

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-821

PHARMACOLOGY REVIEW(S)



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: **21-821**
SERIAL NUMBER: **000**
DATE RECEIVED BY CENTER: **10/22/04—rolling submission**
PRODUCT: **Tygacil (tigecycline)**
INTENDED CLINICAL POPULATION: **patients with complicated skin/skin structure
infections or complicated intra-abdominal infections**
SPONSOR: **Wyeth Pharmaceuticals**
DOCUMENTS REVIEWED: **Electronic submission.**
REVIEW DIVISION: **Division of Anti-Infective Drug Products (HFD-520)**
PHARM/TOX REVIEWER: **Wendelyn J. Schmidt, Ph.D.**
PHARM/TOX SUPERVISOR: **Robert Osterberg, Ph.D.**
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Date of review submission to Division File System (DFS): 6/14/05

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability: Tigecycline can be approved on the basis of pharmacology/toxicology.

1.2 Recommendation for nonclinical studies: There are no recommendations at this time.

1.3 Recommendations on labeling:

The sponsor stated that the human AUC used for comparisons was 6.1 ug.h/mL and noted that a conservative estimate would be obtained with this system. Similar values were obtained when using the human AUC of 4.7 ug.h/mL from the pool efficacy studies in the annotated label, pharmacokinetics section.

- 1) “in vivo micronucleus assay” should read in vivo mouse micronucleus assay”.
- 2) Comparison factor for fertility, is 5.
- 3) Teratology should use a comparison factor of 5 for rat, 1 for rabbit.
- 4) “An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with (b) (4).
- 5) In the animal toxicology section, the AUC comparison for rats and dogs should be (b) (4). It should be noted that this is from a 2 week study.
- 6) The (b) (4) data is not as relevant given the difference in infusion times bolus vs. 30-60 minutes and should be deleted.
- 7) Tigecycline should be a Pregnancy Category D, (b) (4) based on tetracycline class effects.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

2.2 Pharmacologic activity

2.3 Nonclinical safety issues relevant to clinical use

Tigecycline is a minocycline analog and member of the tetracycline antibiotic class. Like other tetracyclines, tigecycline has activity against both Gram positive and negative bacteria. Drug is widely distributed, particularly into bone and teeth (where permanent stains can be seen from prenatal and childhood use). Gastrointestinal irritation (nausea/vomiting, diarrhea with oral administration) are common with the class. Other major toxicities with the class are photosensitivity, hepatic toxicity, and renal toxicity.

The main toxicities from the human clinical trials with tigecycline were nausea, vomiting and diarrhea. Some liver enzyme elevations were observed. However, renal changes and decreases in RBC, WBC and platelet number were rare in the trials.

Tigecycline is administered intravenously. Minimal gender differences were noted in the rat or dog; however, the toxicokinetic studies investigated females only. In humans, gender differences were observed. Distribution was widespread, except for within the blood-brain barrier. The drug did cross the placental barrier. Tigecycline tended to localize in bone and persist there. Excretion was via both urine and feces in

both rats and dogs. A similar pattern was seen in humans. Tigecycline was also excreted in milk in rats but excretion in milk was not investigated in humans. Protein binding was in the range of 80-90% in mouse, rat, rabbit, dog and human. Cytochrome P450 enzyme functions were unaffected by tigecycline.

Toxic effects were extremely similar in the rat and dog with tigecycline. The AUCs at the NOAEL in dogs and rats were within 2 fold of each other. Although no cardiac *in vitro* tests were conducted (e.g. hERG assay), no effects on telemeterized dogs on QT intervals were noted at doses up to 12 mg/kg in the dog in safety pharmacology studies. Further, no significant changes in ECG profiles have been seen in clinical trials. Although tetracyclines are not known for prolonging the QT interval, the class has not been studied extensively. Histamine was released in the rat and dog upon tigecycline administration with confirmation shown by measuring histamine levels in the toxicology studies. Vomiting has been observed in the shorter dog studies, but in the 13 week study, doses were low enough that this was not an issue. Gastrointestinal distress is the major toxicity in the clinical trials. Elevations in liver enzymes were seen in the clinical trials as well, but no liver toxicity (either enzyme elevation or histopathology change) other than occasional decrements in total protein and “fatty changes in the liver” were noted in the 2 week dog at 20 mg/kg. These changes could be attributed to vomiting and diarrhea. Another common human toxicity with tetracyclines, uremia, was not observed with tigecycline.

A major toxicity seen in the animal studies, that did not appear to carry over to humans at the doses in the clinical trials, was myelosuppression. Both rats and dogs had decreased numbers of red and white cells as well as platelets. Marrow hypocellularity, lymphoid depletion and atrophy in the thymus and lymph nodes, indicative of immunosuppression, were also observed.

Tigecycline was not phototoxic and was negative in an antigenicity assay. Local tolerance (eye, skin) was not tested.

Tigecycline affected male fertility at doses of 4 mg/kg in the rat (decreased sperm count). Decreased testes' weights were also noted in dogs treated daily with 20 mg/kg tigecycline for 2 weeks. Tigecycline was not teratogenic in either the rat or the rabbit at maternotoxic doses; decreased fetal viability was seen at 12 mg/kg in the rat (AUC 28.5 ug.h/mL) and > 4 mg/kg in the rabbit (AUC >7 ug.h/mL). There were no effects on post-natal development when dams were administered tigecycline at up to 12 mg/kg through weaning.

Tigecycline was negative for mutagenicity and clastogenicity in the ICH battery of genotoxicity tests including mouse lymphoma L5178Y, CHO HGPRT, CHO chromosomal aberrations, and mouse micronucleus assays. Carcinogenicity testing was not required for the short-term, intermittent use of this drug.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21821

Review number: 1

Sequence number/date/type of submission: 000/October 22, 2004/rolling submission

Information to sponsor: Yes () No ()

Sponsor and/or agent:

Wyeth Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101-8299

Manufacturer for drug substance:

Reviewer name: Wendelyn J. Schmidt, Ph.D.

Division name: Division of Anti-Infective Drug Products

HFD #: 520

Review completion date: 5/27/05

Drug:

Trade name: Tygacil

Generic name: Tigecycline

Code name: GAR-936

Chemical name: (4*S*,4*aS*,5*aR*,12*aS*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,10,12,12*a*-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

CAS registry number: information not found.

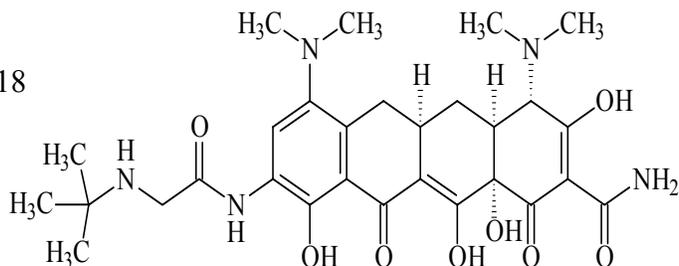
Molecular formula/molecular weight: C₂₉H₃₉N₅O₈, mw = 585.65.

Structure:

Relevant INDs/NDAs/DMFs: IND 56518

Drug class: Tetracycline antibiotic

Indication: Treatment of complicated skin and skin structure infections and complicated intra-abdominal infections.



Clinical formulation: Lyophilized powder reconstituted in 0.9% NaCl or 5% dextrose

Route of administration: Intravenous

Clinical Dose: 100 mg infused over 30-60 minutes followed by 50 mg every 12 hours for 5-14 days

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: Almost all studies have been previously reviewed by Dr. Terry Peters. The study reviewed by W. Schmidt is starred. The submission numbers for the reviews are noted.

Pharmacology:

Primary Pharmacodynamics: Reviewed by the Microbiologists.

Secondary Pharmacodynamics:

1. RPT-55502: Tigecycline (GAR-936): (b)(4) side effect profile of CL346635 (monohydrochloride salt of tigecycline and WAY 152288 (PAM-minocycline). Serial #000

Safety Pharmacology:

1. RPT-51794: Tigecycline (GAR 936): single dose intravenous central nervous system safety pharmacology study in male rats. Study # 02 1397.
2. RPT-50293: Tigecycline (GAR-936): single dose i.v. respiratory safety pharmacology study in male rats. Study # 02 1398.
3. GTR-30524: CLX 346635 and WAY 152288: A single dose intravenous infusion cardiovascular study in conscious male rats. Study # 95390. Serial # 000
4. GTR-32072: GAR-936: An escalating dose intravenous infusion cardiovascular study in dogs. Study # 96262. Serial # 000
5. RPT-42292: GAR-936: Safety pharmacology study. Serial # 072

Pharmacokinetics:

1. GTR-36282: GAR 936: single dose pharmacokinetics of GAT-936 given intravenously to cannulated rats. Study # 95571. Serial # 000
2. GTR-37282: GAR-936: pharmacokinetics of total radioactivity and unchanged drug following a single (5.0 mg/kg) i.v. dose of ¹⁴C-GAR-936 in male rats. Study # 95718. Serial #072
3. GTR-31749: GAR-936: single ¹⁴C intravenous dose (5.0 mg/kg) pharmacokinetics and metabolism study in male dogs (study # 95685). Serial # 032
4. GTR-37280: GAR-936: a single intravenous (5 mg/kg) and oral (15 mg/kg) dose pharmacokinetic study in monkeys (study # 95714PR). Serial # 032
5. GTR-36470: GAR-936: tissue distribution in male Sprague-Dawley rats following a single intravenous infusion dose (3 mg/kg) of ¹⁴C-GAR-936. Study # 95631.
6. RPT-40186: GAR-936: tissue distribution of ¹⁴C-GAR-936-derived radioactivity by whole-body autoradiography following a single 3 mg/kg/intravenous infusion (30minute) dose of ¹⁴C-GAR-936 in male Sprague Dawley and Long-Evans rats. Study # 95631.
7. RPT-49970: GAR-936: Tissue distribution of ¹⁴C-tigecycline following a single bolus intravenous (3 mg/kg) administration and once daily bolus intravenous (3 mg/kg) for 6 and 10 days in male (Sprague-Dawley) rats. Study 96652.
8. GTR-37511: ¹⁴C-GAR-936: in vitro protein binding in mouse, rat, rabbit, dog and human plasma. Study # 96450. Serial # 032

9. RPT-53963: Tigecycline: in vitro protein binding of ^{14}C -tigecycline in mouse, rat, rabbit, dog, and human plasma using ultracentrifugation. Study # 04-0129/04-0465/04-1156. Serial # 065
10. RPT-47491: GAR-936: placental transfer of ^{14}C -GAR-936 following a single bolus intravenous (3 mg/kg) administration to gravid Sprague-Dawley rats. Study # 96666. Serial #
11. RPT-43753: GAR-936: transfer of ^{14}C -GAR-936 in breast milk of rats following a single 5 mg/kg iv dose. Study # 96664. Serial # 000
12. GTR-37286: GAR-936 (WAY156936): metabolism in male rats following intravenous administration of ^{14}C -GAR936 (30 mg/kg). Study # 98806. Serial # 072
13. GTR-37285: GAR-936 (WAY156936): metabolism in male dogs following intravenous administration of ^{14}C -GAR-936 (5 mg/kg). Study # 95685. Serial # 072
14. RPT-55407: Tigecycline: analysis of serum and urine from humans, dogs, and rats for the N-acetyl-9-amino-minocycline metabolite. Study # 3074A1-104-US/04-1368/041373.
15. RPT-42931: GAR-936 (WAY156936): in vitro metabolism of GAR-936 in cryopreserved human hepatocytes, human liver slices and liver microsomes of Sprague-Dawley rats, beagle dogs, and humans. Study # 01-0026. Serial # 104
16. RPT-42413: GAR-936 (WAY156936): evaluation of the inhibition of human cytochromes P450 3A4, 2D6, 2C9, 2C19, 2C8, and 1A2 by GAR-936. Serial #072
17. GTR-35418: GAR-936: single ^{14}C intravenous dose (5 mg/kg mass balance study in male rats. Study # 95605.
18. GTR-37697: GAR-936: urinary and biliary excretion of the parent compound after a single intravenous administration of GAR-936 to male rats
19. GTR-33020: GAR-936: single ^{14}C intravenous dose (5 mg/kg) mass balance study in male dogs. Study # 95590.
20. RPT-42293: Preliminary pharmacokinetic interaction studies between GAR-936 and thiopental in mice.
21. RPT-54958: Tigecycline (GAR-936): multiple intravenous (bolus) dose pharmacokinetics study in male rats. Study # 04 0931.
22. Miracl-24491: A 2-week pharmacokinetic (gavage) study of CL318,614 (antibacterial) in rats. Study # 91022.
23. Miracl-25293: Absorption, bioavailability and pharmacokinetics following a single intravenous and oral dose of ^{14}C -CL318614 in the dog. Study # A9163.
24. Miracl-23899: Mass balance, excretion, and metabolic profiles following a single oral dose of ^{14}C -CL318,614 in the rat. Study # A9146.

Toxicology:

Acute

1. GTR-31860: GAR- 936: acute intravenous toxicity study in mice. Study # 96214. Serial # 000
2. GTR-31861: GAR-936: acute intravenous toxicity study in rats. Study # 96215. Serial # 000

Repeat dose

3. GTR-31411: GAR-936: Three day intravenous tolerability study in male rats. Study # 96196. Serial # 000

4. GTR-31741: A seven day intravenous infusion toxicity study of antibacterial analogs in the albino rat. Study # 95287. Serial # 000
5. Miracl-26228: An exploratory infusion two-week tolerability study of CL 346,790 (TBG MIMO) in surgically catheterized rats. Study E 93-3504. Serial # 000
6. GTR-32074: CL 346,635 and WAY 152,288 A 14 day intravenous infusion pilot toxicology study in male rats. Study # 95354. Serial # 000
7. GTR-31608: GAR-936: Fourteen day intravenous toxicity and toxicokinetic study in rats. Study # 96195. Serial # 000
8. RPT-42195: A 14 day intravenous toxicity study of GAR-936 in the albino rat with a 3-week recovery. Study # 98209.
9. RPT-41074: A 13-week intravenous toxicity study of GAR-936 in the albino rats. Study # 98211. Serial # 065
10. RPT-41347: GAR-936 a 13-week intravenous toxicity study of GAR-936 in the albino rat (protocol 98211): bioanalytical and toxicokinetic report. Serial # 065
11. GTR-30595: CLX 346,635 and WAY-152,288: a 2-day bolus intravenous tolerability study in beagle dogs. Study # 95378. Serial # 000
12. GTR-30663: WAY 152,288 and CLX 346,635: A 2-week intravenous dose ranging pilot toxicity study in dogs. Study # 96100. Serial # 000
13. GTR-31609: GAR-936: Fourteen day intravenous toxicity and toxicokinetic study in dogs. Study # 96194. Serial # 000
14. RPT-42488: A 14-day intravenous toxicity study of GAR-936 in the beagle dog with a 3-week recovery. Study # 98210.
15. RPT-41664: A 13-week intravenous toxicity study of GAR-936 in the beagle dog. Study # 98212. Serial # 065
16. RPT-42763: GAR-936 a 13 week intravenous toxicity study of GAR-936 in the Beagle dog (protocol 98212): bioanalytical and toxicokinetic report. Serial #065
17. GTR-30594: CLX 346,635/WAY 152,288: a 2-day bolus intravenous tolerability study in cynomolgus monkeys. Study # 95379. Serial # 000

Genotoxicology:

1. GTR-32202: Mutagenicity test on GAR-936 CHO HGPRT forward mutation assay with a confirmatory assay. Study # 96159. Serial # 000
2. GTR-31695: Mutagenicity test of CLX 346,635 in the L5178Y TK +/- mouse lymphoma forward mutation assay. Study # 95393. Serial # 000
3. GTR-32201: Mutagenicity test on GAR-936 in the L5178Y TK +/- mouse lymphoma forward mutation assay with a confirmatory assay. Study # 96157. Serial # 000
4. GTR-32066: Mutagenicity test on GAR-936 measuring chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with a confirmatory assay with multiple harvests. Study # 96156. Serial # 000
5. GTR-31896: Mutagenicity test on GAR-936 in the in vivo mouse micronucleus assay. Study # 96158. Serial # 000

Reproductive Toxicology:

1. GTR-32617: GAR-936: Intravenous fertility and developmental toxicity dose ranging study in rats. Study # 96230. Serial # 015

2. RPT-42298: GAR-036: intravenous injection fertility and embryo-fetal development study in the rat. Study # 98205. Serial # 072
3. RPT-41346: GAR-936: intravenous injection fertility and embryo-fetal development study in the rat (protocol 98205): bioanalytical and toxicokinetic report. Serial # 072
4. GTR-33185: GAR-936: intravenous developmental toxicity dose ranging study in CD-1 mice. Study # 96229. Serial #072
5. GTR-32600: GAR-936: 2-week intravenous dose ranging study in female rabbits. Study # 96228.
6. RPT-33215: GAR-936: Intravenous developmental toxicity dose ranging study in gravid rabbits. Study # 97045. Serial #072
7. GTR-35159: GAR-936: intravenous developmental toxicity dose ranging study in gravid rabbits: bioanalytical and toxicokinetics report (Protocol; 97045). Serial # 015
8. RPT-42304: GAR-936: intravenous injection teratology study in the rabbit. Study # 98206. Serial # 072
9. RPT-41646: GAR-936: intravenous injection teratology study in rabbits (protocol 98206): bioanalytical and toxicokinetic report. Serial # 072
10. RPT-53525: Tigecycline: an intravenous bolus injection pre and postnatal study in the rat (protocol # 03 1633). *Current Submission

Special Toxicology:

1. GTR-33263: GAR-936: passive cutaneous anaphylaxis (PCA) assay in rodents. Study # 97016. Serial #015
2. GTR-33124: GAR-936 ascending intravenous and subcutaneous dose-range finding study in guinea pigs. Study # 97017. Serial # 015
3. RPT-55695: Tigecycline: (b)(4) qualification of the 4-epimer of tigecycline.
4. RPT-54677: Tigecycline: qualification of the (b)(4) 9-aminomincycline.
5. RPT-56037: Tigecycline: 14-day intravenous impurity qualification study in rats (protocol 14- 1696).
6. GTR-33279: GAR-936: 14-day intravenous hematotoxicity study with a recovery period in dogs. Study # 97040. Serial # 000
7. RPT-55059: Tigecycline: single dose phototoxicity study to determine the effects of intravenous administration on the eyes and skin in pigmented male rats. Study # 040001. Current Submission.
8. RPT-39987: Lederle Japan study on the emetogenic potential of GAR-936 in Suncus murinus (shrews).
9. GTR-32502: GAR-936: In vitro compatibility testing of the GAR-936 intravenous formulation with rat, dog and human blood. Study # 96199. Serial #000
10. MIRACL-26519: In vitro studies to assess the effects of DMG-DMDOT (CL331, 928) DMG-mino (CL344,677) TBG-mino (CL346-790), minocycline (CL59,806) and tetracycline on cellular and mitochondrial protein synthesis. Study # 93151.
11. MIRACL-24409: A single dose exploratory (gavage) study of CL318,614 (antibacterial) in mice. Study # 90300).
12. MIRACL-25212: A single dose intraperitoneal toxicity study of CL318,614 (9-aminomincycline, an antibiotic agent in mice. Study # 91093.

13. MIRACL-24408: A single dose exploratory (gavage) study of CL318,614 (antibacterial) in rats. Study # 90229.
14. MIRACL-25211: A single dose intraperitoneal toxicity study of CL 318,614 (9-aminomincycline, an antibiotic agent) in rats. Study # 91092.
15. MIRACL-24411: A two week oral toxicity (gavage) study of CL318,614 (antibacterial) in rats. Study # 91024.
16. MIRACL-24488: A single escalating oral (gavage) toxicity study of CL 318,614 (antibacterial) in dogs. Study # 90231.
17. MIRACL-25299: A 2-week oral (gavage toxicity study of CL318,614 (antibacterial) in dogs. Study 91019.
18. MIRACL-26105: Evaluation of CL 318,614 (9-aminomincycline HCL) in a microbial mutagenicity assay. Study # 91074.
19. MIRACL-24694: CHO/HPRT mammalian cell forward gene mutation assay on CL 318,614—9-aminomincycline. Study # 91076.
20. MIRACL-24191: Test for chemical induction of unscheduled DNA synthesis in rat primary hepatocyte cultures by CL318,614 (9-aminomincycline HCL). Study # 91078.

Studies not reviewed within this submission: None of the studies using non-intravenous routes of administration were reviewed.

3.2 PHARMACOLOGY

3.2.1 Brief summary

Tigecycline is a member of the tetracycline family of antibiotics and acts by inhibition of tRNA binding to ribosomes . Tigecycline has activity against Gram positive and negative bacteria as well as against some MRSA and VRE lines.

3.2.2 Primary pharmacodynamics: This information is reviewed by the microbiologist.

3.2.3 Secondary pharmacodynamics

In the (b) (4) assay, there was no significant interference/binding to the various receptors with tigecycline at concentrations up to 10 uM.

3.2.4 Safety pharmacology

Neurological effects:

Effects were minimal until 30 mg/kg in the rat, where decreased activity, writhing responses, and irritability were noted. In a separate study, 30 mg/kg had no effect on CNS parameters (clinical signs plus grip strength, hindlimb footsplay, and rectal temperature). In a second rat study with 5, 15, and 30 mg/kg tigecycline, no significant changes in behavior or functional parameters were noted.

Cardiovascular effects:

In the telemeterized rats (1 month wash-out from previous drugs), there were no significant effects on blood pressure, heart rate or gross activity over a 24 hour period at

doses of 5 or 25 mg/kg infused over 1 hour. In the dog, a dose of 12 mg/kg was associated with an initial increase in blood pressure, followed by a decrease in blood pressure for the remaining 23 hours; increased activity and increased heart rate in the first hour after infusion; but no changes in ECG. In the rabbit, similar effects were seen at 30 mg/kg.

Pulmonary effects:

Bronchoresistance was fatal in immobilized guinea pig at 30 mg/kg. The response was reduced with anti-histamines. In the rat with 5, 15, or 30 mg/kg tigecycline, no effect on respiratory rate, tidal volume or minute volume were noted.

Renal effects:

With 30 mg/kg, a decrease urinary pH and an increase in potassium excretion was noted in the rat. The findings were not toxicologically relevant.

Gastrointestinal effects:

No effects on transit time was seen with up to 30 mg/kg tigecycline.

Abuse liability: None.

Other: None.

3.2.5 Pharmacodynamic drug interactions: No interactions were investigated.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

All of the studies were conducted by the intravenous route using a normal saline vehicle. Tigecycline has a longer half-life in dogs and monkeys than in rats. Gender differences in pharmacokinetics are only briefly explored in the toxicokinetic studies, where there did not appear to be a significant difference between genders. Distribution of tigecycline was widespread, with the exception of not crossing the blood-brain barrier. Like most tetracyclines, tigecycline was bound to bone with the accompanying discoloration (although dental discoloration was not mentioned in the reports from the post-natal rat study. Tigecycline was excreted in milk, but the actual pup plasma exposure to parent compound was extremely low (even the remaining metabolites were just above 10% of the level in the plasma of the dams. Metabolism was not extensive. Excretion was via both the urine and feces.

3.3.3 Absorption

The initial set of single dose pharmacokinetic studies were conducted only in males. No gender comparisons can be made without including the toxicokinetic data. In several studies, both total radioactivity and parent compound by HPLC were measured, suggesting that metabolites do not contribute much to the initial C_{max}, but have longer half-lives and contribute significantly to overall exposure. The results of these studies are shown in the table below.

<u>Ref #</u>	<u>Species</u>	<u>N</u>	<u>Sex</u>	<u>Dose mg/kg</u>	<u>Analysis method</u>	<u>Time course</u>	<u>Cmax ug/mL</u>	<u>AUC ug.hr/mL</u>	<u>T_{1/2} h</u>
1	SD rat	4	M	5	HPLC	0-24 h	7.44±0.59	3.55±0.28	1.0±0.2
				30			120±49	64.6±20.6	2.9±0.1
				70			287±53	227±38	4.3±0.9
2	SD rat	4	M	5	¹⁴ C/HPLC	0-168 h	^t 4.94±0.56	4.28±0.35	3.5±0.2
							^p 3.60±0.70	1.86±0.18	1.1±0.1
5	SD rat		M	3	¹⁴ C	0-168 h	1.14	3.64	36
	Gravid SD rat	1	F	3	¹⁴ C/HPLC	0-72 h	1.35	2.45	7.7
3	Beagle dog	4	M	5	¹⁴ C/HPLC	0-168 h	^t 10.5±3.8	22.2±3.8	30±10
							^p 9.93±4.24	13.2±2.1	8.1±2.1
4	C. monkey	4	M	5 (iv)	HPLC	0-48 h	15.1±6.1	18.3±3.0	14.1±3.4
				15(p.o.)			0.16±0.02	0.16±0.06	---

^t total radioactivity ^p radioactivity from parent drug

The exposure to GAR-936 and metabolites in nursing dams and their pups are shown in the following table. No parent drug was detectable in the pup plasma, and total radiolabel levels in the pups are approximately 1/7th that seen in the dams. The concentration of radioactivity in milk is higher than that in plasma (see table below).

TABLE 7. MEAN (± SE) PHARMACOKINETIC PARAMETERS IN LACTATING RATS AND THEIR NURSING PUPS FOLLOWING A SINGLE 5 MG/KG INTAVENOUS DOSE OF ¹⁴C-GAR-936 TO LACTATING RATS - PHASE I (PROTOCOL 96664)

		C _{15min} /C _{max} (ng/mL)	t _{max} (hr)	AUC ₀₋₄₈ (ng•hr/mL)	t _{1/2} ^a (hr)
Lactating Rats	GAR-936	970 ± 512 ^b	NA	2967 ± 362	ND
	Total Radioactivity	1987 ± 280 ^{b,c}	NA	5997 ± 202 ^d	14.6
Nursing Pups	GAR-936	NC	NC	NC	NC
	Total Radioactivity	39.6 ± 2.8 ^c	12 ± 3	824 ± 92 ^d	ND

a: Half-life was calculated from mean concentration vs time profile using WinNonlin.

b: Concentration at 15 minutes after dosing (1st sampling time point).

c: Units are ng equiv./mL.

d: Units are ng equiv•hr/mL.

NC: Not calculated, all concentrations except two pooled pup serum samples were below the LOQ.

ND: Not determined; the serum concentration-time profiles did not support the estimation of the terminal rate constants.

TABLE 11. MEAN (\pm SD) CONCENTRATIONS OF TOTAL RADIOACTIVITY AND GAR-936 FOLLOWING A 5 MG/KG INTRAVENOUS DOSE OF ^{14}C -GAR-936 TO LACTATING RATS - PHASE II (PROTOCOL 96664)

Time (Hr)	Total Radioactivity (ng equiv./mL)	Unchanged GAR-936 (ng/mL)
	Mean \pm SD	Mean \pm SD
Serum ^a		
0.25	1670 \pm 121	1185 \pm 98.5
1	721 \pm 113	504 \pm 75.6
4	245 \pm 32	167 \pm 16.6
8	133 \pm 34	105 \pm 22.1
Milk		
0.25	4814 \pm 1495 ^b	ND
1	6648 \pm 3057	ND
4	14912 \pm 3132	ND
8	6292 \pm 4344	ND
Milk-to-Serum Ratio		
0.25	2.84 \pm 1.01 ^b	ND
1	9.70 \pm 5.16	ND
4	61.1 \pm 10.3	ND
8	45.0 \pm 21.6	ND

a: Blood sample was taken at end of milk collection.

b: N=3

N = 4 samples per timepoint unless otherwise noted

ND: Not determined

3.3.4 Distribution

Tissue distribution was investigated in the rat with single and daily for 6 or 10 day regimens. Both liquid scintillation counting and whole body autoradiography were used. The duration of dosing did not alter the distribution. The majority of drug after the first hour was found in the bone and persisted there for more than 14 days. Other tissues with exposures to tigecycline exceeding that in plasma included bone marrow, salivary and thyroid glands, kidney and spleen. When gravid rats were examined, the bones in both the dams and feti were obvious in autoradiograms. The AUC in the fetus was 1.5X that of maternal plasma.

Protein binding was investigated by two methods at 0.1 to 15 ug/mL tigecycline. The results are shown in the table below.

Species	% protein binding Filtration	% protein binding Ultracentrifugation
Mouse	13.9	86.2
Rat	49.3	88.5
Rabbit	88.1	80.2
Dog	91.9	84.7
Human	95.3	87.4

3.3.5 Metabolism

The metabolism of tigecycline was investigated in rat and dog by sampling the plasma and urine. Additionally, the effects of Cytochrome P450 enzymes and hepatocyte extracts were studied. The majority of tigecycline in the plasma was in the form of parent compound in both the rat and dog (> 80% of the total dose) with the remainder as the epimer or polar breakdown products. At 0.5 h in the dog, the epimer form accounted for 5% and increased to 15% by the end of 24 hours. Similarly, the amount of “other” polar compounds was initially 2% of the total and increased to 11% of the total at 24 hours. In the urine, 4 other metabolites were found, M1, M2, M3 and M4, where M3 was 9-aminominocycline. These metabolites accounted for less the 2% of the total dose.

In human urine, metabolites M8 and M9, where the label was cleaved, accounted for approximately 11% of the total dose. These were not detected in rat or dog urine, and could be captured when human cytosolic extracts were incubated with tigecycline. M9 was a breakdown product of M3.

3.3.6 Excretion

Excretion patterns of tigecycline were remarkably similar in rat and dog, as is shown in the following table.

<u>Species</u>	<u>N</u>	<u>Interval hours</u>	<u>% of total in 1st 24 h</u>	<u>% in rinse</u>	<u>% in urine</u>	<u>% in feces</u>	<u>Total radioactivity recovered</u>
Beagle dog	4	0-168	63.8 ±9.3	6.8±1.4	35.5±11.6	46.7±2.6	89.1±10.9
SD rat	4	0-168	62.0±3.6	1.7±1.5	34.4±4.6	53.3±4.9	89.4±2.5

3.3.7 Pharmacokinetic drug interactions:

No interactions (inhibition, stimulation or effects on drug metabolism)with Cytochrome P450 enzymes were noted.

3.3.10 Tables and figures to include comparative TK summary

<u>Toxicokinetics for Tigecycline</u>							
<u>Species</u>	<u>Schedule</u>	<u>Dose mg/kg</u>	<u>AUC_{0-∞} (ug h/mL)</u>				<u>Half-life (last day) h in M</u>
			<u>Males</u>		<u>Females</u>		
			<u>Day 1</u>	<u>Last Day</u>	<u>Day 1</u>	<u>Last Day</u>	
CD Rat	DX2 wks	5	---	7.1	---	---	6.7
		30	---	65.9	---	50.0	10.2
		70	---	129	---	---	8.1
SD rats	DX13 wks	2	3.4	6.2	---	---	12.3
		6	10.2	19.9	8.5	14.6	13.7
		20	37.9	87.4	---	---	9.0
Beagle Dog	DX2 wks	2	4.9	6.2	5.2	6.0	---
		5	12.5	12.9	11.9	11.8	---
		12	30.1	33.6	33.1	34.4	---
	DX2 wks	2	6.2	6.2	5.9	4.8	7.2
		5	18.6	15.4	18.3	18.7	15.8
		12	49.0	61.4	46.6	58.5	10.8
	DX13 wks	20	101	---	91.3	148	---
		0.5	1.5	1.6	1.4	1.6	14.4
		1.5	4.6	4.5	4.3	4.5	14.5
	5.0	15.5	20.4	15.1	18.1	16.8	

---Values not collected

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:

The toxicology studies for tigecycline were conducted in rat and dog using bolus intravenous dosing with 0.9% saline solution as vehicle. Like other tetracyclines, tigecycline bound to bone and caused discoloration (yellow). A histaminic response was seen in both rat and dog (and was confirmed by measuring histamine levels). Both species also showed significant effects on blood elements (RBCs, WBCs and platelets were all decreased). Minor renal damage was noted (tubular degeneration which resolved within 3 weeks). No effects on the liver were seen. Finally, at higher doses, gastrointestinal effects were seen, primarily on the small intestine. As a secondary effect to vomiting, ulcerations and erosions in the esophagus and mouth were reported (dog only). No additional toxicities were observed with increased duration of administration. No differences in toxicity were noted with gender.

<u>Species</u>	<u>N</u>	<u>Schedule</u>	<u>Doses mg/kg</u>	<u>Results</u>
CD-1 Mouse	3/sex	1X bolus	87.5, 175	LD50=124 mg/kg in males, 98 mg/kg in females; NOEL< 87.5 mg/kg Toxicities: decreased activity, ptosis, dyspnea, exophthalmus
CD rat	3/sex	1X bolus	75, 150, 300	LD50 = 106 mg/kg, NOEL <75 mg/kg Toxicities: decreased activity, dyspnea, erythema, edema
	5 M	DX3 d bolus	70	Histaminic response, blood in feces, bright yellow urine
	15/sex	DX14d bolus	5, 30, 70	NOAEL = 5 mg/kg. Histaminic response, blood in feces/urine, Decr. in RBC parameters, WBC #, platelets; discoloration of bone, injection site rxn. Histopathology: lymphoid atrophy in bone marrow, thymus, spleen, lymph nodes; atrophy of prostate, seminal vesicles.
SD rat	15/sex	DX14 d bolus+ 3 wk recovery	20, 50, 70	NOAEL<20mg/kg; LLD= 20 mg/kg. Main cause of death at 70 mg/kg—marrow hypocellularity, several with cardiac inflammation/mineralization. Clinical signs: histamine release. Hematology: RBCs decreased at 70 mg/kg, WBCs and platelets decreased at all doses. Serum Chemistry: total protein decreased at all doses. Histopathology: yellow discoloration of bone at 50, 70; marrow hypocellularity, lymphoid atrophy in thymus, lymph nodes; myocardial inflammation/myofiber degeneration/ necrosis/mineralization. Kidneys: tubular degeneration. Stomach: ulceration of glandular mucosa. Injection site: hemorrhage, inflammation, thrombosis, necrosis. End of recovery period: bone, injection site and heart effects were still seen.
	15/sex	DX13 wks, bolus	2, 6, 20	NOAEL= 2 mg/kg Clinical signs: histaminic response. Hematology: pancytopenia at 20 mg/kg. Serum chemistry: decreased total protein at 6, 20 mg/kg. Organ weight: decreased spleen and thymus

				weight. Histopathology: yellow bone discoloration at 20 mg/kg. lymphoid atrophy in thymus at 20 mg/kg.
Cyn. Monkey	1/sex	DX2 bolus	5, 15	NOAEL < 5 mg/kg, liquid feces
Beagle dog	1/sex	DX2d Bolus	5, 15	NOAEL<5 mg/kg; clinical signs: lacrimation, facial erythema, emesis, hypoactivity.
	2/sex	DX 14d Bolus	2, 5, 12	NOAEL < 2 mg/kg, Signs: erythema, changes in feces, salivation and emesis, decreased motor activity and lacrimation (histaminic response) Decr RBC #, no gross pathology
	3/sex	DX14 d bolus	2, 5, 12, 20	LLD= 20 mg/kg, NTEL = 5 mg/kg; histamine response (>2 mg/kg), HD weight loss, blood in feces/urine, decreased motor activity. 12 and 20 mg/kg: pancytopenia w/ marrow hypocellularity. Increases in BUN/creatinine at 12/20 mg/kg, decreased total protein. Thyroxine decreased by 50% at 12, 20 mg/kg. Histopathology at 12/20 mg/kg: lymphoid depletion in lymphoid tissues, atrophy of intestinal mucosa, erosion/ulceration/ inflammation of mouth/esophagus (consistent with vomiting), fatty changes in liver.
	6/sex	DX 14 d bolus + 3 week recovery	5, 12	NOAEL < 5 mg/kg. Clinical signs: histaminic response (measured). Hematology: RBC at 12, WBC at 5, 12, APTT increased at 12 mg/kg males. Serum chemistry: increases in BUN at 12 mg/kg, decreased in total protein at 5, 12. Hematology and serum chemistry resolved by 3 weeks. Histopathology: lymphoid atrophy in the thymus, partially resolved. Tubular degeneration resolved (basophilia) by 3 weeks. No marrow damage found.
	3/sex	DX13 wk, bolus	0.5, 1.5, 5.0	NOEL = 1.5 mg/kg. Clinical signs: histaminic response at HD (confirmed by assay). Histopathology: lymphoid atrophy in thymus at HD

Genetic toxicology:

The full recommended ICH battery of genotoxicity tests was conducted with tigecycline. Tigecycline was negative for mutagenicity in the mouse lymphoma L5178Y and CHO HGPRT assays. The CHO chromosomal aberrations assay demonstrated no genotoxicity for tigecycline. The in vivo mouse micronucleus test was also negative with tigecycline at appropriate doses of 150 mg/kg.

Carcinogenicity: No studies were necessary for the short-duration use of this product.

Reproductive toxicology:

Fertility, fetal toxicity and developmental toxicity were investigated in the mouse, rat and rabbit. Tigecycline was not teratogenic in either the rat or the rabbit; however, there were increased resorptions in both species at doses above the maternally toxic level. The fetotoxic doses and AUCs are shown in the following table. The paternal NTEL in the combined rat fertility/fetal development study was 1 mg/kg. At higher doses, a slight decrement in sperm counts were seen. Other toxicity studies also showed some effects on testicular weights. In the rat development and postnatal study, using the same doses in

the teratology study, there were no effects on the feti and their postnatal development at the highest dose tested, 12 mg/kg. The maternal NTEL was the MD, 4 mg/kg. Based on the pharmacokinetic/distribution studies in the pregnant dams, tigecycline is excreted in the milk and clearly crossed the blood-brain barrier as the fetal skeletons were visible in autoradiographs.

<u>Species</u>	<u>Doses tested</u> <u>mg/kg</u>	<u>Fetal NTEL</u> <u>mg/kg</u>	<u>Fetotoxic Dose</u> <u>mg/kg</u>	<u>AUC @</u> <u>fetotoxic dose*</u> <u>ug.h/mL</u>
Rat	1, 4, 12	4	12	28.5
Rabbit	0.25, 1, 4	4	>4	6.75

AUC on last day of dosing

Special toxicology:

A major issue for tigecycline is whether, based on the myelosuppressive effects, there is also immunosuppression. Consistently in the toxicity studies, bone marrow hypoplasia, and lymphoid atrophy were observed. The passive cutaneous antigenicity study in the rat was negative, but this test would not be expected to predict immunosuppressive potential. The intravenous guinea pig study on airways did show a response, but that may also be associated with the histaminic effects of tigecycline. This is the one area where further pharmacology/toxicology studies might be useful.

Local tolerance was not tested (i.e. skin or eye irritation).

3.4.2 Single-dose toxicity: Previously reviewed by Dr. Terry Peters.

3.4.3 Repeat-dose toxicity: Previously reviewed by Dr. Terry Peters.

3.4.4. Genetic toxicology: Previously reviewed by Dr. Terry Peters.

3.4.5. Carcinogenicity: There were no carcinogenicity studies required due to the short duration of use for this drug.

3.4.6. Reproductive and developmental toxicology

Fertility and early embryonic development: These studies were previously reviewed by Dr. Terry Peters.

Embryofetal development: These studies were previously reviewed by Dr. Terry Peters.

Prenatal and postnatal development

Study title: RPT-53525: Tigecycline: an intravenous bolus injection pre- and postnatal study in the rat (protocol 03_1633).

Conducting laboratory and location: (b) (4)

Date of study initiation: 1/26/04

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: Tigecycline, Lot # X42946A, 047ETEC, (b) (4)

Vehicle: 0.9% sodium chloride

Methods

Doses: 0, 1, 4, 12 mg/kg

Species/strain: Sprague Dawley rats, 11 weeks old, 235-296 g

Number/sex/group: 25 females/dose

Route, formulation, volume, and infusion rate: intravenous, 1 mL/kg/day

Satellite groups used for toxicokinetics: None.

Study design: mated female rats were dosed once daily on presumed gestation day 6 through post-partum day 20.

Parameters and endpoints evaluated: Dams: maternal clinical signs (daily), body weights (twice weekly), food consumption (every 3 days), gross pathology; Pups: malformations, # live/dead, weight (twice weekly), startle response (beginning post-partum day 12, vaginal opening/preputial separation, papillary closure response, passive avoidance, motor activity, water maze swimming, mating indices. F2 generation: malformations and variations.

Results

F₀ in-life: One HD dam died during lactation with no remarkable clinical signs or gross pathology. There were no remarkable differences between treated and control dams in clinical observations. Body weights at the end of gestation decreased with dose, but not to a remarkable extent and are shown in the following table. Body weight gains were decreased to a relevant level in the HD group. Food consumption was increased in the treated groups, but not to a statistically significant extent. There were no significant differences in parturition parameters (length of gestation, duration of parturition).

Body weight and body weight gain in the F0 dams as compared to controls.				
Dose (mg/kg)	End of Gestation		End of lactation	
	Body weight	Body weight gain (GD 6-21)	Body weight	Body weight gain (LD1-21)
1	---	---	↑4%	↑41%
4	↓2%	↓11%	↑2%	↑48%
12	↓5%	↓18%	↑1%	↑70%

F₀ necropsy: There were no remarkable differences between treated and control dams.

F₁ physical development: There were no differences in the number of pups/litter, malformations, or male: female ratios. Pup weights did not differ significantly with dose, nor did weights significantly differ during maturation. At necropsy (following culling at lactation day 4), 4/74 HD females had dilatation of the pelvis. There were no remarkable gross pathology observations.

F₁ behavioral evaluation: Time to auricular startle, papillary closure, time to vaginal opening/preputial separation, passive avoidance, water maze times, and group mean activity counts did not differ significantly between groups. Estrus cycling in females did not differ significantly between groups.

F₁ reproduction: There were no significant differences in the mating performance of the F1 generation. Maternal weights during gestation did not differ significantly measured as body weight or body weight gain. There were no significant findings at necropsy.

F₂ findings: There were no significant differences between groups in mating/fertility index, total number of corpora lutea, implantation sites, male:female ratio, live feti, resorptions, or gravid uterine weights.

Comments and conclusions:

The fetal NOAEL is the 12 mg/kg/d, while the maternal NOAEL, based on decrements in body weight gain is the 4 mg/kg/d.

3.4.7 Local tolerance: Previously reviewed by Dr. Terry Peters

3.4.8 Special toxicology studies:

1. RPT-55059: Tigecycline: single dose phototoxicity study to determine the effects of intravenous administration on the eyes and skin in pigmented male rats. Study # ADO00001.

Conducting laboratory and location: (b) (4)

Date of study initiation: June 10, 2004

GLP compliance: Yes

QA reports: Yes (X) No ()

Drug, lot #, and % purity: tigecycline (GAR 936), batch # ADO00001-B, C and D. (b) (4) pure.

Formulation/vehicle: 0.9% saline

Doses: 0, 10, 30, 70 mg/kg, intravenous

Study Design: 5 male Long-Evans rats/dose were dosed with drug, then at either 5 minutes or 2 hours exposed to ½ the minimal erythema dose for ½ hour on one eye, one dark patch and one light patch. Positive control was 8-methoxypsoralen (8-MOP) at 1 hour post-dose. Rats were evaluated for mortality, cutaneous response, body weight ophthalmology, and microscopic ocular exams through day 3.

RESULTS:

Mortality and clinical signs: One/5 of the 70 mg/kg rats died on day 1 and was attributed to anesthesia effects. The positive controls had grade 1 erythema and edema at the skin sites. No signs, other than the swelling of mouth/ears/limbs and ataxia, which were expected with the histaminic response to tigecycline, were noted in the tigecycline rats.

Body weights: There were no toxicologically significant changes with treatment.

Eye exams: All of the MOP treated rats showed diffuse superficial corneal edema. One or 2 rats in each dose group with tigecycline showed either corneal edema or focal corneal scarring, but there were no significant dose-related effects.

Conclusions: The study was adequate in that toxic effects from tigecycline were seen at the high dose; no significant increases in UV damage with tigecycline were noted.

2. RPT-39987: Lederle Japan study on the emetogenic potential of GAR-936 in *Suncus murinus* (shrews).

Conducting laboratory and location: Medical Research Laboratories, Wyeth Lederle (Japan), LTD, Saitama, Japan

Date of study initiation: 9/1/98

GLP compliance: No

QA reports: Yes () No (X)

Drug, lot #, and % purity: Gar-936, Lot # OC7650, (b) (4) pure; also GAR-936 + 4-epimer and GAR-936 + oxidation products (150 mg/kg)

Formulation/vehicle: 0.9% normal saline; positive control: cisplatin, 40 mg/kg

Doses: 100, 300, 600 mg/kg

Study Design: Female shrews (3/dose, weight approximately 40 g) were administered the test compounds and observed for vomiting, # of episodes, and time between episodes for up to 6 hours.

RESULTS:

Doses of 100 or 300 mg/kg GAR-936 had not effect on vomiting or mortality. At 600 mg/kg, 2/4 shrews died while the other 2 vomited. Cisplatin caused vomiting in 2/2 animals. The first episode of vomiting with GAR-936 was at 36 or 73 minutes in the 600 mg/kg group. Copper sulfate (40 mg/kg) caused vomiting in 3/3 animals within an average of 5.7 minutes. Mixtures of the epimer and oxidation products with GAR-936 (150 mg/kg) did cause vomiting in 2/4 and 3/4 animals respectively.

Conclusions: The shrew is not a good model for investigating vomiting with tigecycline.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Tigecycline is a minocycline analog and member of the tetracycline antibiotic class. Like other tetracyclines, tigecycline has activity against both Gram positive and negative bacteria. Drug is widely distributed, particularly into bone and teeth (where permanent stains can be seen from prenatal and childhood use). Gastrointestinal irritation (nausea/vomiting, diarrhea with oral administration) are common with the class. Other major toxicities with the class are photosensitivity, hepatic toxicity, and renal toxicity.

The main toxicities from the human clinical trials with tigecycline were nausea, vomiting and diarrhea. Some liver enzyme elevations were observed. However, renal changes and decreases in RBC, WBC and platelet number were rare in the trials.

Tigecycline is administered intravenously. Minimal gender differences were noted in the rat or dog; however, the toxicokinetic studies investigated females only. In humans, gender differences were observed. Distribution was widespread, except for within the blood-brain barrier. The drug did cross the placental barrier. Tigecycline tended to localize in bone and persist there. Excretion was via both urine and feces in both rats and dogs. A similar pattern was seen in humans. Tigecycline was also excreted

in milk in rats but excretion in milk was not investigated in humans. Protein binding was in the range of 80-90% in mouse, rat, rabbit, dog and human. Cytochrome P450 enzyme functions were unaffected by tigecycline.

Toxic effects were extremely similar in the rat and dog with tigecycline. The AUCs at the NOAEL in dogs and rats were within 2 fold of each other. Although no cardiac *in vitro* tests were conducted (e.g. hERG assay), no effects on telemeterized dogs on QT intervals were noted at doses up to 12 mg/kg in the dog in safety pharmacology studies. Further, no significant changes in ECG profiles have been seen in clinical trials. Although tetracyclines are not known for prolonging the QT interval, the class has not been studied extensively. Histamine was released in the rat and dog upon tigecycline administration with confirmation shown by measuring histamine levels in the toxicology studies. Vomiting has been observed in the shorter dog studies, but in the 13 week study, doses were low enough that this was not an issue. Gastrointestinal distress is the major toxicity in the clinical trials. Elevations in liver enzymes were seen in the clinical trials as well, but no liver toxicity (either enzyme elevation or histopathology change) other than occasional decrements in total protein and “fatty changes in the liver” were noted in the 2 week dog at 20 mg/kg. These changes could be attributed to vomiting and diarrhea. Another common human toxicity with tetracyclines, uremia, was not observed with tigecycline.

A major toxicity seen in the animal studies, that did not appear to carry over to humans at the doses in the clinical trials, was myelosuppression. Both rats and dogs had decreased numbers of red and white cells as well as platelets. Marrow hypocellularity, lymphoid depletion and atrophy in the thymus and lymph nodes, indicative of immunosuppression, were also observed.

Tigecycline was not phototoxic and was negative in an antigenicity assay. Local tolerance (eye, skin) was not tested.

Tigecycline affected male fertility at doses of 4 mg/kg in the rat (decreased sperm count). Decreased testes' weights were also noted in dogs treated daily with 20 mg/kg tigecycline for 2 weeks. Tigecycline was not teratogenic in either the rat or the rabbit at maternotoxic doses; decreased fetal viability was seen at 12 mg/kg in the rat (AUC 28.5 ug.h/mL) and > 4 mg/kg in the rabbit (AUC >7 ug.h/mL). There were no effects on post-natal development when dams were administered tigecycline at up to 12 mg/kg through weaning.

Tigecycline was negative for mutagenicity and clastogenicity in the ICH battery of genotoxicity tests including mouse lymphoma L5178Y, CHO HGPRT, CHO chromosomal aberrations, and mouse micronucleus assays. Carcinogenicity testing was not required for the short-term, intermittent use of this drug.

Conclusions: There are no objections to approval from a pharmacology/toxicology standpoint.

Unresolved toxicology issues: In the animals, myelosuppression is the major toxicity with tigecycline; however it is not clear if tigecycline is immunosuppressive.

Recommendations: The drug can be approved from the pharmacology toxicology perspective. No new studies are recommended at this time, especially given that the

decreases in RBCs, WBCs and platelets seen in the rat and dog do not appear to carry over to humans tested in clinical trials.

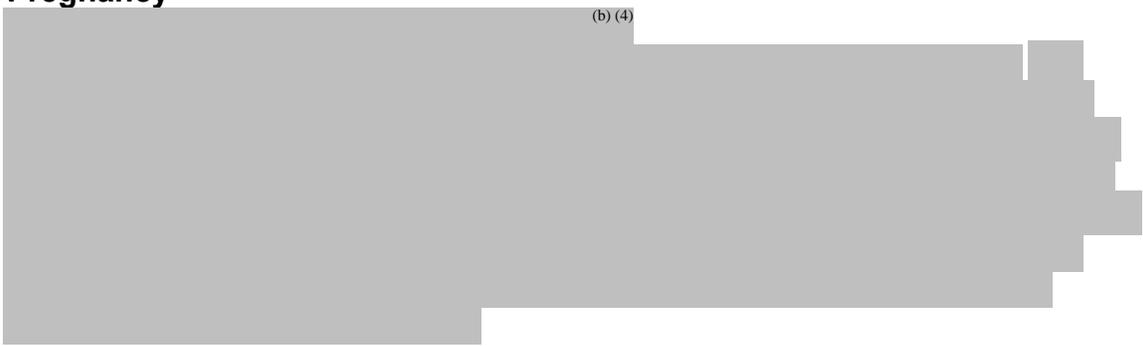
CURRENT LABELING

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including in vitro chromosome aberration assay in Chinese hamster ovary (CHO) cells, in vitro forward mutation assay in CHO cells (HGRPT locus), in vitro forward mutation assays in mouse lymphoma cells, and in vivo micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 4.7 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 4.7 times the human daily dose based on AUC.

Pregnancy

(b) (4)



There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Labor and Delivery

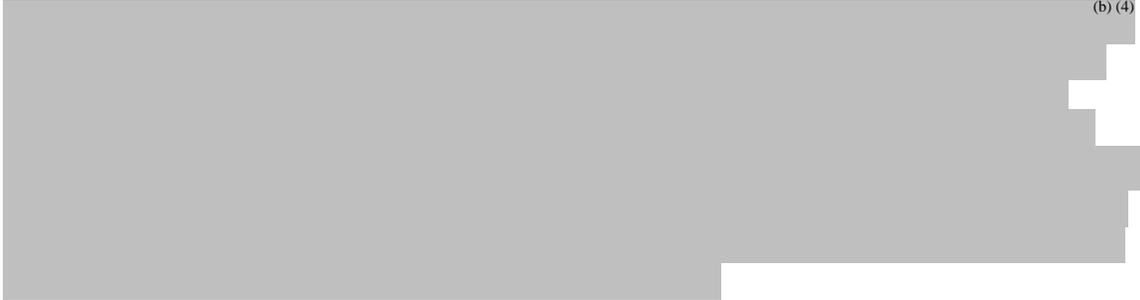
TYGACIL has not been studied for use during labor and delivery.

Nursing Mothers

Results from animal studies using ¹⁴C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman. (See **WARNINGS**.)

ANIMAL TOXICOLOGY



SUGGESTED LABELING:

The sponsor stated that the human AUC used for comparisons was 6.1 ug.h/mL and noted that a conservative estimate would be obtained with this system. Similar values were obtained when using the human AUC of 4.7 ug.h/mL from the pool efficacy studies in the annotated label, pharmacokinetics section.

- 1) “ in vivo micronucleus assay” should read in vivo mouse micronucleus assay”.
- 2) Comparison factor for fertility, is 5.
- 3) Teratology should use a comparison factor of 5 for rat, 1 for rabbit.
- 4) “An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with (b) (4)
- 5) In the animal toxicology section, the AUC comparison for rats and dogs should be (b) (4) It should be noted that this is from a 2 week study.
- 6) The (b) (4) not as relevant given the difference in infusion times bolus vs. 30-60 minutes and should be deleted.
- 7) Tigecycline should be a Pregnancy Category D, (b) (4) based on tetracycline class effects.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

Deputy Division Director Signature _____

Concurrence Yes ___ No ___

3.7. APPENDIX/ATTACHMENTS: None

**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
6/14/05 12:37:42 PM
PHARMACOLOGIST

this is the corrected version

Robert Osterberg
6/14/05 01:45:03 PM
PHARMACOLOGIST

Lillian Gavrilovich
6/15/05 04:14:50 PM
MEDICAL OFFICER