

ISSUES FOR DISCUSSION

- 1. Non-inferiority Margin Justification**
- 2. Clinical Efficacy**
- 3. Clinical Safety (Risk)**
- 4. Microbiology**
- 5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP**

1. Non-inferiority Margin Justification

Is there sufficient scientific justification to support the Applicant's proposed non-inferiority clinical trial design with a non-inferiority margin of 20% in nosocomial pneumonia, including ventilator-associated pneumonia?

(continued)

1. Non-inferiority Margin Justification

(continued)

- a. Has the treatment effect of antibacterials been adequately quantified in the treatment of nosocomial pneumonia?

(continued)

1. Non-inferiority Margin Justification

(continued)

- b. Given the proposed margin of 20%, is it reasonable to accept this amount of loss in efficacy and still conclude that the study drug is non-inferior to the active comparator, considering the seriousness of the disease?

(continued)

1. Non-inferiority Margin Justification

(continued)

- c. Does the Committee recommend a different non-inferiority margin for this indication? If so, what is the recommended margin?

(continued)

2. Clinical Efficacy

Has the clinical efficacy of doripenem at dosages of 500 mg q8h 1-hour i.v. infusion and 500 mg q8h 4-hour i.v. infusion been adequately demonstrated to support approval in patients with nosocomial pneumonia, including ventilator-associated pneumonia?

3. Clinical Safety (Risk)

Based on the overall safety profile, is doripenem safe for use in the proposed indication (nosocomial pneumonia, including ventilator-associated pneumonia) at dosages of 500 mg q8h 1-hour i.v. infusion and 500 mg q8h 4-hour i.v. infusion for the proposed 7-14 day treatment duration?

4. Microbiology

Please discuss whether the *in vitro* and clinical susceptibility data suggest that doripenem is inappropriate for the treatment of nosocomial pneumonia or ventilator-associated pneumonia due to *Pseudomonas aeruginosa* or any other organism.

5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP

- a. Discuss the appropriate study populations for clinical efficacy trials in NP and VAP (including the proportion of patients with VAP) and discuss whether clinical trials for this indication should be designed to enrich the study population for infections due to *Pseudomonas aeruginosa*.

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5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP

(continued)

- b. Describe the appropriate diagnostic criteria for NP and VAP (clinical, radiologic, and microbiologic).

(continued)

5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP

(continued)

- c. Discuss whether non-inferiority studies are appropriate for this indication.

(continued)

5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP

(continued)

- d. Describe the appropriate primary endpoint for clinical efficacy trials for this indication (e.g., mortality, clinical outcome, other endpoints)

(continued)

5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP

(continued)

- e. Describe the appropriate primary analysis population or co-primary analysis populations.

(continued)

5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP

(continued)

- f. Describe the indication(s) for concomitant antibacterial agents in NP and VAP, and discuss how the treatment effect of study drug will be determined in patients administered combination antibacterial therapy.

(continued)

5. Study Design Issues for Future Clinical Trials for Antibacterial Drug Development for the Treatment of NP and VAP

(continued)

- g. Describe the role of switch to oral medication, and discuss how the treatment effect of study drug will be determined if oral switch is permitted.

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