dog in behavior or EEG. Imipenem and Meropenem both caused seizures/convulsions or EEG spikes at 100 ug/dog.

4. Inhibitory effects of S-4661 on GABA receptor binding in mouse synaptic membranes. Study # S-4661-SB-552-N.

Conducted at Shionogi in 2003.

Test system: Isolated synaptic membranes from CD-1 mice; inhibition of ³H-muscimol binding.

Drugs: Doripenem compared to imipenem, meropenem, panipenem, and cefazolin; 0.3-10 mmol/L

Vehicles: Water or DMSO

Results: The IC50 concentrations are shown in the following table.

IC50 values for 3H muscimol binding to mouse synaptic membranes	
Drug	IC50 (mmol/L)
Doripenem	46.44
Imipenem	0.48
Meropenem	15.63
Panipenem	0.63
Cefazolin	0.99

Conclusion: The sponsor is using GABA inhibition as an index of pro-convulsive activity. Thus, doripenem has low pro-convulsive potential.

5. Proconvulsive effects of S-4661 following intracerebroventricular injection in mice. Study # S-4661-SB-553-N.

Conducted at Shionogi Research in 2003.

Test system: Male CD-1 mice, injected intracerebrally (lateral ventricle), 10 /dose group

Drug: Doripenem, imipenem, meropenem, panipenem or cefazolin at concentrations between 2.5 and 100 ug/mouse

Vehicle: Physiological saline

Results: The drugs were monitored for their ability to cause convulsions in the first 10 minutes after injection. Neither meropenem nor doripenem caused convulsions at doses up to 100 ug/mouse. The CD50 (dose which caused convulsions in 50% of the mice) values are shown in the following table.

CD50 values in mice	
Drug	CD50 (ug/mouse)
Doripenem	>100
Imipenem	4
Meropenem	>100
Panipenem	13
Cefazolin	20

Conclusions: Doripenem is less convulsive in mice than most of the other penems tested.

6. Effects of S-4661 on convulsion induced by pentylenetetrazol or electroshock in mice. Study # S-4661-SB-554-N.

Conducted at Shionogi Research in 2003.

Test system: CC-1 mice, male and female, 8/dose group

Drug: Doripenem at 100, 200, 400 mg/kg; imipenem, meropenem, panipenem at 100, 200, 400 mg/kg

Vehicle: Physiological saline

Results: The threshold current or pentylenetetrazol concentration necessary to cause convulsion was measured in the presence of a series of penems and cefazolin. At doses up to 400 mg/kg, no changes in thresholds were noted for any of the compounds.

Conclusions: There were no effects with doripenem at single doses up to 400 mg/kg on convulsion threshold for electroshock or pentylenetetrazol.

7. Effects of S-4661 on pentylenetetrazol-induced convulsion in mice. Study # S-4661-SB-570-N.

Conducted at Shionogi Research in 2003.

Test system: CC-1 mice, male and female, 8/dose group

Drug: Doripenem at 250, 500 mg/kg; imipenem, meropenem, panipenem at 250, 500 mg/kg

Vehicle: Physiological saline

Results: Doripenem at 250 or 500 mg/kg had no effects on the incidence of pentylenetetrazol-induced convulsion. Only imipenem saw potentiation at both 250 and 500 mg/kg.

Conclusions: There were no effects with doripenem at single doses up to 500 mg/kg on convulsion for pentylenetetrazol.

8. Effects of S-4661 on electroencephalogram and behavior in rats. Study # S-4661-SB-555-N.

Conducted at Shionogi Research in 2003.

Test system: Male Sprague Dawley rats, n=6/group

Drug: Doripenem (lot # B0602) at 100, 200, or 400 mg/kg i.v.; imipenem, meropenem at 100, 200, 400 mg/kg

Vehicle: Physiological saline

Analysis: EEG and visual observation at least 5 days after surgery to implant electrodes, observed over 2 hours post-injection.

Results: There were no effects on behavior or EEG in the doripenem group up to and including 400 mg/kg. Meropenem showed "wet dog shakes" at 200 and 400 mg/kg in most animals, while imipenem showed wet dog shakes beginning at 100 mg/kg, spikes in EEG beginning at 200 mg/kg, and convulsions at 400 mg/kg.

Conclusions: Doripenem, on a mg/kg basis, was less likely than meropenem or imipenem to cause CNS effects.

9. Effects of S-4661 on central nervous system in rats. Study # S-4661-SF-538-L.

Conducted at _____ in 2003. GLP and QA.

Test system: Sprague Dawley rats, n=8

Drug: Doripenem (lot # B0602), at 30, 100, 300 mg/kg i.v.; single dose

Analysis: Visual observation

Results: There were no significant differences in behavior, righting reflex, pain response (tail pinch), startle reflex or grip with single treatments of doripenem at up to 300 mg/kg.

Overall conclusions:

The central nervous system effects of doripenem were investigated in mouse, rat and dog by several techniques. Other penems, e.g. imipenem, either cause seizures, or lower the potential for a seizure (in particular those caused by electroshock or pentylentetrazol). This may be through effects on GABA receptors. Doripenem did not cause seizures by itself when administered intravenously at doses up to 1000 mg/kg in the mouse or 300 mg/kg in rat; nor when administered intra-cisternally at up to 1000 ug/animal in dogs or mice. No seizure potentiation was seen with doripenem and electroshock or pentylentetrazol at doses up to 400 mg/kg (mouse, rat). Further, no changes in the anti-convulsant effects of sodium valproate were noted with doripenem. A rat dose of 400 mg/kg is the human equivalent of 65 mg/kg, more than twice the human total daily dose of 25 mg/kg.

Cardiovascular effects:

1. Effects of S-4661 on cardiovascular system in conscious dogs. Study # S-4661-SF-539-L.

Conducted at _____ in 2003 with GLP, QA.

Test system: Beagle dogs (male), 7-8 months old, 7.9-8.8 kg, n= 4

Drug: Doripenem, Lot # B0602, at 0, 10, 30, 100 mg/kg i.v.; at least 7 days between each treatment.

Vehicle: Physiologic saline

Analysis: Dogs were telemeterized for blood pressure, heart rate, and ECG. Readings were taken over 30 seconds at -1 hour, 5, 10, 30 minutes, 1, 2, 4, and 6 hours post-dose.

Clinical observations were also made.

Results: The effects on cardiac parameters were seen within the first hour following dosing. There were no statistically significant differences in heart rate, blood pressure or QT interval between treated and control dogs.

Conclusions: Doripenem did not affect cardiac parameters significantly in dogs at doses up to 100 mg/kg, the NOAEL in this study.

Overall conclusions:

To investigate the cardiac effects of doripenem, hERG, Purkinje and telemeterized dogs were used. Doripenem was negative in the purkinje fiber assay at concentrations up to 300 umol/L. Similarly, the hERG assay was negative at up to 300 umol/L. Telemeterized dogs did not show any effects on cardiac parameters at up to 100 mg/kg doripenem intravenously as a single dose.

Pulmonary effects:

1. Effects of S-4661 on respiratory system in rats. Study # S-4661-SF-540-L.

Conducted at _____ in 2003 according to GLP with QA.

Test system: Male Sprague-Dawley rats, 5 weeks old. N=6.

Drug: Doripenem in physiologic saline at 0, 30, 100, 300 mg/kg as a single i.v. dose.

Analysis: Measurements of respiratory rate, tidal volume, and minute volume before and 5 minutes after drug administration.

Results: There were no significant differences in tidal volume, respiratory rate, or minute volume between pretest and 5 minutes post-dose or between treatments.

Conclusions (and Overall Conclusions): Doripenem did not affect respiratory parameters at doses of up to 300 mg/kg in the first 5 minutes.

Renal effects: See studies listed under “Acute Toxicology”.

Gastrointestinal effects: No studies on the gastrointestinal effects of doripenem were conducted.

Abuse liability: There is no reason to suspect abuse liability for doripenem.

Other: None.

2.6.2.5 Pharmacodynamic drug interactions

With the exception of sodium valproate (see above), drug interactions were not investigated.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The pharmacokinetics of doripenem have been investigated in multiple species including mouse, rat, dog, rabbit, and monkey. Toxicokinetic studies were not conducted concurrently with the one and three month rat and dog studies. The half life was generally less than 1 hour. No gender differences were noted. No accumulation with multiple doses was observed. Exposure was relatively linear with dose. In the pregnant rat, exposures were higher than those seen in the non-pregnant rat (or males). Whether this was due to inter-experimental variation could not be determined. The data from the different species and studies are summarized in the table at the end of the pharmacokinetics section of this document.

Doripenem is widely distributed in both rat and dog. The majority of drug in both species was found in the kidney, and subsequently, in urine. A secondary site was the bone. Extremely low levels were found in brain and eye suggesting poor passage through the blood brain barrier. Levels of doripenem were at least 40 fold greater in the maternal circulation than in fetal circulation. The highest fetal concentration of doripenem was seen in the fetal kidney.

Doripenem has relatively little binding to plasma proteins. In the mouse and rat, 25 and 35% of the drug is protein bound, while in dogs, monkeys, and humans, 10% or

less of the drug is bound to plasma proteins. Protein binding of doripenem is approximately 12% in the rabbit.

Doripenem is metabolized in rat and dog to the dicarboxylic acid moiety (D-DC). In the urine of rats, D-DC accounts for approximately 50% of the total dose excreted. D-DC accounts for approximately 15% of the dose excreted in the dog. D-DC is inactive. Doripenem is not a substrate for human P450 enzymes. DHP-1 (dihydropeptidase) appears to be responsible for the breakdown of doripenem to D-DC and the activity is inhibited by cilastatin.

Excretion in the rat, monkey and dog is primarily via the urine. With the exception of a single study in female rats (Sprague Dawley where 88% of the dose was found in the urine), between 90 and 97% of the initial dose is excreted in urine with the majority excreted within the first 2 hours. Fecal excretion accounted for between 0.1% (male rats) and 10% (female rats). As up to 3% of the dose of doripenem can be detected in the bile when only 0.1% is seen in the feces, some enterohepatic recycling may be occurring. These studies did not differentiate between parent and the D-DC metabolite. In the studies where parent versus metabolite were measured in the urine, the metabolite accounted for approximately 30% of the dose, but when cilastatin was added only 5% of the dose was excreted as D-DC. Rats excreted 10% of the total dose as D-DC. Renal tubular secretion was partly responsible for doripenem elimination in the rabbit, but not in dog.

Doripenem did not affect the pharmacokinetics of valproic acid.

2.6.4.2 Methods of Analysis: [see under individual study reviews, and in summary tables.]

2.6.4.3 Absorption

1. Dose linearity of plasma concentration in rats following single administration of S-4661. Study # S-4661-PB-558-N.

Conducted at: Shionogi Research, in 2003.

System studied: Male and female Sprague Dawley rats, n=4-5.

Drug: Doripenem at 0, 5, 20, 40 mg/kg in males, 20 mg/kg in females, single i.v. dose

Analysis method: Parent drug, antimicrobial activity, sampling at 0, 5, 15, 30, 60, 90 and 120 minutes post-dose (bolus).

Results: The sponsor noted that no active metabolites had been detected in plasma or urine. Drug was no longer detectable by 1, 1.5 or 2 hours in the 5, 20 and 40 mg/kg rats respectively. The PK values are shown in the following table.

Single dose PK of doripenem in rats			
Dose	Gender	AUC (ug.h/mL)	T _{1/2} (hours)
5	M	2.3 ± 0.3	0.088 ± 0.004
20	M	9.8 ± 1.0	0.125 ± 0.007
	F	11.2 ± 0.7	0.145 ± 0.046
40	M	16.6 ± 1.1	0.132 ± 0.024

Conclusions: AUC was linear with dose in the 5-40 mg/kg range. No significant gender differences were noted. The half-life is less than 10 minutes.

2. Plasma concentration in rats following repeated administration of S-4661. Study # S-4661-PB-559-N.

Conducted at: Shionogi Research, in 2003.

System studied: Male Sprague Dawley rats, n=5.

Drug: Doripenem, lot # B0602 in 1% physiologic saline; 20 mg/kg, i.v. dose, once daily for 10 days

Analysis method: Parent drug, antimicrobial activity, sampling at 0, 5, 15, 30, 60, 90 and 120 minutes post-dose (bolus).

Results: Plasma levels were non-detectable (<0.03 ug/mL) by 90 minutes post-dose.

The AUC was 9.8 ± 0.7 ug.hr/mL with a half-life of 0.118 hours.

Conclusions: The pharmacokinetics of single and repeated dose doripenem in rats did not differ significantly.

3. Measurement of plasma concentration of S-4661 in rat dose-linearity study.

Study # S-4661-PB-560-N.

Conducted at Shionogi Research, in 2004

System studied: Male SD rats from study # S-4661-PB-558-N (male rats treated i.v. at 5, 20, 40 mg/kg, females at 20 mg/kg only).

Method of analysis: antimicrobial assay using *E. coli*. The detection limit was 0.03 ug/mL.

Results: There were no significant differences between the two types of antimicrobial assays.

4. Measurement of plasma concentrate of S-4661 in rats repeated dosing study.

Study # S-4661-PB-561-N.

This is also a repeat measurement using a different strain/procedure of bacterial assay with the plasma from the rats in study S-4661-PB-559-N. Differences between the two techniques were minimal.

5. Plasma concentration of S-4661 in safety pharmacology study in rats. Study # S-4661-TF-564-L.

Conducted at _____ in 2003

System studied: Male Sprague Dawley rats, 5 weeks old, n=4

Drug: Doripenem in physiologic saline at 30, 100, 300 mg/kg i.v. sampling at 5, 15, 30, 60, 90, 120, 240 minutes post-dose

Analysis: Although the concentration of the test solution was measured by HPLC, the methodology for analyzing the plasma samples was not given other than the samples were shipped to Shionogi for measurements. (The method is discussed below in PK #8)

Results: The pharmacokinetic parameters are shown in the following table.

Pharmacokinetics of i.v. doripenem in rats			
Dose (mg/kg)	Cmax (ug/ml)	AUC (ug.hr/mL)	T _{1/2} (min)
30	53.7 ± 1.8	9.6 ± 0.5	6.3 ± 1.6
100	166.4 ± 8.3	29.9 ± 2.0	7.6 ± 1.5

300	547.9 ± 51.5	99.4 ± 8.1	10.3 ± 1.8
-----	--------------	------------	------------

Conclusions: The pharmacokinetic parameters of doripenem are nearly linear through 300 mg/kg.

6. Plasma concentration of S-4661 in safety pharmacology study in dogs. Study # S-4661-TF-565-L.

Conducted at _____ in 2003

System studied: Male Beagle dogs, 9-10 months old, n=4

Drug: Doripenem (Lot B0602) in physiologic saline at 10, 30, 100 mg/kg i.v. sampling at 5, 10, 30, 60, 120, 240, 360 minutes post-dose

Analysis: HPLC assay with internal standard

Results: The pharmacokinetic parameters are shown in the following table.

Pharmacokinetics of i.v. doripenem in rats			
Dose (mg/kg)	C _{max} (ug/ml)	AUC (ug.hr/mL)	T _{1/2} (min)
10	55.9 ± 6.3	35.5 ± 0.5	38.1 ± 4.1
30	178.2 ± 41.7	98.9 ± 8.1	35.9 ± 2.5
100	536.9 ± 109.5	309.9 ± 22.9	37.9 ± 0.4

Conclusions: The pharmacokinetic parameters of doripenem are nearly linear through 100 mg/kg. The half-life is approximately 3-5 times longer than in rat.

7. Plasma concentration of S-4661 in safety pharmacology study in rats: determination of S-46612 in rat plasma. Study # S-4661-TB-566-L.

The sponsor included the protocol for the plasma analysis of the rat safety pharmacology study. The method was HPLC analysis with monitoring at 300 nm.

8. Toxicokinetics at 5-day intravenous administration of doripenem hydrate in rats. Shionogi Study # S-4661-TF-612-L. Document ID # EDMS-PSDB-5810222.

Species studied: Male and female Sprague Dawley rats.

Drug: Doripenem in physiological saline

Route, schedule, duration: Once daily for 5 consecutive days, intravenous at 0, 30, 100, 300 mg/kg

Method of Analysis: HPLC with detection at 300 nm for parent, MS for metabolites

Sampling times: 0-2 hours post-dose on day 1 and day 5 of consecutive daily i.v. treatment.

Results: The PK parameters are shown in the table below.

Text Table 1. Concentrations of Doripenem and its metabolite in plasma (Day 1)

Analytes	Dose (mg potency/kg/day)	Sex	Day 1 of administration			
			T _{1/2} (min)	C _{max} (ng/mL)	AUC ₀₋₄ (µg·min/mL)	AUC _{0-∞} (µg·min/mL)
Doripenem	30	Males	6.54	62.78	761.70	762.93
		Females	6.33	66.15	746.49	747.50
	100	Males	6.69	253.41	2821.57	2825.53
		Females	6.71	239.40	2452.53	2455.63
	300	Males	6.67	858.55	9756.88	9775.46
		Females	6.49	789.97	8196.82	8205.33
Doripenem dicarboxylic acid (Doripenem metabolite)	30	Males	19.74	41.89	1684.53	1710.17
		Females	18.27	40.21	1481.03	1496.85
	100	Males	20.78	128.05	5287.41	5394.45
		Females	18.25	155.25	5497.04	5553.12
	300	Males	18.66	429.47	17482.78	17713.97
		Females	18.89	436.71	15203.33	15401.71

Text Table 2. Concentrations of Doripenem and its metabolite in plasma (Day 5)

Analytes	Dose (mg potency/kg/day)	Sex	Day 5 of administration			
			T _{1/2} (min)	C _{max} (µg/mL)	AUC ₀₋₄ (µg·min/mL)	AUC _{0-∞} (µg·min/mL)
Doripenem	30	Males	6.46	65.63	711.39	712.50
		Females	6.27	72.55	792.97	793.96
	100	Males	6.16	235.33	2447.29	2450.04
		Females	6.43	285.54	2955.55	2960.19
	300	Males	6.69	953.52	9658.01	9677.68
		Females	6.32	730.45	7922.17	7933.37
Doripenem dicarboxylic acid (Doripenem metabolite)	30	Males	19.11	42.29	1618.71	1640.22
		Females	18.66	42.38	1511.90	1529.94
	100	Males	19.12	156.21	5650.26	5726.95
		Females	19.35	131.15	4836.07	4903.90
	300	Males	18.79	412.17	16365.09	16562.20
		Females	16.76	450.33	14727.10	14825.04

Conclusions: There were no gender differences, no accumulation, nor differences between AUC_{0-2h} and AUC_{0-∞}.

9. Toxicokinetics at 5-day intravenous administration of doripenem hydrate in dogs. Shionogi Study # S-4661-TF-613-L. Document ID # EDMS-PSDB-5810229.

Species studied: Male and female Beagle dogs, males 8.1-9.1 kg; females 7.8-8.5 kg.

Drug: Doripenem in physiological saline

Route, schedule, duration: Once daily for 5 consecutive days, intravenous at 0, 10, 30, 100 mg/kg.

Method of Analysis: HPLC with detection at 300 nm for parent, MS for metabolites

Sampling times: 0-6 hours post-dose on day 1 and day 5 of consecutive daily i.v. treatment.

Results: The PK parameters are shown in the table below.

TK Parameters of Doripenem (Mean, n=3)

Sex	Dose*	T _{1/2} (min)		C _{max} (µg/mL)		AUC _{0-6h} (µg·min/mL)		AUC _{0-∞} (µg·min/mL)	
		Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
Males	10	41.16	43.91	30.40	24.49	1670.77	1712.27	1700.56	1726.32
	30	40.26	44.43	107.66	90.89	5589.89	5320.48	5600.33	5337.37
	100	40.12	45.10	404.74	367.89	19439.94	17919.61	19473.90	17972.83
Females	10	38.37	40.91	32.97	28.66	1710.63	1737.86	1734.81	1754.96
	30	37.55	41.93	90.92	100.27	5030.10	5115.78	5035.88	5127.09
	100	36.69	43.62	436.81	404.52	19631.51	17434.25	19665.30	17481.83

*Unit: mg potency/kg/day

TK Parameters of DRPM-DC (Mean, n=3)

Sex	Dose*	T _{1/2} (min)		C _{max} (µg/mL)		AUC _{0-6h} (µg·min/mL)		AUC _{0-∞} (µg·min/mL)	
		Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
Males	10	89.99	110.43	0.99	0.81	102.62	95.22	145.53	154.13
	30	79.23	86.23	2.41	2.47	297.02	391.77	365.63	427.02
	100	63.99	78.24	10.09	12.12	1247.12	1561.19	1392.78	1631.63
Females	10	80.24	93.80	1.00	0.91	106.74	84.06	144.33	146.59
	30	62.34	83.29	2.27	2.53	298.84	389.25	323.57	422.07
	100	63.40	72.42	11.13	13.31	1348.26	1611.39	1378.68	1668.65

*Unit: mg potency/kg/day

Conclusions: In the dogs, there were no significant differences between the pharmacokinetic parameters with gender, Day 1 vs. Day 5, or AUC_{0-6h} and AUC_{0-∞}.

10. Toxicokinetics at intravenous administration of doripenem hydrate in pregnant rats. Shionogi Study # S-4661-TF-614-L. Document ID # EDMS-PSDB-5810246.

Species studied: Female copulated Sprague Dawley rats, 11 weeks old

Drug: Doripenem in physiological saline

Route, schedule, duration: Once daily for 11 consecutive days (Gestation day 7-17), intravenous at 0, 30, 100, 300 mg/kg.

Method of Analysis: HPLC with detection at 300 nm for parent, MS for metabolite

Sampling times: 0-2 hours post-dose on Gestation Day 7 and 17 of consecutive daily i.v. treatment.

Results: The PK parameters are shown in the table below.

PK parameters in pregnant rats, Parent compound (doripenem)						
Dose (mg/kg)	C _{max} (ug/mL)		AUC _{0-2h} (ug.min/mL)		T _{1/2} (min)	
	GD 7	GD 17	GD 7	GD 17	GD 7	GD 17
30	106.2	82.1	1219.3	957.7	6.86	7.26
100	379.3	486.6	4394.0	5511.1	7.26	9.63
300	1150.6	1354.7	13352.4	15789.7	6.77	12.74

PK parameters in pregnant rats, Doripenem Dicarboxylic Acid						
Dose (mg/kg)	C _{max} (ug/mL)		AUC _{0-2h} (ug.min/mL)		T _{1/2} (min)	
	GD 7	GD 17	GD 7	GD 17	GD 7	GD 17
30	54.0	33.8	2199.6	1544.0	21.6	24.4
100	165.5	175.5	7160.6	7751.8	20.3	23.2
300	487.8	495.0	21028.8	23428.0	18.7	20.4

Conclusions: There were no significant differences between pharmacokinetic parameters on GD 7 and 17. AUC and Cmax were relatively linear with dose up to 300 mg/kg. The plasma levels were higher in pregnant than non-pregnant rats, although the elimination half-lives did not differ significantly.

11. Toxicokinetics at intravenous administration of doripenem hydrate in pregnant rabbits. Shionogi Study # S-4661-TF-615-L. Document ID # EDMS-PSDB-5180261.

Species studied: Female Japanese White rabbits, 14 weeks old

Drug: Doripenem in physiological saline

Route, schedule, duration: Once daily for 13 consecutive days (Gestation day 6-18), intravenous at 0, 12.5, 25, 50 mg/kg.

Method of Analysis: HPLC with detection at 300 nm for parent, MS for metabolite

Sampling times: 0-4 hours post-dose on Gestation Day 6 and 18 of consecutive daily i.v. treatment.

Results: The PK parameters are shown in the table below. The LOQ was 0.1 ug/mL/

PK parameters in pregnant rats, Parent compound (doripenem)						
Dose (mg/kg)	Cmax (ug/mL)		AUC _{0-4h} (ug.min/mL)		T _{1/2} (min)	
	GD 6	GD 18	GD 6	GD 18	GD 6	GD 18
12.5	33.3±8.3	30.9±5.9	1182.6±296.0	1194.6±291.4	15.7±1.1	16.5±0.8
25	73.6±9.9	84.1±9.4	2556.5±210.0	2836.3±248.2	14.6±0.7	17.0±2.3
50	161.3±10.1	167.2±25.8	5491.3±104.6	5526.5±192.7	15.2±0.8	15.5±1.0

PK parameters in pregnant rats, Doripenem Dicarboxylic Acid						
Dose (mg/kg)	Cmax (ug/mL)		AUC _{0-4h} (ug.min/mL)		T _{1/2} (min)	
	GD 6	GD 18	GD 6	GD 18	GD 6	GD 18
12.5	2.9±0.7	2.8±0.6	237.7±57.6	216.5±52.7	38.5±1.6	35.9±1.2
25	6.9±0.5	7.2±1.7	532.5±82.0	615.0±159.0	37.9±8.6	42.8±9.7
50	15.9±1.1	13.3±1.6	1335.1±162.0	1174.9±99.2	39.2±2.5	43.1±3.4

Conclusions: While the plasma half life in rabbits is longer than that in rats, there is still no accumulation.

12. Pharmacokinetic studies of S-4661 in juvenile dogs. Shionogi Study # S-4661-B-69-N. Document ID # EDMS-PSDB-5280581.

Species studied: Male Toyo Beagle dogs, age 24-25 days, 0.9-1.1 kg

Drug: Doripenem in physiological saline

Route, schedule, duration: Single dose, 20, 50 mg/kg intravenous.

Method of Analysis: Bioassay (bacteria)

Sampling times: Plasma and urine, 0-6 hours post-dose.

Results: The PK parameters are shown in the table below. The LOQ was 0.1 ug/mL.

Pharmacokinetic values in juvenile dogs by bacterial assay (n=4)			
Dose (mg/kg)	Cmax (ug/mL)	AUC (ug.h/mL)	T _{1/2} (h)
20	63.0 ± 6.3	53.0 ± 3.8	0.7 ± 0.03
50	139.0 ± 23.3	111.2 ± 9.2	0.7 ± 0.1

Dogs excreted $73 \pm 3\%$ and $64 \pm 7\%$ of the dose at 20 and 50 mg/kg respectively in the urine within 24 hours with the majority of the drug removed within the first 2 hours.

2.6.4.4 Distribution

1. Tissue distribution of ^{14}C -doripenem, as studied by whole-body autoradiography, in the pigmented male rat after single intravenous administration of ^{14}C -doripenem at 20 mg/kg.

Species studied: Long-Evans rat; n=5, approximately 245 g

Drug: ^{14}C -Doripenem in physiological saline

Route, schedule, duration, dose: Single dose, intravenous, 20 mg/kg

Method of Analysis: Whole body autoradiography; LSC for blood, eye

Sampling times: 5 minutes, 6 hours, 1, 3, 14 days

Results: In every tissue except bone, the highest level of label was seen at 5 minutes.

The only organ with tissue concentrations higher than blood was the kidney, which had detectable levels of radioactivity through 96 hours. Levels of radioactivity in brain, eye and testes were lowest.

Conclusions: Minimal levels of doripenem were noted in the brain. Highest levels of drug were observed in the kidneys. Doripenem was not sequestered in any organ and was rapidly cleared.

2. Basic Pharmacokinetic studies of S-4661: Whole body ARG in rats after single intravenous dosing of ^{14}C -S-4661. Shionogi Study # S-4661-B-12-N(2).

Species studied: Sprague Dawley rats, male, 8 weeks old, 324-350 g, n=1 rat/timepoint

Drug: ^{14}C -Doripenem in physiological saline

Route, schedule, duration, dose: Single dose, intravenous, 20 mg/kg

Method of Analysis: Whole body autoradiography (no densitometry analysis).

Sampling times: 5, 15, 30 minutes; 1, 2, 6, 24, 48 hours

Results: The highest levels of radiolabel were observed at 5 minutes post-dose. The greatest concentration of label was in the kidneys, with radiolabel present in urine even at 5 minutes. Radiolabel remained higher in the liver through 30 minutes, with some label seen in the GI tract. Most of the organs only showed background levels of radiolabel by 6 hours, with kidney still showing the most label.

Conclusions: Doripenem is rapidly excreted from the rat with minimal sequestration within organs.

3. Basic Pharmacokinetic studies of S-4661: Tissue distribution of radioactivity after single intravenous administration of ^{14}C -S-4661 to dog. Shionogi Study # S-4661-B-12-N(5).

Species studied: Aburahi beagle, male, 10 months old, 8.6-10 kg, n=3, 1/timepoint

Drug: ^{14}C -Doripenem in physiological saline

Route, schedule, duration, dose: Single dose, intravenous, 20 mg/kg

Method of Analysis: LSC (liquid scintillation counting)

Sampling times: 10 minutes, 2.5 and 24 hours

Results: Only the kidneys showed higher levels of radiolabel than that in plasma and still showed some label at 24 hours (almost every other organ was nearing background levels). At 2.5 hours, significant levels of label were noted in the bile. Minimal radiolabel was seen in the brain and eyes.

Conclusions: Kidney was the main organ for tissue distribution. Radiolabel was quickly cleared from all organs, with no sequestration.

4. Whole-body ARG in rats after repeated intravenous dosing of ^{14}C -S-4661.

Shionogi Study # S-4661-B-27-N.

Species studied: Sprague Dawley rats, male, 7 weeks old, 253-271 g.

Drug: ^{14}C -Doripenem in physiological saline, — pure

Route, schedule, duration, dose: Intravenous, 20 mg/kg, daily for 10 consecutive days

Method of Analysis: Whole body autoradiography

Sampling times: 5 min, 1, 6, 24, 48, 96, 168 hours (1 rat/timepoint)

Results: The greatest degree of radioactive label was seen in the kidneys and persisted (albeit weakly) through 168 hours. Although less than that seen in blood, the next highest and most persistent, was the radiolabel in the liver and bone.

Conclusions: The distribution of radioactivity did not differ significantly between single and multiple doses of doripenem in the rat.

5. Fetal transport of radioactivity after dosing of ^{14}C -S-4661 to pregnant rats.

Shionogi Study # S-4661-B-37-N.

Species studied: Sprague Dawley rats, females, 11-12 weeks old; 343±19 g at GD 13, 417±20 g at GD 19.

Drug: ^{14}C -Doripenem in physiological saline, — pure

Route, schedule, duration, dose: Intravenous, 20 mg/kg, on GD 19, or 1000 mg/kg on GD 13 or 19.

Method of Analysis: liquid scintillation counting (LSC)

Sampling times: Maternal and fetal tissues; 20 mg/kg: 6, 24 hours; 1000 mg/kg: 0.5, 6 hours

Results: With 20 mg/kg, the initial timepoint, 5 minutes, the highest levels of radioactivity were noted for all organs including bone. Kidneys were the only organ that showed higher levels of radiolabel than plasma. Maternal blood at the initial timepoint had 42 fold higher levels of radioactivity than fetal blood. Fetal kidney had the highest level of radioactivity of the organs measured and maternal kidney had 420 fold higher levels of radiolabel. Fetal tissues had longer half-lives of radioactivity as compared to maternal tissues. With the 1000 mg/kg dose, the maternal blood levels were 77 fold higher than the entire fetus.

2.6.4.5 Metabolism

1. Cytochrome P450 reaction phenotyping for radiolabeled doripenem. Dori-PK-001.

System studied: Human liver microsomes with NADPH generating system, incubation for 0, 30, 120 minutes; positive control, testosterone.

Drug: Radiolabeled doripenem (lot # 2003-0040-031-01), 100 uM

Analysis method: HPLC

Results: Approximately 90% of the radioactivity was associated with the parent drug peak in the presence of NADPH and up to 120 minutes of reaction time. Testosterone was metabolized in this system at historic control levels.

Conclusions: Doripenem was not a substrate for P450 enzymes.

2. Basic pharmacokinetic studies of S-4661: examination for metabolites of S-4661. Shionogi Study # S-4661-B-12-N(7).

Species studied: Sprague Dawley rats, males, 8-16 weeks old; 341-596 g

Drug: Doripenem in physiological saline. pure

Route, schedule, duration, dose: Intravenous, single administration at 5, 20, 40 mg/kg

Method of Analysis: HPLC separation with LC/MS identification

Samples: Urine (solid phase extraction) collected within the first hour after dosing.

Results: The urinary metabolite of doripenem was identified as the open ring form of doripenem, doripenem dicarboxylic acid.

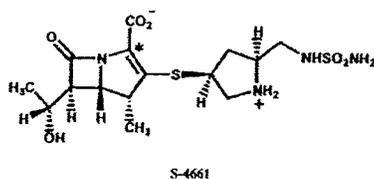


Fig. 1. Chemical Structure of S-4661 (*: ¹⁴C labeled position)

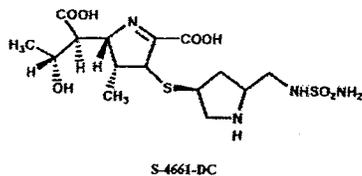


Fig. 2. Chemical Structure of S-4661-DC

3. Basic pharmacokinetic studies of S-4661: Quantitative examination for S-4661 and S-4661-DC in plasma and urine after single administration of S-4661 to dogs. Shionogi Study # S-4661-B-12-N(8).

Species studied: Beagle dogs, male, 8-9 months old, approximately 10 kg.

Drug: Doripenem in physiologic saline

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: HPLC

Samples: Plasma at 5, 10, 20, 30 minutes, 1, 2, 4, 6, 8, 24 hours; urine at 0-1, 1-2, 2-4, 4-6, 6-8 (all via catheter), 8-24, 24-48 hours (cage collection).

Results: Parent and the dicarboxylic acid form of doripenem were the only components found in dog urine and plasma. The pharmacokinetic parameters are shown in the following tables.

Table 6. Pharmacokinetic parameters of S-4661 and S-4661-DC after intravenous administration of S-4661 (20 mg/kg) to male dogs

	AUC*1 µg·hr/mL	Cmax*2 µg/mL	CL _{tot} mL/hr/kg	CL _r mL/hr/kg	CL _{nr} mL/hr/kg	T _{1/2α} hr	T _{1/2β} hr
S-4661	91.36 ±3.43		239 ±8	167 ±11	72 ±4	0.06 ±0.02	0.71 ±0.05
S-4661-DC	3.83 ±1.86	2.27 ±0.10					

*1: µg equivalent of S-4661-hr/mL for S-4661-DC

*2: µg equivalent of S-4661/mL for S-4661-DC

CL_r = CL_{tot} × Excretion ratio, CL_{nr} = CL_{tot} - CL_r

Table 7. Cumulative excretion of S-4661 and S-4661-DC in urine after intravenous administration of S-4661 (20 mg/kg) to male dogs

	Cumulative excretion (% of dose)					
	Time after administration (hr)					
	0-1	0-2	0-4	0-6	0-8	0-24
S-4661	47.37 ±4.00	62.73 ±3.11	69.17 ±3.01	69.79 ±2.48	69.85 ±2.46	69.85 ±2.46
S-4661-DC	7.57 ±0.82	11.44 ±0.22	15.35 ±0.54	16.00 ±0.90	16.09 ±0.86	16.09 ±0.86

Each value represents Mean±SD of three dogs

4. Basic pharmacokinetic studies of S-4661: quantitative examination for S-4661 and S-4661-DC in plasma and urine after single administration of S-4661 to rats. Shionogi Study # S-4661-B-12-N(9).

Species studied: Sprague Dawley rats, male, 8 weeks old, 282-332 g

Drug: Doripenem in physiologic saline

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: HPLC

Samples: Plasma at 2, 5, 10, 20, 30 minutes, 1, 2 hours; urine at 0-1, 1-2, 2-4, 4-6, 6-8, 8-24 hours (cage collection).

Results: The pharmacokinetic parameters for parent and metabolite in plasma and urine are shown in the following tables. Plasma levels were undetectable at 2 hours and urine levels were undetectable after 8 hours.

Table 6. Pharmacokinetic parameters of S-4661 and S-4661-DC after intravenous administration of S-4661 (20 mg/kg) to male rats

	AUC µg-hr/mL	C _{max} µg/mL	CL _{tot} mL/hr/kg	CL _r mL/hr/kg	CL _{nr} mL/hr/kg	T _{1/2α} hr	T _{1/2β} hr
S-4661	11.54		1732	669	1063	0.02	0.11
S-4661-DC	19.51*1	33.62*2					

CL_r = CL_{tot} × 0.3860 (excretion ratio)CL_{nr} = CL_{tot} - CL_r

*1: µg equivalent of S-4661-hr/mL

*2: µg equivalent of S-4661/mL

Table 7. Cumulative excretion of S-4661 and S-4661-DC in urine after intravenous administration of S-4661 (20 mg/kg) to male rats

	Cumulative excretion (% of dose)				
	Time after administration (hr)				
	0-1	0-2	0-4	0-6	0-8
S-4661	36.64 ±4.75	38.54 ±3.66	38.54 ±3.66	38.54 ±3.66	38.60 ±3.61
S-4661-DC	42.24 ±6.00	49.91 ±6.15	51.41 ±6.16	51.79 ±5.89	51.97 ±6.04

Each value represents Mean±SD of five rats

5. Study for the metabolic site of S-4661 in rats. Shionogi Study # S-4661-B-51-N.

Species studied: Homogenates from Sprague Dawley rats (male), Beagle dogs (male) and Cynomolgus monkeys (female) of kidney, liver and lung.

Drug: Doripenem in physiologic saline

Method of Analysis: DHP-I activity by spectrophotometry, HPLC for S-4661 breakdown to S-4661-DC

Results: The DHP-I activity in kidney, liver and lung of rat, dog and monkey are shown in the following table. Activity is highest in the dog and monkey in the kidney, while in rat it is higher in the lung.

Table 1. DHP-I activity of liver, kidney and lung in various animals

	nmol/min/mg protein		
	Liver	Kidney	Lung
Rat	2.05 ±0.25	3.60 ±0.43	9.31 ±1.39
Dog	1.17 ±0.15	4.54 ±1.31	2.27 ±0.91
Monkey	1.57 ±0.49	19.58 ±6.98	2.17 ±0.69

DHP-I activity was assayed using glycyldehydrophenylalanine as a substrate

The correlation between DHP-I levels and breakdown in S-4661 is shown in the following figure. Cilastatin inhibited the breakdown.

Conclusion: Conversion of S-4661 to S-4661DC correlated with DHP-1 activity levels and occurred primarily in the kidneys in dog and monkey and to a lesser extent in rat (lungs were also a primarily site in the rat.)

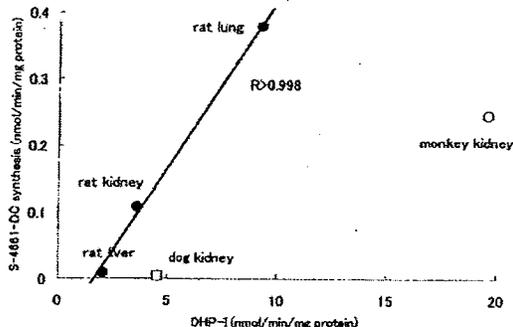


Fig.7. Correlation of DHP-1 activity and hydrolytic activity in various animals

6. Studies on the stability of S-4661 against DHP-1 from various animals. Shionogi Study # S-4661-EB-526-N.

Species studied: Homogenates from kidneys of ICR mice, Sprague Dawley rats (male), Japanese White rabbits, Toyo Beagle dogs (male) and Cynomolgus monkeys (male).

Drug: Doripenem in physiologic saline

Method of Analysis: zone of inhibition bacterial assay after a 90 minute incubation

Results: The following table shows that doripenem was less susceptible to the effects of DHP-1 than meropenem or imipenem. Dog had the least metabolism, while rabbits had the most.

Table 1. Stability against kidney homogenate derived from various animals

Species	Time (h)	Residual rate (%)		
		S-4661	MEPM	IPM
Mouse (n=20)	0	100 (87.5) ¹⁾	100 (100)	100 (104)
	0.5	92.6 (89.3)	81.4 (82.4)	84.3 (82.5)
	1	81.1 (79.7)	31.7 (33.1)	39.6 (40.1)
	1.5	78.1 (76.1)	12.1 (12.1)	25.7 (26.2)
Rat (n=1)	0	100 (104)	100 (103)	100 (111)
	0.5	73.5 (76.4)	62.6 (66.4)	56.0 (51.1)
	1	62.8 (63.5)	47.6 (55.1)	38.5 (38.8)
	1.5	54.8 (54.0)	31.6 (33.5)	21.9 (26.5)
Rabbit (n=30)	0	100 (99.1)	100 (93.2)	100 (111)
	0.5	79.4 (89.8)	13.5 (14.7)	51.7 (48.5)
	1	56.2 (55.7)	1.7 ²⁾ (1.56)	28.1 (31.5)
	1.5	40.8 (40.5)	n.d. ³⁾ (20.063)	15.1 (17.5)
Dog (n=10)	0	100 (93.5)	100 (107)	100 (107)
	0.5	91.9 (91.7)	83.1 (89.2)	45.7 (48.7)
	1	82.0 (81.8)	75.0 (80.8)	22.5 (23.7)
	1.5	83.3 (82.2)	74.5 (80.8)	11.5 (12.5)
Monkey (n=1)	0	100 (98.3)	100 (103)	100 (111)
	0.5	74.3 (73.5)	48.4 (48.0)	18.5 (19.7)
	1	69.0 (69.3)	24.8 (25.2)	63.8 (72.1)
	1.5	54.8 (53.7)	11.9 (12.5)	54.3 (56.5)

1) Diffusion rate
2) Residual concentration (µg/mL)
3) Not detected

7. Studies on the stability of S-4661 against human DHP-1 (Shionogi Study # S-4661-EB-527-N).

Species studied: Homogenates from kidneys of ICR mice, human recombinant DHP-1.

Drug: Doripenem in physiologic saline, 200 µg/mL

Method of Analysis: zone of inhibition bacterial assay after 90 minute incubation

Results: Doripenem was relatively stable in respect to human DHP-1

Best Possible Copy

Table I. Stability against purified renal DHP-I

Source	Time (h)	Residual rate (%)		
		S-4661	MSPM	IFM
Human (0.174 unit/mL)	0	100 (98.4) ¹⁾	100 (110)	100 (116)
	0.5	90.7 (89.2)	88.5 (97.4)	67.9 (74.7)
	1	89.6 (88.2)	83.5 (91.9)	58.5 (64.3)
	1.5	87.5 (86.1)	79.1 (87.0)	50.1 (55.5)
Human (0.300 unit/mL)	0	100 (95.1)	100 (102)	100 (98.4)
	0.5	91.4 (90.9)	81.1 (82.7)	59.9 (59.0)
	1	89.5 (84.6)	80.3 (81.9)	38.0 (37.4)
	1.5	82.4 (78.4)	78.1 (79.7)	23.2 (22.5)
Mouse (0.174 unit/mL)	0	100 (92.0)	100 (97.1)	100 (105)
	0.5	86.5 (74.1)	42.9 (41.7)	44.8 (47.0)
	1	72.8 (67.0)	16.8 (16.4)	22.9 (24.1)
	1.5	61.2 (56.3)	6.19 (6.01)	9.90 (10.4)

1) Residual concentration ($\mu\text{g/mL}$)

2.6.4.6 Excretion

1. Basic pharmacokinetic studies of S-4661: Biliary excretion in female rats following single intravenous administration of ^{14}C -S-4661. Shionogi Study #S-4661-B-12-N(3).

Species studied: Sprague Dawley rats, female, 9 weeks old, 240-255 g, n=3

Drug: Doripenem in physiologic saline. — pure

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: LSC

Samples: bile (cannulated rats) at 0-6, 6-24 and 24-48 hours, urine at 0-6, 6-24, 24-48 hours, feces at 24 and 48 hours

Results: The results are shown in the table below. The majority of radioactivity was excreted in the urine, mostly over the first 6 hours.

Dose	Cumulative excretion (% of dose)		
	Time after administration (hour)		
	0-6	0-24	0-48
Urine	62.36 \pm 53.94	93.14 \pm 4.52	93.35 \pm 4.55
Bile	2.67 \pm 0.33	2.84 \pm 0.32	2.87 \pm 0.33
Feces		0.09 \pm 0.05	0.13 \pm 0.02
Total			96.36 \pm 4.22

Each value represents Mean \pm S.D. of three rats.

1. Basic Pharmacokinetic Studies of S-4661: Plasma concentration, urinary and fecal excretion of radioactivity after single intravenous administration of ^{14}C -S-4661 to dog. Shionogi Study # S-4661-B-12-N(4).

Species studied: Beagle dogs, male, 9 months old, 8.6-10.5 kg, n=3

Drug: Doripenem in physiologic saline, — pure

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: LSC

Samples: Blood at 5, 10, 20, 30 minutes, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 hours; urine (catheter) at 0-1, 1-2, 2-4, 4-6, 6-8, 24, 48 hours, 72, 96, 120, 144 hours; feces at 24, 48, 72, 96, 120, 144 hours

Results: The AUC was 73.7 ± 11.2 , the α half-life was 0.5 hours, and the elimination half-life was 18.5 hours. The plasma protein binding was 10% or less until approximately 4 hours, where the binding began to increase markedly. Urinary excretion accounted for approximately 97% of the dose, with an additional 0.7% found in the feces. Almost 70% of the dose was excreted in the first hour following dosing.

3. Basic pharmacokinetic studies of S-4661: plasma concentration, urinary and fecal excretion of radioactivity after single intravenous administration of ^{14}C -S-4661 to monkey. Shionogi study # S-4661-B0-12-N(6).

Species studied: Cynomolgus monkeys, female, 9 years old, 2.77-3.22 kg, n=3

Drug: Doripenem in physiologic saline. — pure

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: LSC

Samples: Blood at 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 96, 120 hours; urine at 0-2, 2-4, 4-6, 6-8, 8-24, 48, 72, 96, 120, 144, 168 hours; feces at 24, 48, 72, 96, 120, 144, 168 hours

Results: The AUC was 73.7 ± 11.7 , the C_{\max} was 77.3 ± 7.0 , the α half-life was 0.5 hours, and the elimination half-life was 18.5 hours. Urinary excretion accounted for approximately 92.5% of the dose, with an additional 3.4% found in the feces. Almost 80% of the dose was excreted in the first 2 hours following dosing.

4. Urinary and fecal excretion of radioactivity after single intravenous dosing of ^{14}C -S-4661 to male rats. Shionogi study # S-4661-B-20-N.

Species studied: Sprague Dawley rats, male, 8 weeks, 254-302 g, n=4

Drug: Doripenem in physiologic saline. — pure

Route, schedule, duration, dose: Intravenous, single dose, 5, 20, 40 mg/kg.

Method of Analysis: LSC

Samples: Urine at 0-6, 6-24, 24-48, 48-72, 72-96 hours; feces at 24, 48, 72, 96 hours

Results: In the male rat, approximately 96% of the radioactivity was excreted in the urine, with almost 90% of the dose excreted within 6 hours of administration. An additional 3-4% of the administered dose was excreted via the feces.

Conclusions: The major route of excretion for doripenem in rats is via urine. No gender related differences were noted. No dose-related differences were noted with a range of intravenous administration between 5 and 40 mg/kg.

Table 1. Cumulative excretion of radioactivity in urine and feces after intravenous administration of ¹⁴C-S-4661 to male rats

Dose		Cumulative excretion (% of dose)				
		Time after administration (hour)				
		0-6	0-24	0-48	0-72	0-96
5 mg/kg	Urine	89.55 ± 1.33	91.86 ± 0.74	92.34 ± 0.73	92.56 ± 0.72	92.74 ± 0.79
	Feces		3.40 ± 1.33	3.71 ± 1.31	3.79 ± 1.30	3.83 ± 1.30
	Cage wash					N.D.
	Total					96.57 ± 1.21
20 mg/kg	Urine	91.15 ± 1.77	93.01 ± 1.35	93.42 ± 1.29	93.60 ± 1.25	93.80 ± 1.18
	Feces		2.52 ± 0.86	2.89 ± 0.90	2.94 ± 0.90	2.96 ± 0.90
	Cage wash					0.01 ± 0.03
	Total					96.77 ± 0.74
40 mg/kg	Urine	82.79 ± 14.93	92.49 ± 1.85	92.85 ± 1.82	93.00 ± 1.79	93.19 ± 1.78
	Feces		2.79 ± 0.75	3.23 ± 0.86	3.27 ± 0.86	3.29 ± 0.85
	Cage wash					0.03 ± 0.04
	Total					96.52 ± 1.05

Each value represents the Mean ± S.D. of four rats.

5. Biliary excretion in male rats following single intravenous administration of ¹⁴C-S-4661. Shionogi Study # S-4661-B-21-N.

Species studied: Sprague Dawley rats, male, 8 weeks, 262-276 g, n=3, bile duct cannulated.

Drug: Doripenem in physiologic saline. — , pure

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: LSC

Samples: Bile and urine at 0-6, 6-24, 24-48 hours; feces at 24, 48 hours

Results: Biliary and fecal excretion counted for less than 2% of the administered dose with the majority of radioactivity excreted in the urine within the first 6 hours.

Table 1. Cumulative excretion of radioactivity in urine, bile and feces after intravenous administration of ¹⁴C-S-4661 to male rats

Dose		Cumulative excretion (% of dose)		
		Time after administration (hour)		
		0-6	0-24	0-48
20 mg/kg	Urine	89.87 ± 7.84	96.99 ± 0.67	97.18 ± 0.62
	Bile	1.57 ± 0.18	1.69 ± 0.19	1.69 ± 0.19
	Feces		0.13 ± 0.06	0.14 ± 0.05
	Total			99.01 ± 0.47

Each value represents Mean ± S.D. of three rats.

6. Urinary and fecal excretion in female rats following single administration of ^{14}C -S-4661. Shionogi Study # S-4661-B-25-N.

Species studied: Sprague Dawley rats, female, 9 weeks, 226-232 g, n=4

Drug: Doripenem in physiologic saline. — pure ;

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: LSC

Samples: Urine at 0-6, 6-24, 24-48, 48-72, 72-96 hours; feces at 24, 48, 72, 96 hours

Results: Again, the majority of radioactivity was present in the urine within the first 6 hours.

Table 1. Cumulative excretion of radioactivity in urine and feces after intravenous administration of ^{14}C -S-4661 to female rats

Dose	Cumulative excretion (% of dose)				
	Time after administration (hour)				
	0-6	0-24	0-48	0-72	0-96
Urine	80.57 ± 7.59	85.09 ± 6.44	86.53 ± 5.74	87.38 ± 5.33	87.77 ± 5.26
Feces		8.11 ± 3.99	9.84 ± 4.16	10.03 ± 4.28	10.09 ± 4.33
20 mg/kg Cage wash					N.D.
Total					97.86 ± 0.94

Each value represents Mean ± S.D. of four rats.

N.D.; Not detected.

7. Urinary and fecal excretion in rats following repeated intravenous administration of ^{14}C -S-4661. Shionogi Study # S-4661-B-28-N.

Species studied: Sprague Dawley rats, male, 7 weeks, 257-274 g, n=5

Drug: Doripenem in physiologic saline, — , pure

Route, schedule, duration, dose: Intravenous, Daily for 10 consecutive days, 20 mg/kg.

Method of Analysis: LSC

Samples: Whole blood and urine at 24 hours post-dose daily, Urine on Day 9 at 0-6, 6-24, 24, 48, 72, 96, 120, 144, 168 hours; feces at 24, 48, 72, 96, 120, 144, 168 hours

Results: The radioactivity in whole blood at 24 hours post-dose doubled between Day 1 and 9 from 0.031 to 0.079 ± 0.006 ug/mL. Urinary levels of radioactivity did not differ significantly and ranged from 91.3 ± 7.8 to 94.8 ± 2.5% of the total daily dose. Fecal excretion was 4-5% of the total dose.

Table 2. Daily excretion of radioactivity in urine and feces during and after repeated intravenous administration of ^{14}C -S-4661 for 10 days to rats (20 mg/kg/day)

Number of dosing	Excretion (% of daily dose)		
	Urine	Feces	Total
1	91.30 ± 7.84	5.18 ± 4.22	96.48 ± 3.70
2	93.93 ± 3.22	5.59 ± 3.93	99.51 ± 0.97
3	94.34 ± 3.54	4.78 ± 2.48	99.12 ± 2.15
4	91.92 ± 4.11	5.29 ± 2.41	97.21 ± 1.82
5	94.87 ± 2.52	4.55 ± 2.66	99.42 ± 0.44
6	94.89 ± 0.84	3.81 ± 0.72	98.69 ± 0.62
7	94.65 ± 1.22	3.95 ± 0.95	98.60 ± 0.59
8	93.13 ± 2.19	4.96 ± 1.81	98.09 ± 0.39
9	93.63 ± 2.48	4.22 ± 0.34	97.85 ± 2.51
10	94.64 ± 1.40	4.04 ± 1.09	98.68 ± 0.70

Each value represents the Mean ± S.D. of five rats.

The data show the excretion in every 24 hr after dosing.

Conclusions: There was no significant accumulation or changes in excretion patterns with multiple daily doses of doripenem.

8. Lacteal transport of radioactivity after dosing of ^{14}C -S-4661 to lactating rats. Shionogi Study # S-4661-B-38-N.

Species studied: Sprague Dawley rats, female, 12 weeks old at breeding, postpartum Day 12, 386 ± 22 g

Drug: Doripenem in physiologic saline, — pure

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg.

Method of Analysis: LSC

Samples: Blood and milk at 0.5, 2, 6, 24 hours

Results: The results are shown in the following table. Given the similar elimination curve, the AUC in milk is roughly 20% of the AUC of doripenem in plasma.

Conclusion: Doripenem is excreted into milk, but the exposure level is a fraction of that in plasma.

Table 1. Plasma, whole blood and milk levels of total radioactivity after intravenous administration of ¹⁴C-S-4661 to lactating rats (20 mg/kg)

		Concentration (µg equiv. of S-4661/mL)			
		0.5 hr	1 hr	6 hr	24 hr
Plasma	Mean	29.83	1.12	0.13	0.06
	± S.D.	± 3.78	± 0.45	± 0.02	± 0.01
W.B.	Mean	11.51	0.68	0.11	0.05
	± S.D.	± 2.92	± 0.23	± 0.01	± 0.00
Milk	Mean	3.56	1.76	1.34	0.21
	± S.D.	± 2.50	± 0.30	± 0.99	± 0.08

Each value represents the Mean ± S.D. of five rats.

2.6.4.7 Pharmacokinetic drug interactions

1. Basic pharmacokinetic study of S-4661: quantitative examination for S-4661 and S-4661-DC in plasma and urine after administration of S-4661 or co administration of S-4661 with cilastatin to monkey. Shionogi Study # S-4661-B-12-N.

Species studied: Cynomolgus monkeys, > 8 years, female, 3.2-3.8 kg, n=3

Drug: Doripenem in physiologic saline → pure

Route, schedule, duration, dose: Intravenous, single dose, 20 mg/kg. (Cilastatin dose not clear—40 mg/mL solution made.....)

Method of Analysis: HPLC

Samples: Plasma at 0.08, 0.25, 0.5, 1, 2, 4, 6 hours; urine at 0-1, 1-2, 2-4, 4-6, 6-24 hours

Results: The pharmacokinetics of doripenem (20 mg/kg +/- cilastatin) in monkeys is shown in the following table.

Treatment	Parent or metabolite?	AUC	Cmax	Half-life (β, hours)
Dori alone	Parent	63.2±17.6	103.2±13.8	0.5±0.1
	Dori-DC	5.7±3.8	3.2±0.9	---
Dori + Cilastin	Parent	69.0±25.4	101±20.9	0.6±0.1
	Dori-DC	ND	ND	---

ND= not detected

Table 9. Cumulative excretion of S-4661 and S-4661-DC in urine after intravenous administration of S-4661 to monkeys

	Cumulative excretion(% of dose)				
	Time after administration(hr)				
	0-1	0-2	0-4	0-6	0-24
S-4661	43.22 ±11.38	55.17 ±10.24	58.11 ±10.02	58.57 ±10.22	58.57 ±10.22
S-4661-DC	19.02 ±11.91	24.09 ±13.81	26.65 ±14.64	27.55 ±14.21	28.97 ±13.34

Each value represents Mean ±SD of three monkeys

Table 10. Cumulative excretion of S-4661 and S-4661-DC in urine after intravenous administration of S-4661/cilastatin to monkeys

	Cumulative excretion(% of dose)				
	Time after administration(hr)				
	0-1	0-2	0-4	0-6	0-24
S-4661	57.15 ±14.30	74.91 ±8.52	81.41 ±3.25	82.08 ±2.58	82.08 ±2.58
S-4661-DC	1.20 ±0.64	2.44 ±0.81	3.74 ±0.65	4.32 ±0.97	4.94 ±1.96

Each value represents Mean ±SD of three monkeys

2. Basic pharmacokinetic studies of S-4661: Quantitative examination for S-4661 and S-4661-DC in plasma and urine after co administration of S-4661 with cilastatin to rats. Shionogi Study # S-4661-B-12-N(10).

Species studied: Sprague Dawley rats, male, 8 weeks old, 287-335 g, n=5

Drug: Doripenem in physiologic saline, — pure

Route, schedule, duration, dose: Both cilastatin and doripenem: Intravenous, single dose, 20 mg/kg.

Method of Analysis: HPLC

Samples: Plasma at 2, 5, 10, 20, 30, 60, 120 minutes; urine at 0-1, 1-2, 2-4, 4-6, 6-8, 8-24 hours

Results:

Treatment	Parent or metabolite?	AUC	Cmax	Half-life (β, hours)
Dori + Cilastin	Parent	27.3	112.8	0.2
	Dori-DC	2.1	3.89	---

Table 7. Cumulative excretion of S-4661 and S-4661-DC in urine after intravenous administration of S-4661/cilastatin to male rats

	Cumulative excretion(% of dose)				
	Time after administration(hr)				
	0-1	0-2	0-4	0-6	0-8
S-4661	76.22 ±2.41	81.19 ±2.13	81.50 ±2.21	81.61 ±2.25	81.61 ±2.25
S-4661-DC	5.55 ±1.28	8.13 ±1.57	9.08 ±1.79	9.08 ±1.79	9.08 ±1.79

Each value represents Mean ±SD of five rats

3. Influence on plasma concentration of VPA after co administration of VPA with S-4661 or other carbapenems to monkeys. Shionogi Study # S-4661-B-52-N.

Species studied: Cynomolgus monkeys, > 8 years, female, 3.2-3.8 kg, n=3

Drug: Doripenem in physiologic saline, — pure

Route, schedule, duration, dose: Doripenem (also meropenem, panipenem) intravenous, single dose, 20 mg/kg. Valproic acid at 25 mg/kg p.o; cilastatin administered 30 minutes prior to antibiotic, then 1 week later alone for comparison.

Method of Analysis: HPLC for VPA only

Samples: Plasma at 0.25, 0.5, 1, 2, 4, 6 hours

Results: There were no statistically significant differences in valproic acid pharmacokinetic parameters (AUC, Cmax, Tmax, MRT) with or without doripenem (or panipenem, meropenem).

2.6.4.8 Other Pharmacokinetic Studies

1. Mechanism of renal excretion of S-4661 in rabbits. Shionogi Study # S-4661-B-45-N.

Species studied: Japanese White Rabbits, male, 2.9-3.2 kg, n=6

Drug: Doripenem in physiologic saline. — pure

Route, schedule, duration, dose: 5 mg/kg/hour as intravenous infusion, single dose

Method of Analysis: Stop flow test and free flow renal clearance test, drug analysis in urine by bacterial inhibition; PAH, inulin, NA/K, creatinine measured

Results: The peak of doripenem excretion coincided with the peak of PAH excretion, suggesting glomerular filtration; however, as the excretion of doripenem was reduced 4 fold with the addition of probenecid, tubular excretion is also involved (responsible for 57% of renal excretion).

2. Mechanism of renal excretion of S-4661 in dogs. Shionogi Study # S-4661-B-47N.

Species studied: TOYO beagles, male, 11-14 months, 7.6-10.0 kg, n=5

Drug: Doripenem in physiologic saline

Route, schedule, duration, dose: 5 mg/kg/hour as intravenous infusion, single dose

Method of Analysis: Stop flow test and free flow renal clearance test, drug analysis in urine by bacterial inhibition; PAH, inulin, NA/K, creatinine measured

Results: No change in doripenem concentration in the urine was noted after the addition of probenecid, suggesting that tubular excretion was minimal.

2.6.4.9 Discussion and Conclusions

While the pharmacokinetics of doripenem have been adequately investigated, the toxicokinetics were largely ignored (the exception was PK in the pregnant rats and rabbits).

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Single dose pharmacokinetics of Doripenem						
Species	Dose mg/kg	AUC ug.h/mL	Cmax ug/mL	Half-life hours	Excretion	
					Urinary	Biliary
Beagle dog	20	75.4 ± 10.4	85.2 ± 12.2	0.9 ± 0.1	83.2 ± 15.1	---
	20	91.4 ± 3.43	106.7 ± 0.4	0.7 ± 0.1	85.9*	---
	20 ^S	111.8 ± 12.2	104.5 ± 1.3	21.1 ± 1.2	97.1 ± 0.7	---
	10	35.5 ± 0.5	55.9 ± 6.3			
	30	98.9 ± 8.1	178.2 ± 41.7			
	100	309.9 ± 22.9	536.9 ± 109.5			
Juvenile dog	20	53.3 ± 3.8	63.0 ± 6.3	0.7 ± 0.1	73 ± 3	---
	50	11.2 ± 9.2	139.0 ± 23.3	0.7 ± 0.1	64 ± 7	---
Cynomolgus monkey	5	13.4 ± 1.8	23.2 ± 3.3	0.9 ± 0.1	61.4 ± 8.6	---
	10	23.1 ± 3.8	39.8 ± 6.9	0.9 ± 0.1	63.8 ± 8.8	---
	20	40.5 ± 6.5	73.2 ± 15.4	0.8 ± 0.3	51.5 ± 10.7	<0.1
	50	141.5 ± 24.1	220 ± 22	1.2 ± 0.3	60.8 ± 14.8	---
	20 + P	98.5 ± 26.6	128 ± 38	0.9 ± 0.1	51.6 ± 7.2	---
	20 ^S	73.7 ± 11.7	77.3 ± 7.0	18.5 ± 3.8	92.5 ± 5.1	---
	20*	63.2 ± 17.6	103.2 ± 13.8	0.5 ± 0.1		
Rabbit	20	43.7 ± 2.6	90.9 ± 9.9	1.3 ± 0.5	47.6 ± 15.2	---
Rat	20	8.8	33.0 ± 8.9	0.1	42.1 ± 6.4	0.2
	20 + P	8.2	31.7 ± 4.2	0.2	41.1 ± 12.5	<0.2
	20	11.5	87.6	0.1	90.5*	---
	5	2.3 ± 0.3	---	0.09	---	---
	20	9.8 ± 1.0	---	0.12	---	---
	40	16.6 ± 1.1	---	0.13	---	---
	30	9.6 ± 0.5	53.7 ± 1.8			
	100	29.9 ± 2.0	166.4 ± 8.3			
	300	99.4 ± 8.1	547.9 ± 51.5			
Rat pup CSF	100 sc	14.5	6.01 @ 1 h	~3 h	---	---
Rat pup plasma	100 sc	59.2	88.2	---	---	---
Mouse	5	3.5	12.8 ± 1.8	0.2	35.9 ± 3.8	2.4
	10	7.2	25.0 ± 1.7	0.2	33.0 ± 8.9	< 2.4
	20	13.3	44.8 ± 4.0	0.2	36.3 ± 6.2	< 0.7
	50	32.9	132 ± 10	0.3	31.8 ± 5.9	0.7
	100	68.0	248 ± 13	0.3	40.2 ± 5.6	1.0

P = probenecid. * excretion of parent and dicarboxylic acid metabolite ^SMeasured 14C-label

Multiple dose pharmacokinetics of intravenous doripenem						
Species	Schedule	Dose (mg/kg)	Sex	Cmax (ug/mL)	AUC (ug.hr/mL)	T _{1/2} (min)
Rat	DX10	20	M	---	9.8 ± 0.7	7.2
		30	M	65.6	11.8	6.5
	DX5 ^a	30	F	72.6	13.2	6.3
		100	M	235.3	40.8	6.2
		100	F	285.5	49.3	6.4
		300	M	953.5	161.3	6.7
Pregnant rats	GD7-17 ^a	30	F	82.1	15.9	7.3
		100	F	486.6	91.8	9.6
		300	F	1354.7	263.2	12.7
		Pregnant rabbits	GD-18 ^a	12.5	F	2.8
		25	F	7.2	10.2	42.8
		50	F	13.3	19.6	43.1
		Dog	DX5 ^a	10	M	24.5
			F	28.7	29.2	40.9
		30	M	90.9	88.9	44.4
			F	100.3	85.4	41.9
		100	M	367.9	299.5	45.1
			F	404.5	291.4	43.6

Note: all of the measurements listed above were from the final day of dosing
^ametabolite (doripenem dicarboxylic acid) was also measured.

Toxicokinetic measurements were not collected in the 1 and 3 month studies in rat and dog.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Acute intravenous toxicology studies were conducted in the rat, rabbit, and dog. The doses, target organs, and toxicokinetics are summarized in the following table. With doses up to 1 to 2 grams of doripenem, no seizure activity was noted. The major targets of toxicity were kidney, hematologic cells (primarily WBC #), gastrointestinal tract (vomiting in dogs), and possibly liver. While the table seems to emphasize the renal toxicity due to the two rabbit studies, those studies were designed to focus only on the serum chemistry and pathology of the kidney by excluding all other organs from examination.

Subchronic dosing was conducted in the rat and dog. Toxicokinetics were not monitored in these studies. The major targets of toxicity were kidney, gastrointestinal tract and hematologic cells. The changes in WBC and RBC numbers, while usually mild, may possibly be associated with immune responses. This seems likely as splenic hypertrophy was also noted in these studies. An alternate explanation for the RBC decrements would be GI bleeding. Other hematologic changes were variable across studies and species, suggesting that they may be artifacts or not toxicologically relevant. The two 1 month dog studies differed in that lethality occurred at 500 mg/kg in one

study, but only at 1000 mg/kg in the other study. QT prolongation was noted in both the 1 month and the 3 month studies in the dogs. Gastrointestinal damage was also noted in both dog studies (hemorrhage and inflammatory cells as well as some vomiting). No new toxicities were noted between 1 month and 3 months in dog or rat. The two week dog study with the new formulation of doripenem did not result in any significant changes in the toxicologic profile. Juvenile dogs actually showed less toxicity than their adult counterparts in that no renal toxicity was noted in the juvenile dogs, nor was there splenic hypertrophy. Direct comparisons of plasma concentrations of drug are not possible as toxicokinetics were not monitored in the adults, although these measurements were part of the juvenile protocol.

Species	Schedule	Doses (mg/kg)	NOAEL (mg/kg)	LLD (mg/kg)	Targets of Toxicity
Rat	1X	2000	<2000	>2000	Kidney (basophilic alterations), lung (focal hemorrhage)
	DX 14 days	0, 100, 300, 1000	<100	>1000	WBC # increased, AST/ALP increases, ketonuria/urobilirubin, spleen germinal center activation
Rabbit	1X	200, 400, 600	200 (renal only)	>600	Designed for renal only. Increases in BUN, creatinine, glucosuria, proteinuria, occult blood; renal necrosis
	1X	250, 400	<250 (renal only)	400	BUN, creatinine increased; proteinuria, glucosuria, occult blood; tubular necrosis
	DX5	0, 50, 100, 200	50 (renal only)	100	Deaths at 100, 200 mg/kg (D3, 4); diarrhea, increased creatinine (mild), renal medullary congestion, tubular necrosis in early death animals only
Dog	1X	1000, 2000	<1000	>2000	Vomiting/abnormal feces, increases in WBC #, increased BUN/creatinine, increases in AST/ALT, ALT, LDH, cholesterol and triglycerides, increased glucose, decreased electrolytes. Urinary glucose, protein and occult blood. Renal necrosis/mineralization, GI hemorrhage/erosion, spleen white pulp hypertrophy/hemorrhage, males only: swelling of hepatocytes.

LLD= Lowest Lethal Dose

Species	Schedule	Doses tested (mg/kg)	NOAEL mg/kg	Targets of Toxicity	Hematology
Rat	DX 1 month	0, 100, 300, 1000	100 LLD >1000	Kidney (weight increase, glomerular epithelium), spleen (increased weight, white pulp).	neutrophils (decrease), RBC (decrease #, F only)
	DX 3 months	0, 100, 300, 1000	100 LLD > 1000	kidney (increased weight), spleen, (increased weight)	RBC (decreased #), Decreased # monocytes, neutrophils
Dog	DX 1 month	0, 250, 500, 1000	250 LLD= 1000	GI (vomiting/ diarrhea), hemorrhage/necrosis; renal protein, ketones, occult blood in urine and tubular necrosis/calcification.	---
	DX 1 month	0, 125, 250, 500	<125 LLD =500	Death in HD males (2/5), reddening of ears after dosing, abnormal feces. HD males increased QT interval@ D23, recovery D27. Decreased glucose, increased triglycerides. Early death dogs: increased AST/ALT/ALP, CPK. GI erosion, ulcers, hemorrhage; liver atrophy; pancreatic congestion/atrophy; splenic white pulp hypertrophy; protein material in Bowman's space in kidney in early death dogs. Survivors: GI hemorrhage @ 250, 500, splenic hypertrophy, kidney vacuolization.	RBC # decreased after D3; Increased neutrophils, monocytes.
	DX 3 months	0, 40, 100, 250	<40, LLD> 250	No deaths. Redness of paws/scrotum. Increased QT interval MD and HD males, all females. ALP, CPK, triglyceride, bilirubin increase. Stomach inflammatory cells/hemorrhage, renal epithelium vacuolization, splenic white pulp hypertrophy.	WBC decrease. APTT prolong
Juvenile dog	DX 1 month	0, 40, 100, 250	40, LLD> 250	Bloody stool at MD, HD	RBC # decreased

* AUC in males at last measurement in ug.hr/mL

Genetic toxicology:

Mutagenicity of doripenem was investigated in both bacterial (Ames at up to 5 ug/plate) and mammalian (Chinese Hamster Ovary at up to 5000 ug/mL) cells. Both systems were negative. Doripenem was negative for clastogenicity in the Chinese Hamster Lung cell assay. Doripenem was also negative in the *in vivo* mouse micronucleus assay at 2000 mg/kg.

Carcinogenicity: No carcinogenicity studies were required based on the short-term, intermittent use of doripenem.

Reproductive toxicology:

Studies have been conducted in the rat and rabbit to investigate the potential of doripenem to cause reproductive toxicity. The preliminary dose-ranging studies were conducted at the same doses (up to 1000 mg/kg/day i.v.) as the definitive studies and showed no significant effects on the feti or on other reproductive parameters (e.g. maternal toxicity, placental weights, implantation sites, abortions etc). The studies are summarized in the table below, along with the relevant toxicokinetic data from separate studies. Additionally, doripenem did not affect fertility in male or female rats. Nor did doripenem affect the gestation period, behavior or maturation/reproductive potential of the F1 generation where the dams were administered doripenem through weaning. No data on the pharmacokinetic parameters at 1000 mg/kg/day were collected in the separate pharmacokinetic studies.

Reproductive Toxicity Studies with Doripenem				
Segment	Species	Doses tested	NOAEL	AUC (dose in mg/kg/day)
Segment I	Rat	0, 100, 300, 1000	1000	---
Segment II	Rat	0, 100, 300, 1000	1000	263 ug.h/mL (300)
Segment II	Rabbit	0, 12.5, 25, 50	50	92.1 ug.h/mL (50)
Segment II/III	Rat	100, 300, 600, 1000	1000	---

Special toxicology:

The special toxicity studied explored the local effects of doripenem on vascular/muscular tissue, on antigenicity, and on liver function. Renal and cardiac function have already been explored in the safety pharmacology section of the NDA. Intravenous injection daily for 8 days in the rabbit ear vein at up to 2% resulted in damage that was not significantly different from that of a normal saline injection. Similarly, a single intramuscular injection of 1% doripenem did not differ in damage from normal saline. Antigenic effects of doripenem were similar to those of imipenem (weak antigenicity in PCA test, FCA positive in ELISA). Guinea pig also showed positive antigenicity in FCA and PCA test. Minimal cross-reactivity between imipenem and doripenem was noted in the guinea pig, but not in the mouse. An *in vitro* Coombs test with human blood was negative.

The sponsor also explored hepatotoxicity in 2 week studies in rats and dogs; however, the doses used were significantly lower than the NOAELs in the 1 month study. It is not surprising that almost no changes were noted.

2.6.6.2 Single-dose toxicity

No new single dose toxicology studies were submitted.

2.6.6.3 Repeat-dose toxicity

1. Toxicological characterization of effective compounds: pre-toxicity of S-4661 in rats. 1T- Y-001.

Conducting laboratory and location: Shionogi Research Laboratories, Japan

Date of study initiation: December 1991.

GLP compliance: No statement included

QA report: yes () no (X), no statement included.

Drug, lot #, and % purity: Doripenem, Lot # 11014, dissolved in water

Methods

Doses: 0, 100, 300, 1000 mg/kg in males; 0, 1000 mg/kg in females

Species/strain: Sprague Dawley rats

Number/sex/group or time point (main study): 6/sex/dose

Route, formulation, volume, and infusion rate: Intravenous, once daily for 14 days, 0.5- 5.0 mL/kg

Satellite groups used for toxicokinetics or recovery: None.

Age: 4 weeks

Observations, times and results:

Mortality and Clinical signs (daily): All rats survived to scheduled sacrifice. Clinical signs included urine discoloration (reddish/brown) and loose feces.

Body weights (daily): There were no remarkable differences between groups in body weight.

Food consumption (weekly): On Day 7, food consumption was doubled in the HD group as compared to the controls. No significant change in body weight accompanied this change.

Water consumption (Day 0, 6, 12): In the males, water consumption increased with both dose and duration of dosing (18% increase over control at the LD, 30% at the HD at Day 14).

Hematology (Day 14): White blood cell numbers were increased by 25% and 64% as compared to controls in the HD males and females respectively. This reflected increases in lymphocyte numbers.

Clinical chemistry (Day 14): AST and ALP values in the HD males increased to almost 2 fold control levels with broad standard errors; however, individual animal data was not provided.

Urinalysis (Day 10): At 1000 mg/kg, males and females had increased specific gravity, which was explainable in females by a decreased urine volume. Increases in ketones, bilirubin and urobilinogen were also noted at the 1000 mg/kg level.

Gross pathology (Day 14): Marked enlargement of the spleen and cecum were noted at necropsy.

Organ weights : Spleen weights (absolute and relative) increased at all doses from about 15% at the LD to 60% at the HD in both males and females. Cecal weights increased

dose dependently with increases from 35% at the LD to 70% at the HD in males and females.

Histopathology (limited battery: heart, lungs, liver, kidney, spleen, adrenals, thymus, testes, prostate, ovaries, cecum, pancreas, thyroid, stomach, duodenum, jejunum, ileum, colon, rectum, urinary bladder, seminal vesicle uterus and femur): The only microscopic finding was activation of the germinal center of the spleen with increasing severity with dose.

Toxicokinetics: Not collected.

Comments and conclusions: The individual animal data were not provided. The urinalysis data suggests renal damage, but no microscopic changes were noted. Changes in spleen were not accompanied by decrements in RBC # but the germinal center activation is consistent with increased lymphocytes. Increases in cecal weights are expected with disruptions in gut flora by an anti-bacterial compound.

2. Preliminary 1 month intravenous toxicity study of S-4661 in dogs. Shionogi Study # S-4661-B-14.Y1-N.

This study is not reviewed thoroughly as there is another 1 month GLP quality study in dogs with an adequate number of animals and significant toxicities. This study was conducted with a single dog/sex at 250, 500 (male only) and 1000 mg/kg/day of doripenem for 28 consecutive days. One female died at day 11 at 1000 mg/kg, while the male at 1000 mg/kg was only dosed for 14 days. Gastrointestinal (vomiting/diarrhea, loss of appetite, hemorrhages/necrosis/regeneration/ cyst formation in the epithelium of the intestines), hemorrhages in the heart, adrenals, reproductive organs, and renal toxicities (protein/ketones/occult blood in urine, tubular necrosis/calcification) were predominant in the HD dogs. The NOAEL was deemed to be 250 mg/kg by the sponsor.

3. Two-week intravenous toxicity study of doripenem hydrate with direct Coombs' test in dogs. SG06104-S-4661-TF-618-L. (Submitted in serial # 001)

Conducting laboratory and location: _____

Date of study initiation: August, 2006

GLP compliance: Yes, Japanese

QA report: yes (X) no ()

Drug, lot #, and % purity: Doripenem hydrate, Lot # 0002, product lot # T6501, _____ pure

Vehicle: Isotonic sodium chloride solution

Methods

Doses: 0, 10, 30, 100 mg/kg/day

Species/strain: Beagle dogs

Number/sex/group or time point (main study): 3/dose/sex

Route, formulation, volume, and infusion rate: intravenous via infusion pump at 1 mL/kg/min (or over 5 minutes),

Age: 9-10 months

Weight: M: 9.8-13.28 kg, F: 9.18-10.86 kg

Duration of treatment: Daily for 14 consecutive days

Observations, times and results:

Mortality and Clinical signs (twice daily): All dogs survived for 2 weeks (the end of scheduled dosing). There were no remarkable, dose-dependent changes in clinical signs with treatment.

Body weights (every 3-4 days): There were no significant changes in body weights during the study in any group.

Food consumption (every 3-4 days): There were no differences in food consumption between the groups.

Ophthalmoscopy (Pretest, Week 2): There were no changes with treatment.

EKG (Pretest, Week 2): There were no remarkable differences in heart rate between groups. The QT interval did not differ between groups. The QTc interval was increased by 12 and 13 ms respectively in the 10 and 100 mg/kg males (statistically significant). There were no significant differences in females.

Hematology (Pretest, Week 2), includes Coombs test: The changes in Hematologic parameters did not reach statistical significance. The direct Coombs test in both males and females was negative.

% change in hematologic parameters in the 2 week dog bridging study		
	Males	Females
RBC #	---	Decrease 13% HD
Reticulocyte #	Decrease 40% HD	Decrease 45% HD
Platelet #	Decrease 25% HD	Decrease 22% HD

Clinical chemistry (Pretest, Week 2): BUN levels in a single HD male were increased by 92% above controls at D14 (50% increase over pretest values). One HD female had a 2 fold increase in AST and a 6 fold increase in ALT. Given the low incidence these findings may not be toxicologically relevant.

Urinalysis (Pretest, Week 2): There were no remarkable dose dependent changes with treatment.

Gross pathology: There were no remarkable observations associated with treatment.

Organ weights: There were no remarkable changes in organ weights with treatment.

Histopathology: There were no remarkable differences between treated and control animals in microscopic observations.

Adequate Battery: yes (X), no ()—explain

Peer review: yes (), no (X)

Toxicokinetics (Day 1 and 14; 2 and 8 minutes post-dose): The plasma concentration measurements at the Cmax (2 minutes post-infusion) are shown in the following table. Doripenem was undetectable prior to dosing on day 14 in all groups. No accumulation or gender differences were noted. Plasma levels were roughly linear with dose.

C_{max} values (Mean plasma concentrations at 2 minutes after dosing)

Dose level (mg potency/kg/day)	Mean plasma concentration (µg/mL)			
	Male		Female	
	Day 1	Day 14	Day 1	Day 14
0	0	0	0	0
10	45.26	44.46	40.45	42.81
30	136.16	129.64	137.85	117.14
100	479.03	479.41	387.12	276.16

Individual study summary and comments: The NOAEL for 2 weeks of doripenem administration in the dog by the intravenous route was 30 mg/kg. At the HD, changes in hematology (reticulocytes, platelets), and single animals with increases in liver enzymes and BUN were noted, although without any accompanying microscopic damage. The 1 month studies had a lowest dose of 125 or 250 mg/kg, thus, the data are difficult to compare, although hints of similar toxicities (hematologic, hepatic and renal) were seen. Again, although the Coombs tests was negative, the duration and doses were less than those used in the other toxicology studies, so no firm conclusion could be drawn.

2.6.6.4 Genetic toxicology

1. CHO HGPRT forward mutation assay of JNJ-38174942 with a confirmatory assay and duplicate cultures. Study TOX7917.

Conducting laboratory and location:

Date of study initiation: July, 2006

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: Doripenem, Manufacturer's Lot # 0002, Product Lot # T6501, pure

Methods

Strains/species/cell line: Chinese Hamster Ovary, CHO-K1-BH₄

Metabolic Activation System: Purchased live S9 fraction from Arochlor induced Sprague Dawley rats.

Doses used in definitive study: 0, 78.5, 157, 313, 625, 1250, 2500, 4000, 5000 ug/mL

Basis of dose selection: Cytotoxicity

Negative controls: 0.9% saline

Positive controls: 5-Bromo-2'-deoxyuridine (BrdU) 50 ug/mL, methylcholanthrene (MCA) 5 ug/mL

Incubation and sampling times: 4 hours with drug, grown for 7 days

Results

Study validity: The study was valid. The average survival was around 80% at 5000 ug/mL in the presence and absence of S9.

Study outcome: The positive controls increased the mutant frequency by more than 10 fold above vehicle controls. There were no consistent or dose dependent increases in mutation frequencies above 2 fold over controls.

2.6.6.5 Carcinogenicity

No carcinogenicity studies were necessary for doripenem based on the short-term use of the compound.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

1. Study on intravenous administration of S-4661 during the period of organogenesis in rats (supplemental study): effects of S-4661 on nursing performance in dams. Shionogi Study # S-4661-B-43-L.

Conducting laboratory and location: Shionogi Research Laboratories, Japan

Date of study initiation: February, 1994

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: S-4661, Lot # 20701, dissolved in normal saline

Methods

Doses: 0, 30, 100, 300, 1000 mg/kg intravenous on days 7 to 17 of gestation

Species/strain: Sprague Dawley rats, males 10 weeks old, females at 8 weeks, 229-273 g

Number/sex/group: 12 presumed pregnant females/group

Satellite groups used for toxicokinetics: None

Study design: Dams and offspring were observed through post-partum day 7.

Parameters and endpoints evaluated: Clinical signs (twice daily), body weights (every 3 days), gross observations of mammary glands, implantation sites, milk in stomach of offspring

Results:

Mortality: One dam in the 1000 mg/kg group died on day 22 of pregnancy without delivering. Clinical signs in this animal included hypoactivity, piloerection and perinasal staining. No changes in the mammary glands were noted in this animal.

Clinical signs: A dose dependent increase in the incidence of loose feces was seen. All dams had abnormal urine color.

Body weight: On day 0 post-partum, only the female pups showed a statistically significant decrease in body weight as compared to controls (decrease of 15% at HD). Although not statistically significant, the maternal weights and fetal weights showed a dose-dependent decrease in body weights (maximum 7% in dams, 14% in male pups).

Food consumption: There was an increase in food consumption in the dams (dose dependent) between days 3 and 7 with increases of approximately 15% at the HD (noteworthy at 300 and 1000 mg/kg).

Toxicokinetics: Not collected.

Necropsy: There were no changes in the mammary glands at necropsy.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):

Only 1 female at the HD was not pregnant. Neither gestation period, number of implantation sites, number of newborns/litter or number of dead feti, or the male:female

ratio, differenced significantly between treated and control rats. Body weight in the female neonates was decreased by 15% as compared to controls (body weight in the HD male feti was decreased by 12%, but was not significantly significant). Milk was found in the stomachs of nearly all the pups on days 4 and 7 (exception 1/17 offspring of a 100 mg/kg dam).

Conclusions: S-4661 did not significantly affect nursing performance in rats when administered on gestation days 7-17. The NOAEL in this study was the HD, 1000 mg/kg. It should be noted that dosing ceased prior to parturition and nursing.

2.6.6.7 Local tolerance: Previously reviewed.

2.6.6.8 Special toxicology studies

1. Hepatotoxicity study of S-4661. Shionogi Study # S-4661-B-49-N. Document ID # EDMS-PSDB-5407595.

Conducting laboratory and location: Shionogi Research Laboratories, Japan.

Date of study initiation: February, 1996

GLP compliance: No statement included.

QA reports: No statement included.

Drug, lot #, and % purity: Doripenem, lot CP4184

Formulation/vehicle: Physiologic saline

Test system: Male Sprague Dawley rats, 7 weeks old, 290-346 g, n= 6 or 12; Mixed breed or Beagle dogs, n=4, 10 mg/kg/day

Doses: 10, 100 mg/kg/day by intravenous route, daily for 14 consecutive days in rats, 10 mg/kg/day for dogs; rechallenge dose on day 42

Parameters monitored: AST/ALT on days 0, 6, 14, 27, 41; gross pathology, clinical signs (daily); liver weight

Results: In the rats, there were no significant changes in AST/ALT, bilirubin, or liver weight. In the dogs, the HD males showed a doubling of ALT at day 42. No changes in other parameters in the dogs were noted. The incidence of microgranulomas in the liver was more frequent in treated rats than control, but was mostly very slight in severity.

Conclusions: The effects on the liver by S-4661 at doses of up to 100 mg/kg (rat) or 10 mg/kg (dog) for 2 weeks were minor.

2. Evaluation of hepatic cell injury caused by S-4661 in in-vitro isolated hepatocytes. Shionogi Study # S-4661-B-50-N. Document ID # EDMS-PSDB-5407611.

Conducting laboratory and location: Shionogi Research Laboratories, Japan.

Date of study initiation: March 1996

GLP compliance: No statement

QA reports: yes () no (X)

Drug, lot #, and % purity: Not provided

Formulation/vehicle: saline

Methods: Using isolated hepatocytes from the animals described in the previous study (#1 above), the cells were treated for 2 hours with 0, 30, 150 or 300 ug/mL S-4661. LDH release was used as an index of injury.

Results:

Hepatocytes isolated from rats and dogs treated with doripenem as described in the previous study showed no difference in release of LDH with up to 300 ug/mL S-4661 readministration.

Conclusions: The sponsor concluded that there was no direct action on liver cells.

3. Hepatotoxicity study of S-4661 in dogs (supplementary study). Shionogi Study # S-4661-B-56-N. Document ID # EDMs-PSDB-5407622.

Conducting laboratory and location: Shionogi Research Laboratories

Date of study initiation: August 1997

GLP compliance: No statement

QA reports: yes () no (X)

Drug, lot #, and % purity: Not provided

Formulation/vehicle: Saline

Methods: Mixed breed and beagle males (n=5/group) were treated with intravenous doripenem at 10 or 100 mg/kg 5 days/week for 3 consecutive weeks. At 7 weeks, all dogs were challenged with 100 mg/kg doripenem. Liver enzymes (AST, ALT, ALP) and bilirubin were measured on days 1, 7, 18, 25, 36, 45 and 46. Clinical signs, body weight and food consumption were measured as usual. Free endotoxins were measured at 1, 2, and 5 hours post administration of days 0, 4, 7, 11, 18, and 45.

Results:

There were no significant changes in AST/ALT/ALP or bilirubin values in the dogs with doripenem treatment. Body weights remained stable during the study. Endotoxin levels were also not altered to a significant extent.

Conclusions: The sponsor did not consider the dog to be an adequate model for the study of the altered liver enzyme values seen in the early clinical trials.

4. Study for the influence of S-4661 on hepatic function of mice with a lung infection. Shionogi Study # S-4661-B-68-N. Document ID # EDMS-PSDB-5306517.

Conducting laboratory and location: Shionogi Research Laboratories, Japan

Date of study initiation: March 1998

GLP compliance: No statement

QA reports: yes () no (X)

Drug, lot #, and % purity: Doripenem, Lot # BP6048

Formulation/vehicle: Distilled water

Methods: Female ICR mice, 5 weeks old, un-infected or infected with *S. pneumoniae* SR1326 strain, weight 23 g, 4 groups (5 mice/group) were treated s.c. with 20 mg/kg S-4661, 50 mg/kg imipenem, 50 mg/kg meropenem, 50 mg/kg flumarin, or 300 mg/kg cefoperazin (doses determined to equal Cmax at human clinical doses) twice daily for 3 days beginning 24 hours after infection. At 4 days post-infection, lung bacterial count, body weights, blood chemistry, TK in plasma and liver, and histopathology of liver, lungs and spleen were examined.

Results:

There were no differences between non-infected groups. All of the infected mice treated with the various antibiotics weighed more (approximately 25%) than the untreated and infected control. In the infected mice, CFU/g were reduced by >80% in doripenem, imipenem and meropenem treated mice, but by 50% or less in the flumarin and cefoperazin groups. In both infected and uninfected mice treated with the drugs, no significant changes in liver, renal or glucose values were noted. The histopathology and PK values were reported in the next items.

Conclusion: In mice with pneumonia, treatment with 20 mg/kg doripenem did not affect body weight or serum chemistry, while eradicating more than 80% of the CFU of *S. pneumoniae* bacteria.

5. Pathological study for the influence of S-4661 on hepatic function of mice with a lung infection: pathological study of the liver in pneumonia model mouse after S-4661 treatment. Shionogi Study # S-4661-B-68.02.N. Document ID # EDMS-PSDB-530-8770.

This is the histopathology report for the study discussed in #4. In the infected but untreated mice, atrophy of the hepatocytes, activation of Kupffer cells and extramedullary granulopoiesis were noted. Infected mice treated with doripenem did not differ significantly from uninfected mice. Lung weights were increased in infected control mice by approximately 30% above treated and uninfected animals. Liver weights in the untreated infected mice were increased by approximately 10%.

Conclusions: Doripenem (and other penem class drugs) mitigated the effects of infection by *S. pneumoniae* in the lungs, liver and spleen, although not quite to the level of uninfected animals.

6. Measurement of drug concentrations in a study of the influence of S-4661 on hepatic function in a mouse pulmonary infection model. Shionogi Study # S-4661-B-68.01-N. Document ID # EDMS-PSDB-5304208.

The pharmacokinetic data from the study described in #4 is shown below. No remarkable differences in S-4661 in plasma or liver were noted regardless of whether the mice were infected with *S. pneumoniae*.

Substances	Concentrations, µg/mL			
	Non-infected group		Infected group	
	Plasma	Liver	Plasma	Liver
S-4661 (20 mg/kg)	18.3±2.4	2.54±0.77	17.4±4.2	2.73±0.48
IPM/CS (50 mg/kg)	50.3±2.8	11.5±2.6	48.3±6.3	9.17±1.39
MEPM (50 mg/kg)	24.6±2.9	7.88±1.42	26.0±4.1	8.18±0.84
FMOX (50 mg/kg)	48.8±8.9	41.1±9.0	43.4±4.7	36.3±12.2
CPZ (300 mg/kg)	145±16	526±73	187±48	470±154

(Mean±SD, n=5)

Best Possible Copy

2.6.6.9 Discussion and Conclusions: See the initial Toxicology summaries at the beginning of this section.

2.6.6.10 Tables and Figures: see above.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Please see the Toxicology conclusions section.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Doripenem is a carbapenem class intravenous drug. It is active against both Gram positive and negative bacteria by inhibiting bacterial cell wall synthesis via inactivation of penicillin binding proteins. Other approved drugs in this class include ertapenem, imipenem and meropenem.

One of the class effects of the penems is the increase in seizures. With doripenem, no seizures or convulsions were noted during the general toxicology studies with doses up to 2000 mg/kg in the single dose rat and dog. In the safety pharmacology studies, lower doses were used in combination with electroshock or pentylenetetrazol without a change in incidence or threshold of seizure. Even direct injection intracisternally did not result in seizure. This is particularly striking when compared to other penems, which were tested alongside the doripenem.

The highest dose tested for safety pharmacology in rats and mice, 400 mg/kg, have a HED (human equivalent dose) of 65 mg/kg, more than twice the human total daily dose of 25 mg/kg.

The cardiac effects of doripenem were tested both in vitro (hERG, Purkinje fibers) and in the *in vivo* dog. While all of the safety pharmacology studies were negative, the toxicology studies (1 and 3 month dog studies) showed significant changes in the QT interval. It should be noted that the maximum dose in the single dose safety pharmacology study was at 100 mg/kg while the 30 or 90 dose toxicology studies were conducted at 500 and 250 mg/kg. No QT prolongation has been associated with other penems at this time. No effects were noted on respiration with doripenem. Gastrointestinal effects were not investigated.

The pharmacokinetics of doripenem have been investigated in multiple species including mouse, rat, dog, rabbit, and monkey. No gender differences were noted. No accumulation with multiple doses was observed. Exposure was relatively linear with dose. In the pregnant rat, exposures were higher than those seen in the non-pregnant rat (or males). Whether this was due to inter-experimental variation could not be determined. The half life was generally less than 1 hour. Similarly, half-life in the human is approximately 1 hour. It should be noted that at the recommended therapeutic dose, 500 mg every 8 hours, the human AUC is 36.3 ug.hr/mL, and the C_{max} 23 ug/mL. This is roughly the same AUC seen at the LD in the dog (10 mg/kg) and rat (30 mg/kg) DX5 studies. No toxicokinetic data was available for the 1 or 3 month rat or dog studies.

Doripenem is widely distributed in both rat and dog. The majority of drug in both species was found in the kidney, and subsequently, in urine. A secondary site was the bone. Extremely low levels were found in brain and eye suggesting poor passage through the blood brain barrier. Levels of doripenem were at least 40 fold greater in the maternal circulation than in fetal circulation. The highest fetal concentration of doripenem was seen in the fetal kidney.

Doripenem has relatively little binding to plasma proteins. In the mouse and rat, 25 and 35% of the drug is protein bound, while in dogs, monkeys, and humans, 10% or less of the drug is bound to plasma proteins. Protein binding of doripenem is approximately 12% in the rabbit.

Doripenem is metabolized in rat and dog to the dicarboxylic acid moiety (D-DC). In the urine of rats, D-DC accounts for approximately 50% of the total dose excreted. D-DC accounts for approximately 15% of the dose excreted in the dog. In the human, the D-DC is approximately 18% of the drug in the plasma, while approximately 15% of the total dose is excreted in the urine as D-DC. Thus, the dog is a better model for investigating doripenem. D-DC is inactive. Doripenem is not a substrate for human P450 enzymes. DHP-1 (dihydropeptidase) is responsible for the breakdown of doripenem to D-DC and the activity is inhibited by cilastatin.

Excretion in the rat, monkey and dog is primarily via the urine. With the exception of a single study in female rats (Sprague Dawley where 88% of the dose was found in the urine), between 90 and 97% of the initial dose is excreted in urine with the majority excreted within the first 2 hours. Fecal excretion accounted for between 0.1% (male rats) and 10% (female rats). As up to 3% of the dose of doripenem can be detected in the bile when only 0.1% is seen in the feces, some enterohepatic recycling may be occurring. These studies did not differentiate between parent and the D-DC metabolite. In the studies where parent versus metabolite were measured in the urine, the metabolite accounted for approximately 30% of the dose, but when cilastatin was added only 5% of the dose was excreted as D-DC. Rats excreted 10% of the total dose as D-DC. Humans also excrete the majority of the doripenem via the urine with 71% as parent drug and 15% as D-DC. Less than 1% of the dose was found in human feces. Renal tubular excretion was partly responsible for doripenem elimination in the rabbit, but not in dog. Glomerular filtration and active tubular secretion were also cited as mechanisms for drug elimination in the human. Doripenem did not affect the pharmacokinetics of valproic acid.

Acute intravenous toxicology studies were conducted in the rat, rabbit, and dog. With doses up to 1 to 2 grams of doripenem, no seizure activity was noted. The major

targets of toxicity were kidney, hematologic cells (primarily WBC #), gastrointestinal tract (vomiting in dogs, hemorrhage/erosion), and possibly liver. While the acute toxicity studies seem to emphasize the renal toxicity due to the two rabbit studies, those studies were designed to focus only on the serum chemistry and pathology of the kidney by excluding all other organs from examination.

Subchronic dosing was conducted in the rat and dog. Toxicokinetics were not monitored in these studies. The major targets of toxicity were kidney, gastrointestinal tract and hematologic cells. The changes in WBC and RBC numbers, while usually mild, may possibly be associated with immune responses. This seems likely as splenic hypertrophy was also noted in these studies. An alternate explanation for the RBC decrements would be GI bleeding. Other hematologic changes were variable across studies and species, suggesting that they may be artifacts or not toxicologically relevant. The two 1 month dog studies differed in that lethality occurred at 500 mg/kg in one study, but only at 1000 mg/kg in the other study. QT prolongation was noted in both the 1 month and the 3 month studies in the dogs. Gastrointestinal damage was also noted in both dog studies (hemorrhage and inflammatory cells as well as some vomiting). No new toxicities were noted between 1 month and 3 months in dog or rat. The two week dog study with the new formulation of doripenem did not result in any significant changes in the toxicologic profile. Juvenile dogs actually showed less toxicity than their adult counterparts. No renal toxicity was noted in the juvenile dogs, nor was there splenic hypertrophy. Direct comparisons of plasma concentrations of drug are not possible as toxicokinetics were not monitored in the adults, although these measurements were part of the juvenile protocol. The major human toxicities have included gastrointestinal and hematologic changes. The table below summarizes the comparison of the NOAEL as an HED in the animal studies as compared to the human dose. The human dose of 500 mg q 8 hour is approximately 1500 mg/day or 25 mg/kg/day.

Species	Schedule	Doses tested (mg/kg)	NOAEL mg/kg	HED (mg/kg) at NOAEL	Margin of Safety
Rat	1X	2000	<2000	<324	<13
	DX14 days	100, 300, 1000	<100 LLD>1000	<16	<1
	DX 1 month	100, 300, 1000	100	16	0.6
	DX 3 months	100, 300, 1000	100	16	0.6
Rabbit	1X	200, 400, 600	200 (renal only)	65	2.6
	1X	250, 400	<250 (renal only)	<81	<3.2
	DX5 days	50, 100, 200	50 (renal only)	16	0.6
Dog	1X	1000, 2000	<1000	<54	<2
	DX 1 month	250, 50, 1000	250	135	5.4
	DX1 month	125, 250, 1000	<125	<68	<3
	DX 3 months	40, 100, 250	<40	<22	<1

The special toxicity studies explored the local effects of doripenem on vascular/muscular tissue, on antigenicity, and on liver function. Renal and cardiac function have already been explored in the safety pharmacology section of the NDA. Intravenous injection daily for 8 days in the rabbit ear vein at up to 2% resulted in damage that was not significantly different from that of a normal saline injection. Similarly, a single intramuscular injection of 1% doripenem did not differ in damage from normal saline. Antigenic effects of doripenem were similar to those of imipenem (weak antigenicity in PCA test, FCA positive in ELISA). Guinea pig also showed positive antigenicity in FCA and PCA test. Minimal cross-reactivity between imipenem and doripenem was noted in the guinea pig, but not in the mouse. An *in vitro* Coombs test with human blood was negative.

The sponsor also explored hepatotoxicity in 2 week studies in rats and dogs; however, the doses used were significantly lower than the NOAELs in the 1 month study. It is not surprising that almost no changes were noted.

Mutagenicity of doripenem was investigated in both bacterial (Ames at up to 5 ug/plate) and mammalian (Chinese Hamster Ovary HGPRT at up to 5000 ug/mL) cells. Both systems were negative. Doripenem was negative for clastogenicity in the Chinese Hamster Lung cell chromosomal aberration assay. Doripenem was also negative in the *in vivo* mouse micronucleus assay at 2000 mg/kg. No carcinogenicity studies were required based on the short-term, intermittent use of doripenem.

Studies have been conducted in the rat and rabbit to investigate the potential of doripenem to cause reproductive toxicity. The preliminary dose-ranging studies were conducted at the same doses (up to 1000 mg/kg/day *i.v.*) as the definitive studies and showed no significant effects on the feti or on other reproductive parameters (e.g. maternal toxicity, placental weights, implantation sites, abortions etc). The studies are summarized in the table below, along with the relevant toxicokinetic data from separate studies. Additionally, doripenem did not affect fertility in male or female rats at doses up to 1000 mg/kg/day. Nor did doripenem affect the gestation period, behavior or maturation/reproductive potential of the F1 generation where the dams were administered doripenem through weaning. The data on the AUC at 1000 mg must be extrapolated from a distribution study in rats with two sampling points: 0.5 and 6 hours. C_{max} (at 0.5 hours is 2047 ug equivalents/mL while the plasma levels at 6 hours was approximately 12 ug/mL. The AUC can be calculated using least squares technique to approximately 5750 ug.h/mL, a gross overestimation.

Reproductive Toxicity Studies with Doripenem				
Segment	Species	Doses tested	NOAEL	AUC (dose in mg/kg/day)
Segment I	Rat	0, 100, 300, 1000	1000	---
Segment II	Rat	0, 100, 300, 1000	1000	263 ug.h/mL (300)
Segment II	Rabbit	0, 12.5, 25, 50	50	92.1 ug.h/mL (50)
Segment II/III	Rat	100, 300, 600, 1000	1000	---

Conclusions: The non-clinical toxicology of doripenem has been adequately investigated. The studies were well conducted and the doses were sufficient to delineate

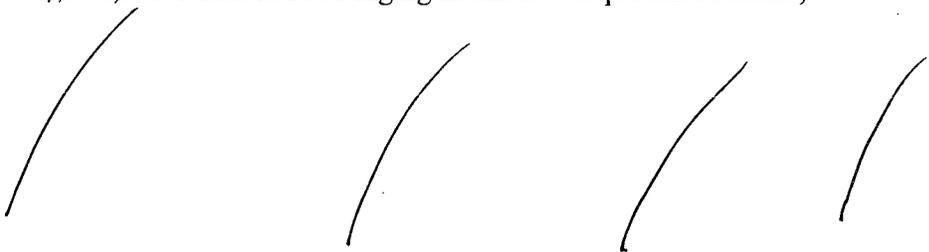
the toxic potential of doripenem. There are no pharmacology/toxicology reasons not to approve this drug.

Unresolved toxicology issues (if any): None.

Recommendations: There are no pharmacology/toxicology objections to approval.

Suggested labeling:

The entire _____ section should be deleted.
The ratios obtained for the animal vs. human AUC exposure are also somewhat different between the FDA and sponsor. The recommended human AUC for 500 mg dose was 36.3 ug.h/mL. There was no adequate exposure data for a pregnant rat dose of 1000 mg/kg (300 mg/kg was the highest dose investigated). No data at 1000 mg/kg in males was presented either, _____



Thus, the pregnancy section of the label should read:

Category B: Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1000 mg/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least _____ times the exposure to humans dosed at 500 mg q8h, respectively). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The fertility section should read:

Intravenous injection of doripenem had no adverse effects on general fertility of treated male and female rats or on postnatal development and reproductive performance of the offspring at doses as high as 1 g/kg/day (based on AUC, _____ times the exposure to humans at the dose of 500 mg q8h).

Signatures (optional):

Reviewer Signature _____

Secondary Reviewer Signature _____ Concurrence Yes ____
No ____

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Wendelyn Schmidt
9/17/2007 02:29:57 PM
PHARMACOLOGIST

Amy Nostrandt
9/17/2007 02:57:53 PM
PHARMACOLOGIST