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Sheraton College Park Hotel, The Ballroom, 4095 Powder Mill Road, Beltsville, MD.

Summary Minutes of the Anti-Infective Drugs Advisory Committee on July 16, 2008.

On July 16, 2008 the committee discussed new drug application (NDA) 022-171, doripenem powder for reconstitution and intravenous administration, Johnson and Johnson Pharmaceutical Research and Development, LLC, proposed for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia.

These summary minutes for the July 16, 2008 meeting of the Anti-Infective Drugs Advisory Committee were approved on Wednesday November 12, 2008.
I certify that I attended the July 16, 2008 meeting of the Anti-Infective Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/S/_____ 11/12/2008
Designated Federal Official
LCDR Sohail Mosaddegh, PharmD., R.Ph.

_____/S/_____ 11/12/2008
Gregory Townsend, M.D
Acting Chair

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A verbatim transcript will be available in about 2 weeks, sent to the Office of Anti-Microbial Products and posted on the FDA website at
http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Gregory Townsend, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by LCDR Sohail Mosaddegh, Pharm.D., R.Ph. (Designated Federal Officer). There were approximately 150 persons in attendance. There were no speakers for the Open Public Hearing session.

Attendance:

Anti-Infective Drugs Advisory Committee Members Present (voting):
Gregory Townsend, M.D., Margo Smith, M.D.

Anti-Infective Drugs Advisory Committee Members Present (Non-voting):
John H. Rex, M.D., F.A.C.P. (industry representative)

Anti-Infective Drugs Advisory Committee Members Absent:
Kathleen M. Gutierrez, M.D., Allan R. Tunkel, M.D., Ph.D., Annie Wong-Beringer, Pharm.D., Bernhard L. Wiedermann, M.D , Carol A. Kauffman, M.D.

Special Government Employee Consultants Present (voting):
Susan Rehm, M.D., Thomas Fleming, Ph.D., Joan F. Hilton, Sc.D., M.P.H., James Leggett Jr., M.D., John E. Edwards Jr., M.D., Mark Brantly, M.D., William J. Calhoun, M.D., F.A.C.P., James K. Stoller, M.D., M.S., Christopher Ohl, M.D.

Regular Government Employee Consultants Present (voting):
Scott Dowell, M.D., M.P.H., John Bennett, M.D.,

FDA Participants:
Edward Cox, M.D., M.P.H., Katherine Laessig, M.D., Thomas Smith, M.D., Alfred Sorbello, D.O., M.P.H., Scott Komo, Dr.P.H.

Open Public Hearing Speakers:
None

Designated Federal Official:
LCDR Sohail Mosaddegh, Pharm.D., USPHS, FDA

Issue:

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The committee discussed new drug application (NDA) 022-171, doripenem powder for reconstitution and intravenous administration, Johnson and Johnson Pharmaceutical Research and Development, LLC, proposed for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia.

The agenda was as follows:

July 16, 2008

Call to Order and Opening Remarks	**Gregory Townsend, MD** Acting Chair, Anti-Infective Drugs Advisory Committee
Introduction of Committee Conflict of Interest Statement	**LCDR Sohail Mosaddegh, PharmD, RPh** Designated Federal Officer FDA - USPHS
Welcome and Meeting Overview	**Katherine Laessig, MD** Deputy Director Division of Anti-infective and Ophthalmology Products CDER, FDA

Applicant Presentations

Applicant	Johnson and Johnson Pharmaceutical Research & Development, LLC (J&JPRD)
Introduction	**Alysia Baldwin-Ferro** Senior Director, Regulatory Affairs J&JPRD
Management of Nosocomial Pneumonia (NP)	**Richard G. Wunderink, MD** Professor, Division of Pulmonary & Critical Care The Feinberg School of Medicine Northwestern University Evanston, Illinois

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Microbiology PK/PD	**Robert Flamm, PhD** Director, Microbiology J&JPRD
Clinical Study Design Clinical Efficacy	**Ian Friedland, MD** Franchise Medical Leader, Clinical Development J&JPRD
Clinical Safety Benefit/Risk Conclusions: Doripenem for NP	**Rebecca Redman, MD** Senior Director, Clinical Development J&JPRD
Questions regarding Applicant's presentation	

FDA Presentations

Clinical Trials for NP and ventilator-associated pneumonia (VAP): Regulatory Approach to the Non-inferiority Margin Justification	**Alfred Sorbello, DO, MPH** Medical Officer Division of Anti-Infective and Ophthalmology Products CDER, FDA and **Scott Komo, DrPH** Statistical Reviewer Division of Anti-Infective and Ophthalmology Products CDER, FDA
Break	
Clinical Efficacy of Doripenem	**Thomas Smith, MD** Acting Clinical Team Leader Division of Anti-Infective and Ophthalmology Products CDER, FDA
Open Public Hearing	
Lunch	
Clinical Safety of Doripenem	**Alfred Sorbello, DO, MPH** Medical Officer

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	Division of Anti-Infective and Ophthalmology Products CDER, FDA
Microbial Resistance	**Peter Coderre, PhD** Microbiology Reviewer Division of Anti-Infective and Ophthalmology Products CDER, FDA
Questions/Clarifications	
Charge and questions to the Committee	**Katherine Laessig, MD** Deputy Director Division of Anti-infective and Ophthalmology Products CDER, FDA

Break

Questions to the Committee

Adjournment

Questions to the Committee:

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?

YES: 3 **NO: 10** **Abstain: 0** **Absent: 0**

The committee came to the general consensus that there was not enough information for the committee to support the proposed non-inferiority margin of 20% in nosocomial pneumonia, including ventilator-associated pneumonia with clinical endpoints as the primary endpoint. Some committee members said that 20% was the wrong value, while others said they did not have enough information to make a decision on the appropriate non-inferiority margin.
(See transcripts for detailed discussion)

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

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

The committee, with the FDA's approval, chose not to vote on each point above since many of the points had already been addressed by members in answering question #1. The committee further discussed all of the points above as one topic. The committee was not able to come to a consensus on all of the various points; however, there was general consensus on the last point in that most members said they were not able to recommend a non-inferiority margin. Some stated that further discussion of the historical trials would be of little value but felt it was very important for the non-inferiority margin to be determined for future studies due to the critical need for new antibiotics. Some members suggested that this matter may be better resolved in a workshop setting similar to the FDA Community Acquired Pneumonia held in early 2008.
(See transcripts for detailed discussion)

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? (When responding, please state why and if your answer is no, please describe what if any additional information you would like to see.)

YES: 7 **NO: 6** **Abstain: 0** **Absent: 0**

The committee discussed this at great length and did not reach consensus about whether the applicant had shown the clinical efficacy of doripenem in patients with nosocomial pneumonia, including ventilator-associated pneumonia as stated above.
Those that voted 'yes' said that in the studies done by the applicant doripenem achieved its clinical endpoints and in light of doripenem's similarity to other currently approved drugs in it's microbiological data it would be plausible to consider that it too would be effective in treating nosocomial pneumonia, including ventilator-associated pneumonia and that there is a practical need for a drug like this.
Those that voted 'no' pointed to irregularities in the methodology and the conduct of the study that made the data somewhat suspect. They also said they had concerns about the excess mortality in the applicant's studies and the use of adjuvant therapy made the data hard to interpret.
(See transcripts for detailed discussion)

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? (When responding, please state why and

if your answer is no, please describe what if any additional information you would like to see.)

YES: 8 NO: 5 Abstain: 0 Absent: 0

The majority of the committee indicated that doripenem was safe for use in nosocomial pneumonia, including ventilator-associated pneumonia at the dosages cited above.
All those that voted 'no' cited excess mortality in the studies as a significant cause for their vote and concern. They also indicated that weak evidence regarding efficacy of doripenem in this indication provided need for greater reassurance regarding safety in order to ensure a favorable benefit to risk profile.
Those that voted 'yes' said that the excess mortalities may have been an anomaly, or possibly due to regional differences. Some also said the apparent excess mortalities may not have been a reflection of safety but rather due to a lack of efficacy. They felt that further analysis of the applicant's data was needed to demonstrate safety.
(See transcripts for detailed discussion)

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.

The committee discussed this topic and came to the consensus that the in vitro and clinical susceptibility data do not suggest that doripenem is inappropriate for the treatment of nosocomial pneumonia nor ventilator-associated pneumonia due to Pseudomonas aeruginosa or any other organisms. Many based this conclusion partly on the fact that Doripenem was similar to other carbopenems and so it probably it behaves like them. Some members suggested careful use of Doripenem due to possible drug resistance issues.
(See transcripts for detailed discussion)

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

- Describe 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.

Many committee members felt that guidance from the FDA will be needed in defining NP and VAP. Some members recommended that future studies should be sensitive to early VAP versus late VAP because of the significant clinical finding in the two. Some members stated that since VAP patients are sicker than NP patients the proportion of VAP to NP could be kept low especially if mortality was the primary endpoint. Different study sizes for future studies were discussed but no consensus was reached.
(See transcripts for detailed discussion)

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

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Some members suggested that whenever possible objective data be used in the study and that the FDA needs to give practical and reasonable rules to identify nosocomial pneumonia and ventilator-associated pneumonia before any future studies take place.
(See transcripts for detailed discussion)

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

Some members agreed that non-inferiority studies are appropriate for this indication but they added that the studies must be high quality, done ethically, blinded, and randomized. Some members suggested different study designs which met those standards. ***(See transcripts for detailed discussion)***

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

The committee discussed various endpoints but the general consensus was that mortality should be either the primary or secondary endpoint for this indication. Other members suggested clinical outcome as a possible primary endpoint.
(See transcripts for detailed discussion)

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

(See transcripts for detailed discussion)

- 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

(See transcripts for detailed discussion)

- 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

It was suggested that a shorter study time frame of 5 days instead of the mentioned 10 to 14 days would avoid the problems of I.V. to oral switching. Also mentioned by some members was the suggestion of capturing clinical data early in the study period for the same reason.
(See transcripts for detailed discussion)