Anti-Infective Advisory Committee

November 19, 2008
(Morning Session)

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Questions to the AIDAC

Background

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AIDAC Meeting, November 19, 2008

Telavancin

- Lipoglycopeptide antibacterial for intravenous use
  - Produced through chemical modification of vancomycin
  - Bactericidal; inhibits bacterial cell wall synthesis
  - Active against Gram positive bacteria including MRSA
  - Formulation contains hydroxypropyl-beta-cyclodextrin (2500 mg per 250 mg telavancin, 7500 mg per 750 mg)
- Applicant's Proposed Indication
  - Treatment of cSSSI caused by *S. aureus* (including methicillin-resistant isolates), *S. pyogenes*, *S. agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis* (vancomycin-susceptible).

Regulatory Background

- Several antibacterials approved for cSSSI
  - Quinupristin/dalfopristin, linezolid, ertapenem, daptomycin, tigecycline, meropenem, moxifloxacin
  - Linezolid, daptomycin, tigecycline approved for cSSSI due to MRSA
  - Vancomycin
    - Treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci
    - Skin and skin structure infections
- Several older antibacterials approved for SSSI, not differentiated as being uncomplicated or complicated
  - Imipenem, ticarcillin-clavulanate, ampicillin-sulbactam, ceftriaxone

Regulatory Background

- December 19, 2006: Applicant (Theravance) submitted a New Drug Application for telavancin for cSSSI indication
- October 18, 2007: The Food and Drug Administration issued an approvable letter.
  - Issues identified at a manufacturing facility had to be resolved
  - To better delineate the overall benefit:risk profile of telavancin
    - Efficacy in patients with renal impairment
    - Renal adverse events, changes in renal laboratory parameters
    - Findings of the thorough QT study
    - Teratogenicity in animals

Regulatory Background

- January 21, 2008: Theravance submitted a complete response to the approvable letter.
- February 27, 2008: Advisory committee meeting to discuss the NDA was planned
  - Meeting was cancelled as the inspectional findings at one clinical site and at a Contract Research Organization (CRO) raised serious concerns about Good Clinical Practice (GCP) violations affecting data integrity.
- Additional inspections became necessary to evaluate extent of the problem and to rule out a systematic pattern.
- October 24, 2008: Press release by EMEA stating that Astellas had withdrawn its marketing authorization application for telavancin:

  http://www.emea.europa.eu/humandocs/PDFs/EPAR/vibativ/56242808en.pdf

Data Integrity Evaluation

- Division of Scientific Investigations (DSI)
  - A total of 13 inspections conducted
    - 11 clinical sites, a CRO, and the Applicant.
  - First cycle: Conducted prior to AC cancellation
    - Four clinical sites, a CRO, and the Applicant.
  - Second cycle: Conducted after AC cancellation
    - Seven clinical sites
- Targeted audit by Theravance

DSI Data Integrity Evaluation

- First cycle: March - December, 2007
- Major deficiencies in GCP noted at Site 38091:
  - Efficacy data were considered unacceptable.
  - Inspectional observations suggested inadequate study monitoring, resulting in an inspection of the CRO.
- CRO that served as the monitor for most clinical investigators was inspected:
  - Failed to implement appropriate corrective actions at Site 38091.
  - Monitoring of the remaining 3 clinical sites by the CRO appeared to be adequate.

DSI Data Integrity Evaluation

- Second cycle: March - August, 2008
- At all 7 sites, the observed level of GCP compliance supported integrity of the data from these sites.
- Major violations with the potential to affect data integrity consisted of ECG data from two sites.
  - Not obtained according to the time frame specified in the study protocols.
- Study monitoring by the CRO was noted to be adequate.

Theravance Targeted Audit

- The Applicant conducted an internal audit from April-June 2008
  - Inspection of 31 sites (24% of all sites) and audit of the records for 683 patients (36% of all patients).
  - Sites selected using prior monitoring reports to identify those suggestive of significant GCP violations; included 5 of the 11 clinical sites inspected by the FDA; Site 38091 was not included in this audit.
- Study monitoring noted to be inadequate at two clinical sites (Sites 37004, 38020, 22 patients).
- The Applicant concluded that there was no systematic pattern or incidence of GCP violations that could affect interpretation of the reported safety and efficacy data.

Assessment of Data Integrity

- Summary
  - In the first cycle of inspections, concern was raised regarding data integrity at 1 of 4 inspected sites and adequacy of monitoring by CRO.
  - Additional inspections and Applicant audit were conducted to evaluate for systemic problems with application
- Overall, data reported in the NDA were reliable with the following exceptions:
  - Efficacy data from three sites considered unreliable:
    - Site 38091 based on inspectional findings by DSI
    - Sites 37004 and 38020 based on the targeted audit by Theravance
  - ECG data from two sites (38016, 38163) were considered unreliable.
  - Data from these sites excluded from FDA and Applicant analyses

Clinical Studies

- Clinical development program for cSSSI
  - Two Phase 3 trials comparing telavancin 10 mg/kg/day to vancomycin
    - In both trials, telavancin was shown to be non-inferior to vancomycin; NI margin used was 10%
  - Two Phase 2 SSSI trials
    - Telavancin dose: 7.5 mg/kg or 10 mg/kg
  - Additional trials
    - One Phase 2 study in uncomplicated *S. aureus* bacteremia
    - Two Phase 3 studies in hospital-acquired pneumonia

Issues

- Overall benefit-risk profile:
  - Bactericidal, efficacy against MRSA
  - Limited treatment options for MRSA
  - Indication studied is cSSSI
  - Availability of other therapies for cSSSI
  - Renal adverse events, teratogenicity in animals, effect on QT interval

Outline of FDA presentations

- Discussion of the Phase 3 cSSSI trials
  - Efficacy: Primary analysis populations and subgroups
  - Safety: Focus on renal toxicity and QT changes; safety update from the HAP trials
- Discussion of non-clinical studies
  - Findings from the embryo/fetal developmental (segment 2) studies in rats, rabbits, and minipigs
  - Renal findings
- Use in pregnant women
  - Pregnancy risk classification
  - Risk: benefit assessment
- Risk management considerations for telavancin
  - Overview of risk management
  - Options and challenges with telavancin

FDA Clinical Review Efficacy and Safety Telavancin for Treatment of Complicated Skin Infections

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November 19, 2008

Overview

- Review the Phase 3 study design and statistical analysis plan
- Outline the FDA populations and analyses used to assess the benefit:risk of telavancin for treatment of cSSSI
- Present FDA clinical and microbiological efficacy results
- Review overall clinical safety, renal toxicity, QTc effect

Study Design

- Two independent studies of identical design
- Randomized, double-blind, active-comparator
- Telavancin 10 mg/kg IV q 24 hr (with placebo infusion at 12 hr) compared to vancomycin 1 g IV q 12 hr
- Adjunctive aztreonam and/or metronidazole at investigator discretion
- Treatment duration of 7-14 days, with duration determined by investigator assessment of clinical status

Study Design

- Primary endpoint: clinical response assessed by the investigator at 7-14 days after the end of study treatment
- Clinical response definitions:
  - Cure: resolution or improvement in signs and symptoms of infection such that no further anti-microbial agents were required for the cSSSI
  - Not cured: inadequate response to therapy
  - Indeterminate: inability to determine outcome
  - Missing: no determination reported

Study Design

- The co-primary efficacy analyses assessed the difference in clinical response rates for telavancin relative to vancomycin at test of cure (TOC) in the all-treated (AT) and clinically evaluable (CE) populations with a prespecified NI margin of 10%
- If both studies demonstrated NI, an additional prespecified goal was to test for superiority of telavancin relative to vancomycin in patients with MRSA as baseline pathogen pooled from both studies

FDA Analysis Population Definitions

- All-Treated (AT)
  - All patients who received any study drug
  - Patients excluded from Study 0018 efficacy analyses:
    - Site #38091 (based on DSI inspection report)
    - Sites #37004 and 38020 (based on Theravance audit)
  - Patients also excluded in Theravance analyses

- Microbiological AT (MAT)
  - AT patients with Gram positive pathogens at baseline

FDA Analysis Population Definitions

- Clinically Evaluable (CE):
  - AT patients using original protocol definitions (i.e. TOC window 7-21 days after EOT, at least 5 days (10 doses) of treatment required for patients assessed as cures)
- Microbiologically Evaluable (ME)
  - Patients in the MAT population who were also CE and had central microbiology confirmation of identification and susceptibility of pathogen

FDA Analysis Populations

- FDA assessed the following patients as clinically evaluable failures:
  - Patients who received effective non-study antimicrobials for primary cSSSI between end of therapy (EOT) and TOC
  - Patients having significant surgical procedures ≥ 96 hrs after study medication initiation
  - Patients who had amputations

Baseline Demographics FDA-All Treated Population

- Study 0017: 862 patients randomized at 40 sites; 429 to telavancin and 433 to vancomycin
- Study 0018: 1035 patients randomized at 89 sites; 517 to telavancin and 518 to vancomycin
- 73% and 65% of the population was from US for Study 0017 and 0018, respectively

- Study populations balanced for age, gender, and race. Mean age was approximately 48 years, with a slight male predominance, and 75% were white
- 25% had diabetes mellitus
- 60-80% received initial treatment in the hospital

Baseline Infection Type FDA All-Treated Population

	Study 0017		Study 0018	
	Telavancin N=426 Number (%)	Vancomycin N=429 Number (%)	Telavancin N=458 Number (%)	Vancomycin N=481 Number (%)
Major abscess	179 (42)	193 (45)	196 (43)	204 (42)
Deep/Extensive Cellulitis	156 (37)	161 (38)	153 (33)	176 (37)
Wound Infection	72 (17)	60 (14)	67 (15)	61 (13)
Other (Ulcers and Burns)	19 (4)	15 (4)	42 (9)	42 (9)

Baseline Characteristics FDA-All Treated Population

	Study 0017		Study 0018	
(CrCL), n/N (%)	Telavancin N=426	Vancomycin N=429	Telavancin N=472	Vancomycin N=489
>80 mL/min	274 (65)	291 (69)	289 (64)	291 (62)
>50-80 mL/min	85 (20)	85 (20)	116 (26)	119 (25)
30-50 mL/min	41 (10)	35 (8)	32 (7)	46 (10)
<30 mL/min	21 (5)	12 (3)	17 (4)	16 (4)

Efficacy Results
FDA-AT and CE Populations

	Telavancin Success	Vancomycin Success	Difference in % Success (telavancin-vancomycin)
Population	n/N, %[1]	n/N, %[1]	%, (95% CI)
AT			
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)
Study 0018	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)
CE			
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.0, 7.0)
Study 0018	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)

[1] n/N = # cured / # in analysis population, % = % cured

Efficacy results

- Due to differences in population definitions and outcome assessments, FDA cure rates may differ from those of Theravance.
- However, the FDA conclusion regarding non-inferiority of telavancin relative to vancomycin for each study did not differ from that of Theravance.

Efficacy Results Patients with MRSA

	Telavancin Success	Vancomycin Success	Difference in % Success (telavancin-vancomycin)
Population	**n/N, %[1]**	**n/N, %[1]**	**%, (95% CI)**
MRSA At Baseline			
Study 0017	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018	135/166 (81.3)	132/172 (76.7)	4.6 (-4.1, 13.2)
Pooled 0017 + 0018	227/301 (75.4)	243/323 (74.9)	0.9 (-5.8, 7.6)

[1] n/N = # cured / # in analysis population, % = % cured

Telavancin MICs
Skin Studies vs Surveillance Isolates

Organism	Study Type	N	MIC (mcg/mL)	
			Range	90%
S. aureus	**Survey**	5148	≤ 0.015-16	0.5
	Clinical	1408	0.03-1	0.5
MRSA	**Survey**	2229	0.06-16	0.5
	Clinical	852	0.06-1	1

Adapted from Microbiology Report, NDA 22-110; Table 48

Vancomycin MICs
Skin Studies vs Surveillance Isolates

Organism	Study Type	N	MIC (mcg/mL)	
			Range	90%
S. aureus	Survey	5149	0.25->128	1
	Clinical	1408	0.25-2	1
MRSA	Survey	2229	0.25->128	2
	Clinical	852	0.25-2	1

Adapted from Microbiology Report, NDA 22-110; Table 49

Subgroup analysis: Cure Rates by Baseline cSSSI Type FDA-CE Population

Wound Type	Telavancin n/N (%)	Vancomycin n/N (%)	Difference % (telavancin – comparator) (95% CI)
Major Abscess	263/303 (86.8)	262/300 (87.3)	-0.5 (-5.9, 4.8)
Wound Infection	87/108 (80.6)	83/96 (86.5)	-5.8 (-15.9, 4.4)
Deep/Extensive Cellulitis	199/240 (82.9)	227/273 (83.2)	-0.2 (-6.7, 6.3)

Subgroup analysis: Cure Rates by Baseline Renal Function FDA-CE Population

Baseline Creatinine Clearance	Telavancin n/N (%)	Vancomycin n/N (%)	Difference % (telavancin – comparator) (95% CI)
> 80 mL/min	403/451 (89.4)	394/458 (86.0)	3.3 (-1.0, 7.5)
>50-80 mL/min	130/164 (79.3)	142/167 (85.0)	-5.9 (-14.1, 2.4)
30-50 mL/min	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)
<30 mL/min	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.5, 5.2)

Clinical Response By-Pathogen at Baseline FDA-CE Population

	Study 0017		Study 0018	
	Telavancin	**Vancomycin**	**Telavancin**	**Vancomycin**
MRSA	90/109 (82.6)	107/126 (84.9)	118/130 (90.8)	118/136 (86.8)
MSSA	70/81 (86.4)	66/79 (83.5)	61/79 (77.2)	65/75 (86.7)
Streptococcus pyogenes	9/10 (90)	9/10 (90)	7/9 (77.8)	10/11 (90.9)
Streptococcus agalactiae	8/9 (88.9)	3/3 (100)	6/10 (60)	10/12 (83.3)

Safety Database

	Number Exposed	
Study Group	**Telavancin**	**Comparator**
Total Clinical Pharmacology Studies	268	150
Efficacy and Safety Studies In cSSSI		
Studies 0017, 0018, and 202b (telavancin 10 mg/kg)	1029	1033
Study 202a, Studies 0017, 0018, 202b (telavancin 7.5 mg/kg)	192	189
Total Clinical Efficacy and Safety Studies	1221	1222
Sites #38091, 37004, 38020 excluded from efficacy analyses.		

Safety – Deaths
All cSSSI Studies

- 9 deaths in each treatment group during reporting period; 5 additional deaths in telavancin and 2 in vancomycin treatment groups after reporting period

- Investigator assessed death as possibly/probably related to study medication in 4 and 1 telavancin-treated patients during each period, respectively

Safety – Deaths
All cSSSI Studies

- Possibly related AEs resulting in death:
  - Respiratory failure, renal insuffciency
  - Renal insufficiency
  - Acute renal failure
  - Ventricular arrhythmia
  - Cardiac arrest (unwitnessed)

Safety: Serious Adverse Events, Phase 3 Studies

- Phase 3:
  - 80 SAEs in 69/929 (7.4%) telavancin-treated patients
  - 65 SAEs in 43/938 (4.6%) of vancomycin-treated patients
- Imbalance by system-organ class (SOC)
  - renal and urinary SOC
    - 11 telavancin and 2 vancomycin patients
  - vascular disorders SOC
    - 9 telavancin and 2 vancomycin patients

Safety: Discontinuation of Study Medication due to AE

- AE-related discontinuations (Phase 3 cSSSI)
  - 73/929 (8%) patients treated with telavancin
  - 53/938 (6%) patients treated with vancomycin
- Skin disorders most common in both groups (2%)
- Imbalances by SOC:
  - Gastrointestinal disorders
    - 13 telavancin and 6 vancomycin
  - Renal disorders
    - 8 telavancin and 0 vancomycin
      - 5 telavancin-treated and no vancomycin treated patients had acute renal failure
  - Infection disorders
    - 12 telavancin and 5 vancomycin

Safety
Common Adverse Events

- The most common AEs reported in the telavancin treatment group were
  - Dysgeusia (altered taste)
    - 34% telavancin vs 7% vancomycin
  - Nausea
    - 27% telavancin vs 15% vancomycin
  - Vomiting
    - 14% telavancin vs 7% vancomycin
  - Foamy urine
    - 13% telavancin vs 3% vancomycin

Safety – Renal Adverse Events

- SAEs in all cSSSI studies (7.5 mg/kg and 10 mg/kg doses) consistent with prespecified definition of renal impairment (renal insufficiency or impairment, acute renal failure, chronic renal failure, and increased Cr) occurred in 14 telavancin-treated and 4 vancomycin-treated patients
  - 3 telavancin-treated patients required hemodialysis; 2 had rising Cr prior to study treatment, refused dialysis and died
  - one of the 4 vancomycin-treated patients was receiving hemodialysis prior to study and continued dialysis
  - 3 patients treated with telavancin had incomplete resolution with Cr still 2x baseline at final laboratory assessment
- Sixteen telavancin-treated patients had study medication prematurely discontinued compared to three vancomycin-treated patients due to AEs consistent with prespecified renal impairment definition

Safety – Renal Laboratory Parameters

- In the Phase 3 studies:

  Increased serum Cr and BUN parameters used to define renal impairment were 2-3 times more likely to be elevated in patients with normal baseline Cr treated with telavancin

Renal Laboratory Parameters Normal Baseline Serum Creatinine

Studies 0017 and 0018	Telavancin		Vancomycin	
Serum Creatinine Maximum change from baseline (normal baseline)	Patients Assessed	#, (%) With Increase	Patients Assessed	#, (%) With Increase
Increase to 1.25 x BL	822	305 (37)	856	177 (21)
Any post-BL Cr ≥ 1.5 mg/dL and at least 0.5 mg/dL > BL	822	52 (6)	856	19 (2)
Any post-BL Cr ≥ 1.5 mg/dL and at least 50% > BL	822	48 (6)	856	17 (2)

Renal Laboratory Parameters
Abnormal Baseline Serum Creatinine

Studies 0017 and 0018	Telavancin		Vancomycin	
Serum Creatinine Maximum change from baseline (normal baseline)	Patients Assessed	#, (%) With Increase	Patients Assessed	#, % With Increase
Increase to 1.25 x BL	83	22 (27)	68	7 (10)
Any post-BL Cr ≥ 1.5 mg/dL and at least 0.5 mg/dL > BL	83	19 (23)	68	11 (16)
Any post-BL Cr ≥ 1.5 mg/dL and at least 50% > BL	83	11 (13)	68	7 (10)

Safety – QT Effect

- Preclinical:
  - In vitro QT effect as demonstrated by hERG effect in HEK 293 cells and effect on canine Purkinje fiber
  - No evidence of treatment related effect on BP, HR, ECG parameters in conscious telemeterized dog study
- Clinical:
  - FDA requested Theravance conduct a thorough QT study (based on 2002 FDA-Health Canada concept paper on QT/QTc prolongation)
  - 7.5 mg/kg and 15 mg/kg dose of telavancin assessed
  - Differences from current QT studies: multiple dose IV comparator (vs single oral dose), mean baseline placebo-corrected QTcF (vs baseline time-matched QTcF)

Safety
Clinical QT Effect

- Based on FDA assessment of the QT study:
  - predicted mean change in QTcF for telavancin was 12-15 msec
  - mean change in QTcF for IV comparator was 24 msec

- Clinical SSSI studies demonstrated that mean post-drug average change and maximum change from baseline QTcF were greater for telavancin-treated patients (9.4 and 15.5 msec for telavancin and 3.0 and 8.4 msec for vancomycin, respectively)

Safety – Cardiac AEs

- Four telavancin-treated and six vancomycin-treated patients had cardiac AEs resulting in death; 2 deaths in the telavancin group considered possibly related to study medication by the investigator
- Thirteen telavancin-treated and thirteen vancomycin-treated patients had at least one SAE in the cardiac SOC; 4 SAEs in telavancin-treated patients and 2 in vancomycin-treated considered possibly related to study medication by investigators
- Patients treated with telavancin had a higher risk of outlier values (QTcF change of >60 msec, or QTcF >500 msec) when treated with medications known to cause QT prolongation than did those treated with vancomycin. This risk was low (4%) and outlier values were not associated with cardiac AEs

Safety Update (Summary data) Hospital-acquired Pneumonia

- 2 Phase 3 HAP studies (0015 and 0019)
- 751 treated with telavancin (10 mg/kg)
- Summary data on deaths, SAEs, discontinuations due to AEs
- Mortality: 20% telavancin versus 18% vancomycin
- AEs resulting in death were most frequent in the respiratory and infection (including sepsis) categories and balanced between treatment groups
- Cardiac events resulting in death were more frequent in the vancomycin treatment group (4% versus 2%), including congestive heart failure and ventricular arrhythmia

Safety Update (Summary data) Hospital-acquired Pneumonia

- SAEs:
  - 31% telavancin versus 26% vancomycin
  - Respiratory and infection (sepsis) related events were most common
  - These SAEs, along with cardiac SAEs generally balanced between treatment groups
    - Pulmonary embolus: 7 telavancin versus 1 vancomycin
  - Renal SAEs:
    - 0015: 17 telavancin versus 7 vancomycin
    - 0019: 8 telavancin versus 8 vancomycin

Conclusions

- The Phase 3 studies support the conclusion that telavancin is non-inferior relative to vancomycin for treatment of cSSSI
- Telavancin did not demonstrate superiority in treatment of patients with MRSA at baseline
- SAEs, discontinuations, and predefined definitions of renal impairment were higher in the telavancin treatment group (2-3x)
- Telavancin prolongs the QT interval
- GI AEs were the most common AEs associated with telavancin treatment

NONCLINICAL SUMMARY OF TERATOGENIC STUDIES FOR TELAVANCIN

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INTRODUCTION

Embryo/fetal developmental (Segment 2) studies were conducted in three species:

- **02-001-15_7057-175: Intravenous Injection Rabbit Developmental Toxicity Study with AMI-6424**
- **02-001-04_7057-126: Intravenous Injection Rat Developmental Toxicity Study with AMI-6424**
- **05-013-04_58857: Telavancin: Study for Effects on Embryo-Fetal Development in the Minipig**

RAT STUDY

Methods:

- **Female Crl:CD®(SD)IGS BR rats, 25/group**
- **Telavancin: 0, 0 (placebo), 50, 100 or 150 mg/kg/day, IV on GD 6-17**
- **Mortality, clinical signs, uterine parameters, pregnancy parameters, fetal parameters and TK**

RAT STUDY

- **Offspring: Significant positive findings**
  - **100 mg/kg: Brachymelia and syndactyly in one fetus**
  - **150 mg/kg: Brachymelia in one fetus**
  - **These findings are not listed in contract lab's control historical data base.**

RABBIT STUDY

Methods:

- **Female NZW rabbits, 20/group**
- **Telavancin: 0 (placebo), 60 or 75 mg/kg/day, slow IV bolus on GD 7-20**
- **Mortality, clinical signs, uterine parameters, pregnancy parameters, fetal parameters and TK**

RABBIT STUDY

- **Offspring: External findings:**
  - **High dose (75 mg/kg): One fetus had flexed front paws, brachymelia, adactyly.**

RABBIT STUDY

- **Offspring Skeletal malformations:**
  - **High dose (75 mg/kg): Absent ulna, fusion of sternebrae, adactyly and vertebral anomalies were noted in single fetuses from 5 litters**
  - **The fetus with the external findings: Absent ulna and adactyly**

RABBIT STUDY

Summary of fetal external/skeletal malformation

Group	Placebo	60 mg/kg/day	75 mg/kg/day
Litters evaluated	**18**	**20**	**19**
Fetuses evaluated	**138**	**172**	**156**
Flexed front paws, brachymelia, adactyly, absent ulna	0	0	1 (0.6% for fetal incidence and 5.3% for litter incidence)

Relevant Covance historical control data (%)

1997-2001, 412 litters, 3528 fetuses	Fetal incidence			Litter incidence		
Anomalies	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**
Flexed front paws	**0.14**	**0**	**1.7**	**0.8**	**0**	**6.7**
Adactyly	**0.03**	**0**	**0.6**	**0.3**	**0**	**5.6**
Brachymelia/micromelia or absent ulna	**No incidence rates were given.**					

RABBIT STUDY

From the contract lab's study report:
"…the limb malformations noted (brachymelia, adactyly, and absent ulna) mimic or are similar to the malformations of brachymelia and syndactyly observed in rats at doses of 150 and 100 mg/kg/day, respectively, in Covance Study 7057-126. These findings further support a direct effect of AMI-6424 (telavancin) on the developing fetus."

MINIPIG STUDY

Methods:

- **Female Ellegaard Göttingen minipigs, 14/group**
- **Telavancin: 0, 0 (placebo), 25, 50, or 75 mg/kg/day, IV on GD 11-35**
- **Clinical observations, PK, uterine parameters, external and internal fetal abnormalities and fetal skeletal findings**

MINIPIG STUDY

Dose (mg/kg)	Mated	Mis-carriage	Not pregnant	Early sacrifice	Preg. Animals	Preg. Rate (# preg. to term/#mated)
Control	14	3	3	3+1	7	50%
Placebo	14	3	6	3+1	5	36%
25	14	1	3	1+1	9	64%
50	14	2	4	2+1	8	57%
75	14	3	5	3+1	5	36%

MINIPIG STUDY

External malformations (fetal incidence/litter incidence)					
	Diluent	Placebo	25 mg/kg/day	50 mg/kg/day	75 mg/kg/day
Litter evaluated	7	5	9	8	5
Fetuses evaluated	34	24	31	36	17
Syndactyly	0	0	0	1/1	0
% litter				12.5%	
Polydactyly		1/1	4/3	5/3	
% litter		20%	33.3%	37.5%	
Misshapen digit, deformed limb (radial agenesis)	0	0	0	1/1	0
	% litter			12.5%	
Total litter incidence	0	20%	33.3%	50%	0

MINIPIG STUDY

Positive findings not listed:

Group	Litter #	Killed in extremis	Fetal findings
25 mg/kg	40	Yes	**A deformed head and misshapen digit**
50 mg/kg	47	Yes	**Legs turned inwards**
50 mg/kg	51		**Multiple absent ossification sites, absent tarsal bones on both legs**
50 mg/kg	43		**Absent ossification sites distal to the metacarpi**
75 mg/kg	60	Yes	**A deformed head, forelegs and snout**
75 mg/kg	61	Yes	**A deformed hind leg**

MINIPIG STUDY

External malformations (fetal incidence/litter incidence)					
Dose (mg/kg/day)	Diluent	Placebo	25	50	75
Litters evaluated	11	8	11	10	9
Fetuses evaluated	56	38	42	51	41
Syndactyly	0	0	0	1/1	0
% litter				10%	
Polydactyly	1/1	1/1	4/3	5/3	
% litter	9.1%	12.5%	27.3%	30%	
Leg turned inward				1/1	
				10%	
Misshapen digit, deformed limb (radial agenesis) or head	0	0	1/1	1/1	2/2
	% litter		9.1%	10%	22.2%
Total litter incidence	9.1%	12.5%	36.4%	50%	22.2%

COMPARISON OF ANIMAL AND HUMAN EXPOSURE

	Segment 2 studies			Clinical studies
Species	Rabbit	Rat	Minipigs	Human
Dose (mg/kg)	75	100	25	10
AUC (μg-hr/mL)	1387	1236	780	666-780
Animal/human ratio	1.78	1.58	1	

SUMMARY

- Limb malformations
- In each species with low incidence
- Across all three species
- Over historical database
- No safety margin based on plasma AUC
- Drug-related
- Safety concern

CDER RDTS EXPERT CONSULTATION CONCLUSION

“It was the consensus of the committee that the limb defects observed in these studies were related to the drug. While the evidence of drug-induced limb malformations in each species is weak, the weight of evidence across all three species strongly supports that the findings are drug-related.”

LABELING

- Risk/benefit profile
- Factors should be considered
  - Seriousness of the indication and the potential for serious complications in pregnancy associated with the indication
  - Availability of alternative treatments
  - Teratogenic effects at or near the proposed human dose

GENERAL TOXICOLOGY STUDIES

- Up to 6 months in rats and 3 months in dogs
- Target organs of toxicity: Kidneys and liver in both species

RENAL FINDINGS IN RATS

- Increased BUN and creatinine levels
- Urinary occult blood
- Increased kidney weight
- Gross necropsy: Enlarged renal lymph nodes, diffusely light kidneys
- Tubular degeneration/necrosis
- Tubular casts and dilatation, cortical tubular vacuolation, and increased interstitial inflammatory cell infiltrates
- $\geq$50 mg/kg, Human Equivalent Dose: 8 mg/kg

RENAL FINDINGS IN DOGS

- Increased BUN and creatinine levels
- Increased urinary volume
- Tubular vacuolation, dilatation, necrosis, and eosinophilic cytoplasmic inclusions
- $\geq$ 25 mg/kg/day, HED: 13.5 mg/kg

COMPARISON OF ANIMAL AND HUMAN EXPOSURE

	General toxicity studies		
Species	Rat	Dog	Human
Dose (mg/kg)	50	25	10
AUC (μg-hr/mL)	1012-1227	600-624	666-780
Animal/human ratio	1.3-1.6	0.77-0.8	

Telavancin use during pregnancy: a maternal health perspective

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Maternal Health Team
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Goals

- Review the role of the Maternal Health Team and its involvement in the telavancin NDA
- Summarize the reproductive toxicology study findings
- Discuss pregnancy labeling and pregnancy category definitions
- Discuss potential telavancin use during pregnancy
  - Risks (and populations at risk)
  - Benefits
  - Alternative therapies and their relative risks and benefits
  - Appropriate pregnancy category
  - Fetal exposure risk management issues

Maternal Health Team (MHT)

- Consult team in the Immediate Office of the Office of New Drugs
- Respond to consult requests from drug review divisions
  - Pregnancy and nursing mothers sections of labeling
  - Pregnancy exposure registries
  - Risk evaluation and mitigation strategies/pregnancy prevention programs
  - Evaluate emerging data on possible drug-associated adverse pregnancy outcomes and effects in nursing infants.
- Support and promote well informed prescribing and use of medicines during pregnancy
  - Improve the clinical utility and relevance of the pregnancy and nursing mothers sections of the label. The label should be a helpful clinical tool.
  - Data awareness (What we know, what we don't, and what we need)

A brief review…

- Dr. Zhou Chen presented reproductive toxicology study results with telavancin HCl in
  - Rats
  - Rabbits
  - Minipigs

Summary of reproductive toxicology study findings

- Rats
  - Brachymelia
  - Syndactyly
- Rabbits
  - Flexed front paws
  - Brachymelia
  - Adactyly
  - Absent ulna
- Minipigs
  - Syndactyly
  - Polydactyly
  - Radial agenesis
  - Bilateral absence of tarsal bones

- Consistent finding of limb anomalies in offspring with telavancin exposure in-utero for all three species
- These anomalies occurred at low incidences but at higher frequencies in treated animals than in historical controls.

Additional findings

- Rabbits:
  - Drug-related increase in post-implantation loss
  - Statistically significant increase in dilated lateral ventricles and missing intermediate lung lobes
- Rats
  - Dose-related increase in stillborn pups and number of dams with stillborn pups
- Mini-pigs
  - Increased late resorptions compared to historical controls
  - 100% increase in post-implantation loss in high dose group compared to placebo and diluent.

Maternal health team consult

- Review study data and make recommendations regarding
  - Pregnancy category
  - Labeling language
  - Need for pregnancy registry

- Current pregnancy categories for teratogenicity
  - Category designations: A, B, C, D, and X
  - This is not a grading system from better to worse
  - The categories have specific definitions based on:
    - Data source (animal vs. human)
    - Study findings (positive vs. negative)
    - Relative clinical benefit vs. fetal risk
  - Categories C, D, and X require consideration of both benefit and risk

Pregnancy categories (language summarized)

A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

A Maternal Health Team perspective:
Telavancin and Risk

- Teratogenicity in 3 species of animal
  - All species have limb anomalies
  - All species have increased pregnancy loss or stillbirth
  - Animal teratogenicity does not always correlate with human teratogenicity but it is more likely when teratogenicity is multi-species
- No human data

Category Options

~~A~~ ~~B~~ C ~~D~~ X

Pregnancy category options

Category C

- Animal reproduction studies have shown an adverse effect on the fetus

AND

- There are no adequate and well-controlled studies in humans

AND

- The benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

Category X

- Studies in animals or humans have demonstrated fetal abnormalities

OR

- There is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both

AND

- The risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

Relative Risk and Benefit

- Alternative therapies:
  - More than 8 anti-infective drugs are FDA approved for the treatment of CSSSI.
- Relative Risk
  - Telavancin is a highly suspected human teratogen based on animal reproductive and developmental toxicity study data
- Ways to demonstrate relative benefit:
  - Show superior efficacy
    - Based on noninferiority trial data submitted with the NDA, telavancin is not superior to vancomycin for the treatment of CSSSI.
  - Offer better safety profile than other therapies

Approved treatments for CSSSIs

- Daptomycin
- Piperacillin/tazobactam
- Ertapenem
- Meropenem

Negative animal studies in two species. No human data. (Category B)

- Levofloxacin
- Linezolid
- Tigecycline*

Increased fetal loss in two species. No anomalies. No human data.
(Category C or D*)

- Vancomycin

No data in label. Published study in rats and rabbits negative. (Category C)

(If yellow, covers MRSA)

Support for Pregnancy category X

- For the current indication of CSSSI, telavancin does not offer clinical benefit above and beyond that offered by vancomycin.
- Teratogenic findings in 3 animal species, all with limb anomalies and increased pregnancy or fetal loss, make telavancin a highly suspected human teratogen.
- Based on available data, the 8 FDA-approved treatments for CSSSI have a lower teratogenic risk.

- For a pregnant woman with CSSSI, telavancin does not offer enough clinical benefit (over current therapies) to justify the additional fetal risk.

Pregnancy category C: Arguments for and against

- For
  - The Unknown
    - The relative efficacy of telavancin compared to other anti-infectives approved for the treatment of CSSSIs and MRSA.
  - Potential clinical benefit
    - Under IND, isolated patients treated successfully with telavancin who failed therapy with vancomycin
- Against
  - Healthcare practitioners may not see the risks for telavancin as different from other category C drugs indicated for CSSSI.
  - Would likely increase the likelihood of fetal exposures to a suspected human teratogen.

Telavancin and managing risk:
What is the goal? Who are we worried about?

- The Goal:
  - Prevent (all or at least unintended) fetal exposures to drug
- Who are we worried about?
  - Women of childbearing potential
  - Based on 2006 U.S. Census data, there are more than 42 million women between the ages of 15 and 44 years in this country.
  - About 10% of women of reproductive age get pregnant each year.
  - That is more than 6 million pregnancies each year
  - 50% of all pregnancies are unplanned.
  - Women of childbearing potential get infections.

Need for Risk Management Strategies

- How telavancin is labeled for use during pregnancy should determine the type of postmarketing data required on fetal exposures.
  - If telavancin use is contraindicated during pregnancy (category X), then fetal exposures should be tracked as part of a risk management program.
  - If the benefits of telavancin use in pregnancy are considered to outweigh the fetal risks in certain clinical situations (category C), then the sponsor should have a postmarketing requirement (PMR) to conduct a pregnancy registry.
    - A pregnancy registry is a prospective cohort study that enrolls pregnant women exposed to drug before pregnancy outcomes are known.

Risk Management: points to consider

- Route of administration:
  - Intravenous
- Indication for use:
  - Complicated skin and skin structure infections (requires timely initiation of therapy)
- Potential settings for use:
  - Hospitals, chronic care facilities, physician offices, and homes with instruction or home care assistance.
- Avoiding fetal exposure to a highly suspected human teratogen:
  - For all women of childbearing potential, same day documentation of a negative serum pregnancy test should be required prior to starting telavancin treatment.
  - One pregnancy test will not detect pregnancies within a few days of conception
  - Acute need for therapy eliminates the ability to require two negative pregnancy tests over an interval of time or use of highly effective contraception for one month before treatment initiation.
- Additional questions:
  - Will healthcare practitioners check for a negative pregnancy test prior to telavancin administration? Should there be a role for the dispensing pharmacy?
  - For therapy in the outpatient setting, should there be contraceptive requirements and how can these requirements be defined to suit telavancin treatment scenarios?

Risk Management Considerations for Telavancin

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Additional slides

Vancomycin reproductive toxicology study

- Byrd RA, Gries C, Buening M. Developmental toxicity studies of vancomycin hydrochloride administered intravenously to rats and rabbits. Fundam appl Toxicol. 1994 Nov; 23(4): 590-7.

Risk Management Considerations for Telavancin

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Outline

- Provide an overview of risk management
- Discuss risk management options for teratogens
- Discuss the challenges creating a risk management program for telavancin

What is Risk Management?

- Risk assessment + risk mitigation = risk management

- Federal Food, Drug, and Cosmetic Act
  - Establishes “routine” risk management
    - Product label (package insert)
    - Spontaneous adverse event monitoring and reporting

What is Risk Management?

Safe Use Strategies

Education for Healthcare Providers

Medication Guides

Labeling + Spontaneous Monitoring/Reporting

What is Risk Management?

- Goals
  - Designed to meet specific goals in minimizing known or potential product risks
- Program components
  - Medication Guides
  - Education for healthcare providers
  - Safe use strategies
- Assessment
  - Performance of the overall risk management plan in achieving its goals

How does Risk Management work?

- Educate healthcare providers
- Empower patients
- Target use to the most appropriate patients
- Encourage/mandate safety-related monitoring

When should Risk Management be considered?

- Factors to consider
  - Disease severity
  - Benefits of treatment
  - Other existing therapeutic options
  - Commonality of the risk to the drug class
  - Preventability of the risk
  - Severity of the risk

When should Risk Management be considered?

- Factors to consider (continued)
  - Need for specialized healthcare setting or skill for “safe and effective use”
  - Duration of use

When should Risk Management be considered?

- Factors to consider (continued)
  - Use in women of childbearing potential
    - 2006 Premier Rx Market Advisor data
      - 10,000 12 to 44yo women discharged with bill for 1 of 8 cSSSI approved anti-bacterials where the primary diagnosis was related to a serious skin infection
      - Data limitations
        - Other anti-bacterials and other uses
        - Out-patient use

Teratogen Risk Management Strategy

- Goals
  - Prevent fetal exposure
    - Prevent fetal exposure → pregnancy detection and prevention
  - Risk assessment
    - Assess the risk of fetal exposure
- Objectives
  - No pregnant women receive teratogen → **pregnancy test**
  - Pregnancy does not occur while women of childbearing potential are exposed → **contraception**
  - Characterize fetal exposure → **pregnancy registry**
    - Assessment for program improvements

Teratogen Risk Management Strategy

- Pregnancy testing
  - Prior to initiating treatment
  - Monthly during treatment
  - Post-treatment

- Contraception
  - 2 forms of “reliable” birth control before, during and following discontinuation

Teratogen Risk Assessment Strategy

- Pregnancy registry
  - Enroll pregnant women with possible exposure to telavancin
  - Data collection
    - Timing of exposure
    - Pregnancy outcome
    - Delivery information
    - Long-term follow-up information
    - Program improvement information

Medication Guides

- Provide information to patients when it is necessary to patients' safe and effective use of drug products
  - Help prevent a serious adverse event
  - Affect patient's decision to use, or continue to use the product
  - Directions for use are crucial to the drug's effectiveness

Education for Healthcare Providers

- Purpose
  - Encourage implementation of an element(s) of the strategy and/or inform HCPs about any serious risks
  - Disseminated through the Sponsor(s) and/or professional societies

Safe Use Strategies

- Purpose
  - Assist healthcare providers in following appropriate prescribing practices
  - Target appropriate patient population
  - Mandatory registration
    - Prescribing, dispensing and/or administering are limited to authorized healthcare providers
  - Mandatory monitoring

Safe Use Strategies

- Examples
  - Prescriber, healthcare setting, pharmacy, and/or patient enrollment
  - Link negative pregnancy test result to drug dispensing
  - Complete patient-physician agreements
  - Utilize specialty pharmacies to dispense drug product after appropriate patient follow-up
  - Limit days supply
  - No refills

Practical Challenges

- In-patient
  - Assure product access is linked to negative pregnancy test result
    - Current programs have independent verification of test results by pharmacies prior to dispensing
  - Patient education tools, such as Medication Guides, are not generally provided to hospitalized patients

Practical Challenges

- Out-patient
  - Should contraception be required in the out-patient setting?
  - Should repeat pregnancy testing be required for longer term therapy?
  - Continuity of care – who will be responsible for the patient after discharge?

Approaches

- In-patient
  - Require education for all prescribers and support staff in hospitals
  - Limit to only in-patient use
  - Hospital-specific programs
    - Educate healthcare providers
    - Create a standard order set for telavancin
    - Create computer order entry stops
    - Limit prescribing to infectious disease consult service

Approaches

- Out-patient
  - Require education of prescribers, home health nurses, pharmacists
  - Further discussion

In Summary

Boxed Warning?

Category X?

Category C?

Safe Use Strategies

Education for HCPs

Medication Guides

Labeling + Further Risk Assessment

Questions

AIDAC Meeting

November 19, 2008

Question 1

- Do the data presented demonstrate the safety and effectiveness of telavancin for the treatment of cSSSI? Please vote Yes/No
  - If your answer is Yes
    - Are there specific issues that should be addressed in labeling?
    - Would you recommend any post-marketing studies to further evaluate nephrotoxicity?
  - If your answer is No, what additional data/trials are needed?

Question 2

- Are there clinical situations when the benefits of telavancin use in a pregnant woman would outweigh the risks? Please vote Yes/No.
  - If your answer is Yes, describe the situations when the benefits of telavancin use would outweigh the risks in a pregnant woman.

Question 3

- Is a risk management strategy needed to prevent unintended use in pregnant women or women of child bearing potential? Please vote Yes/No.
  - If your answer is Yes, what elements should be included?