

## New Drug Update: Telavancin (Vibativ®)

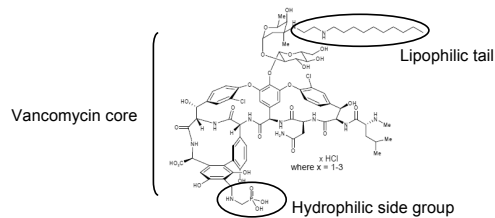
May 21, 2010  
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## Outline

- Mechanism of Action
- Spectrum of Activity
- Pharmacokinetics / Pharmacodynamics
- Adverse Effects and Warnings
- Drug Interactions
- Dosing & Administration
- Clinical Studies

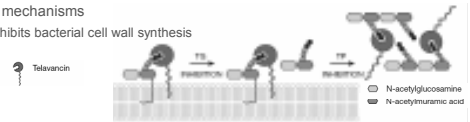
## Telavancin

- Lipoglycopeptide



## Mechanism of Action

- Concentration-dependent, bactericidal activity
- Dual mechanisms
  - Inhibits bacterial cell wall synthesis
  - Disrupts cell membrane potential



Lundin CS, et al. AAC 2009;43:3375-83.  
Higgins DL, et al. AAC 2005;49:1127-34.  
Leonard SN, Ryback MJ. Pharmacotherapy 2008;28:458-68.

## Spectrum of Activity

- *Staphylococcus aureus* and *S. epidermidis*
  - Both methicillin-susceptible and –resistant
  - Retains activity against most vancomycin-intermediate and heteroresistant vancomycin-intermediate *S. aureus*
- *Streptococcus* species
  - *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, and *S. anginosus* group
- *Enterococcus* species
  - Vancomycin-susceptible *E. faecalis* and *E. faecium*
- Anaerobic Gram-positive bacteria
  - *Clostridium*, *Propionibacterium*, *Peptostreptococcus*, and *Corynebacterium* species

D'ighi DC, et al. AAC 2008; 52:2383-8. Saravolatz L, et al. J Antimicrob Chemother 2007; 60:400-6.  
Goldstein EJ, et al. AAC 2004; 48:2149-52. Justice JC, Price JL. Biorg Med Chem Lett 2003; 13:4165-8.

## Susceptibility Breakpoints

- FDA Susceptibility Breakpoints

| Microorganism  | MIC Breakpoint for Susceptibility* |
|--|------------------------------------|
| <i>Staphylococcus aureus</i>   | ≤ 1 mcg/ml                         |
| <i>Streptococcus</i> species<br>(including <i>S. pyogenes</i> , <i>S. agalactiae</i> ,<br>and <i>S. anginosus</i> group) | ≤ 0.12 mcg/ml                      |
| <i>Enterococcus faecalis</i>   | ≤ 1 mcg/ml                         |

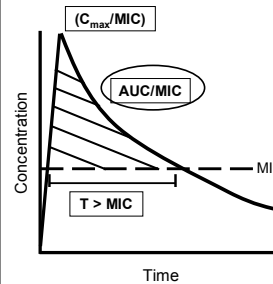
\*Current absence of any resistant isolates precludes determination of intermediate and resistance breakpoints

## Pharmacokinetics

- A** • Intravenous formulation only
- D** • Distribution
  - Volume of distribution = 0.13 L/kg
  - 90% protein binding
  - $C_{max}$  108±26 mcg/ml
  - Good penetration into skin blister fluid and pulmonary epithelial lining fluid and alveolar macrophages
- M** • Minimal metabolism; unknown pathway
- E** • Elimination
  - Primarily by kidneys, 76% recovered unchanged in urine
  - Terminal half-life 7-9 hours; prolonged in renal failure

VIBATV (telavancin) Prescribing Information.  
Sun HK, et al. AAC 2005;50:788-90.

## Pharmacodynamics



- Parameter best correlated with activity in animal infection models was AUC/MIC
- In vitro pharmacokinetic model suggests a target AUC/MIC of 50
- Maximal killing occurred with AUC/MIC 404

Hegde SS, et al. AAC 2004;48:3043-50.  
Odenholt I, et al. AAC 2007;51:331-6.

## Adverse Effects & Warnings

- Nausea, vomiting
- Taste disturbances
- Foamy urine
- Constipation
- Pruritus
- Infusion-related reactions

VIBATV (telavancin) Prescribing Information.

## Adverse Effects & Warnings

- Nephrotoxicity
  - Increases in serum creatinine to 1.5x baseline occurred more frequently (15%) compared with vancomycin (7%)
  - More common in patients with baseline renal dysfunction and concomitant nephrotoxins
  - Lower clinical cure rates in telavancin-treated patients with CrCl ≤ 50 ml/min compared with CrCl > 50 ml/min
- QTc prolongation
  - Mean QTc prolongation 12-15 msec compared to 22 msec for positive control
  - Incidence of QTc prolongation > 60 msec was 1.5% telavancin arm vs. 0.6% vancomycin arm

VIBATV (telavancin) Prescribing Information.  
Barriere S, et al. J Clin Pharmacol 2004;44:689-95.

## Pregnancy

- Pregnancy category C
  - Adverse developmental outcomes (limb and skeletal malformations) in rats, rabbits, and minipigs at clinically relevant dosages
  - No human data
- Avoid during pregnancy; pregnancy exposure registry
- Women of childbearing-age should have a negative pregnancy test prior to administration
- Risk Evaluation and Mitigation Strategy (REMS)
  - Medication guide
  - Communication via Dear Healthcare Provider letter
  - Periodic FDA assessments

VIBATV (telavancin) Prescribing Information.

## Drug Interactions

- Drug-drug
  - Concomitant nephrotoxins
  - Concomitant QTc prolonging agents
- Drug-lab
  - Coagulation test interference
    - Binds to the artificial phospholipid surface interfering with the ability of coagulation complexes to assemble and promote clotting *in vitro*
    - No evidence of hypercoagulability or increased bleeding risk
    - Abnormalities noted for up to 18 hours post-telavancin
  - Tests affected
 

|          |                                     |
|----------|-------------------------------------|
| • PT/INR | • Activated clotting time           |
| • aPTT   | • Coagulation based factor Xa tests |

VIBATV (telavancin) Prescribing Information.

## Dosing and Administration

| Creatinine Clearance (ml/min) | Dosage                   |
|-------------------------------|--------------------------|
| > 50                          | 10 mg/kg every 24 hours  |
| 30 – 50                       | 7.5 mg/kg every 24 hours |
| 10 – 29                       | 10 mg/kg every 48 hours  |
| Hemodialysis                  | Approximately 6% removed |

- Reconstitute vials with 5% dextrose, sterile water, or 0.9% NaCl
  - Hydroxypropyl-beta-cyclodextrin solubilizer
  - Solution pH 4.5
- Stability
  - Room temperature 4-12 hours; refrigeration (2-8°C) 3-7 days
- Infuse over 60 minutes



VIBATIV (Telavancin) Prescribing Information. Data on File, Astellas and Theravance.

## Clinical Studies

- Complicated Skin and Skin Structure Infections

| ATLAS 1 & 2   |   |               |
|---|---|---------------|
| Design  | Phase III, randomized, double-blind   |               |
| Population  | cSSSI (deep abscess/cellulitis, wound, ulcer, burn)<br>Excluded osteomyelitis, necrotizing fasciitis, chronic foot ulcers |               |
| Intervention  | Telavancin 10 mg/kg Q24 hr vs. Vancomycin 1g Q12 hr   |               |
| Results   | Clinical success  | 88% (658/745) |
|   | Micro success   | 90% (473/527) |
| • Micro cure for MRSA 91% telavancin vs. 86% vancomycin |   |               |

- FDA-approved September 2009

Strylewski ME, et al. CID 2008;46:1683-93.

## Clinical Studies

- Hospital-acquired Pneumonia

| ATTAIN 1 & 2 |  |
|--------------|--|
| Design       | Phase III, randomized, double-blind  |
| Population   | HAP due to suspected or confirmed Gram-positive pathogens  |
| Intervention | Telavancin 10 mg/kg Q24 hr vs. Vancomycin 1g Q12 hr  |
| Results      | • Clinical success for clinically evaluable population occurred in 82% (257/312) telavancin and 81% (276/342) vancomycin<br>• Clinical cure rates for MRSA infections were 75% telavancin vs. 75% vancomycin |

- Ongoing review with the FDA

Rubinstein E, et al. [abstract K-533]. Presented at 46th ICAAC/IDSA annual meeting 2008. Data on File, Astellas and Theravance.

## Summary

- Lipoglycopeptide with dual mechanism of action
- Broad spectrum of gram-positive activity
- Once daily dosing; requires adjustments for renal failure
- Higher rates of nephrotoxicity but fewer infusion-related reactions compared to vancomycin
- REMS regarding pregnancy risk
- Non-inferior to vancomycin for the treatment of cSSSTIs



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