

Division Of Anti-infective and Ophthalmology Products Advisory Committee Meeting



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Meeting Objectives

- Discuss NDA 22-171: Doripenem (DORIBAX™)
 - Applicant: Johnson and Johnson
Pharmaceutical Research and
Development, LLC.
 - Formulation: 500 mg for intravenous injection
 - Indication: Adults with nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP)
- Discuss clinical trial design for future NP studies

What are NP and VAP?

- Nosocomial pneumonia:
 - Occurs 48 hours or more after hospital admission
 - Not incubating at time of admission
- Ventilator-associated pneumonia
 - Arises more than 48-72 h after endotracheal intubation
- NP is the 3rd most common cause of healthcare-associated infections
 - Leading cause of death among healthcare-associated infections
 - Approximately 36,000 deaths in 2002 (Klevans et al, 2002)

Doripenem (DORIBAX™)

- Initial US Approval: October 2007
- Doripenem is a carbapenem antibacterial indicated in the treatment of adults with:
 - Complicated intra-abdominal infections (cIAI)
 - Complicated urinary tract infections, including pyelonephritis (cUTI)
- 3 other approved carbapenems: imipenem, meropenem, ertapenem

Antibacterial Armamentarium for NP: 4 approved products

- Ciprofloxacin
- Levofloxacin
- Linezolid
- Piperacillin/tazobactam

*no approved antibacterials for NP that include the specific subset of ventilator-associated pneumonia (VAP)

Doripenem for NP Development Program: Two Phase 3 non-inferiority studies

- DORI-09: open-label, randomized, multi-center, active controlled study
 - doripenem compared to piperacillin/tazobactam in non-ventilated subjects with NP and early-onset (ventilated <5d) VAP
- DORI-10: open-label, randomized, multi-center, active controlled study
 - doripenem compared to imipenem in subjects with early and late-onset VAP

FDA Presentation

- Non-inferiority margin justification
 - Review of historical data
 - Methodology to determine NI margin
- Clinical efficacy and safety of doripenem
 - Review of issues with the phase 3 study design
 - Adverse events (common, serious, treatment-emergent) and deaths
- Microbial resistance of doripenem
 - Based on in vitro and clinical susceptibility data

Issues for Committee Discussion

- Non-inferiority margin
 - Adequacy of information to support and select an appropriate NI margin
- Adequacy of data to demonstrate efficacy of doripenem for NP, including VAP
- Adequacy of data to demonstrate safety of doripenem for NP, including VAP
- Issues of microbial resistance
- Consideration of future trial design for NP
 - Study population, diagnostic criteria, primary endpoint and primary analysis population, concomitant meds and po switch

NDA 22-171 Review Team

Clinical

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