**Food and Drug Administration**
**Center for Drug Evaluation and Research**
5630 Fishers Lane, Room 1066, Rockville, Maryland 20857

Summary Minutes of the Anti-Infective Drugs Advisory Committee meeting on March 6, 2006:

*The committee discussed new drug application (NDA) 21-572/S-008, Cubicin (daptomycin for injection 500 mg/vial); Sponsor Cubist Pharmaceuticals, for the proposed indication of the treatment of Staphylococcus aureus bacteremia, including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.*

These summary minutes for the March 6, 2006 meeting of the Anti-Infective Drugs Advisory Committee were approved on March 8, 2006.

I certify that I attended the March 6, 2006 meeting of the Anti-Infective Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, R.N., B.S.N.
(Acting) Executive Secretary

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James E. Leggett, Jr., M.D.
(Acting Chair)

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the Sponsor. The meeting was called to order by James E. Leggett, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Acting Executive Secretary). There were approximately 140 persons in attendance. There were no speakers for the Open Public Hearing sessions.

**Attendance:**
**Anti-Infective Drugs Advisory Committee Members Present (voting):**
John S. Bradley, M.D.

**Anti-Infective Drugs Advisory Committee Members (non-voting):**
Samuel D. Maldanado, M.D., M.P.H. (Industry Representative); John E. Edwards, M.D. (Guest Speaker)

**Anti-Infective Drugs Advisory Committee Members Absent:**
Donald M. Poretz, M.D.; Keith R. Powell, M.D.; Carol A. Kauffman, M.D.

**Anti-Infective Drugs Advisory Committee Consultants (voting):**
James E. Leggett, M.D. (Acting Chair); Alan S. Cross, M.D.; Steven C. Ebert, Pharm.D. (Consumer Representative); Joan F. Hilton, Sc.D., M.P.H.; James Omel; Jan E. Patterson, M.D.; Gregory C. Townsend, M.D.

**Endocrinologic and Metabolic Drugs Advisory Committee Consultants (voting):**
Dean A. Follmann, Ph.D. (Biostatistician)

**Cardiovascular and Renal Drugs Committee Consultants (non-voting):**
Jeffrey Borer, M.D.

**FDA Participants:**
Mark Goldberger, M.D.; Janice Soreth, M.D.; Sumathi Nambiar, M.D.; Alfred Sorbello, D.O..; Charles Cooper, M.D.; Peter Coderre, Ph.D.

**Open Public Hearing Speakers:**
None

**Issue:** The committee discussed new drug application (NDA) 21-572/S-008, Cubicin (daptomycin for injection 500 mg/vial); Sponsor Cubist Pharmaceuticals, for the proposed indication of the treatment of Staphylococcus aureus bacteremia, including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.

***The agenda was as follows:***

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| **Introduction** | **Janice Soreth, M.D.**<br>Director<br>Division of Anti-Infective and Ophthalmology Products<br>CDER, FDA |

**Food and Drug Administration Guest Speaker Presentation**

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| **S. *aureus* Bacteremia and Endocarditis: Epidemiologic Considerations** | **John Edwards, Jr., M.D.**<br>Professor of Medicine, UCLA School of Medicine<br>Chief, Infectious Diseases, Department of Medicine<br>Harbor- UCLA Medical Center<br>Torrance, CA |

**Cubist Pharmaceuticals Presentation**

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| **Overview of *S. aureus* Disease** | **Henry Chambers, M.D.** |

Professor of Medicine
Chief, Division of Infectious Diseases,
San Francisco General Hospital
San Francisco, CA

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| **Introduction** | **David Mantus, Ph.D.**<br>Vice President, Regulatory Affairs<br>Cubist Pharmaceuticals |
| **Efficacy Results** | **Helen Whamond Boucher, M.D.**<br>Assistant Professor of Medicine<br>Division of Infectious Diseases and Geographic Medicine<br>Tufts University - New England Medical Center<br>Boston, MA |
| **Microbiology** | **Jeff Alder, Ph.D.**<br>Vice President, Drug Discovery and Evaluation<br>Cubist Pharmaceuticals |
| **Safety Results** | **Gloria Vigliani, M.D.**<br>Vice President, Medical Strategy<br>Cubist Pharmaceuticals |
| **Overview of Benefits/Risks** | **G. Ralph Corey, M.D.**<br>Professor of Internal Medicine & Infectious Disease<br>Duke University Medical Center<br>Durham, NC |
| | **Committee Questions to the Sponsor** |

**Food and Drug Administration Presentation**

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| **Efficacy Results** | **Alfred Sorbello, D.O.**<br>Medical Officer<br>Division of Anti-Infective and Ophthalmology Products<br>CDER, FDA |
| **Microbiology** | **Peter Coderre, Ph.D., M.B.A.**<br>Microbiologist<br>Division of Anti-Infective and Ophthalmology Products<br>CDER, FDA |
| **Safety Results** | **Charles Cooper, M.D.**<br>Medical Officer<br>Division of Anti-Infective and Ophthalmology Products<br>CDER, FDA |
| | **Committee Questions to the FDA** |
| | **Open Public Hearing** |
| | **Committee Discussion** |
| | **Questions to the Committee** |

**Questions to the Committee:**

1. Do data from the pivotal study provide substantial evidence of safety and efficacy of daptomycin in the treatment of *S. aureus* bacteremia? Please include in your deliberations a discussion of the significance of patients with persistent or relapsing bacteremias, and whose staphylococcal isolates had increasing MICs to daptomycin.

a. If your response is yes, are there specific comments that you have regarding the product label?

b. If your response is no what additional study or studies would you recommend?

**YES: 9 NO: 0**

**Comments and labeling recommendations included:**

- **MICs should be monitored weekly or more frequently when treating complicated or persistent bacteremias.**
- **Label should state that daptomycin should be used very judiciously coupled with good culture and sensitivity techniques**
- **Community-acquired MRSA is different than typical hospital-acquired MRSA, therefore, clearance and complications of that organism can be expected to be different and more difficult to treat.**
- **Label should emphasize use of the appropriate dose, in order to discourage under dosing during drug therapy,**
- **Increasing MICs or failures may be an indication that the drug is being pushed to the limit and considerations for surgical intervention should be explored; many of these bacteremias require more than simply antibiotic therapy.**

***(See transcripts for detailed discussion)***

2. Do data from this study provide substantial evidence of safety and efficacy of daptomycin in the treatment of patients with infective endocarditis? Please include in your deliberations a discussion of whether the efficacy results in the all-comers population with S. aureus bacteremia can be extrapolated to the subgroup with infective endocarditis.

**YES: 5 NO: 4**

**Comments from the committee included:**

- **Qualifying comments were provided about the difficult nature of diagnosing endocarditis; high risk nature of this patient population at the front end makes it critical to begin treating these patients with something without knowing the precise diagnosis. Echocardiogram and clinical outcomes data may be the best we can do to make a diagnosis although, although specificity is excellent, sensitivity of echocardiography is not high enough.**
- **Problems associated with concluding that there is sufficient data to determine efficacy here lie more with the study than the drug itself; there are not enough total numbers in the study and even fewer in the subgroup populations, which is important in analyzing right-sided versus left-sided endocarditis; caution should be taken in extrapolating data from the all comers population because S. aureus endocarditis and S. aureus bacteremia are not equivalent.**
- **Concerns were discussed in the infective endocarditis patients, regarding the controlled response rates – 20% non-inferiority margin and the difficulty in justifying a 20% non-inferiority margin when, in the left-sided group, there is a 22% control response rate; it is concerning that the control response rate varies dramatically by these diagnostic subgroups.**
- **The Committee discussed the significance of the echocardiogram results in the clinical setting, when treating these patients, citing a study that showed initial therapy was rarely changed based on the results of the echocardiogram; the choice and duration of therapy was based primarily on clinician bias at the outset, even before the echocardiogram was performed.**
- **A labeling suggestion was added here that, if there is clear evidence of left-sided endocarditis by the presence of vegetation, the clinician needs to be cautioned that there is limited data available regarding efficacy and that data on efficacy is not very strong.**
- **Answering this question hinges on whether we define the population for infective endocarditis as entry diagnosis or final diagnosis. Using entry diagnosis, the study clearly showed daptomycin was non-inferior. Labeling should include statements clarifying that daptomycin has been studied and is non-inferior to the comparator for treatment of s. aureus endocarditis where the entry diagnosis was the Duke criteria for endocarditis. Additionally, labeling should address the need for adjunctive therapy for complicated bacteremia (i.e. drainage), in combination with medical therapy.**

- **Additional labeling suggestions by the committee included statements about the overall effectiveness being 44%, making it clear to clinicians that it was not greater, while also clarifying that this data is based on small numbers.**
- **Given the sponsor's observation that 25% of off-label use of daptomycin is for bacteremia at 4 mg/kg, labeling should clarify that we should be using 6 mg/kg for bacteremia.**

***(See transcripts for detailed discussion)***

3. Do you recommend additional studies of daptomycin in the treatment of patients with S. aureus bacteremia, including infective endocarditis?

**After considerable discussion, the Division was satisfied with recommendations from many Committee members that there should, in fact, be additional studies, and the Division did not require a 'Yes/No' vote on Question #3. See Question 4 for comments regarding additional studies and study design.**
***(See transcripts for detailed discussion)***

4. What recommendations do you have for future studies of *S. aureus* bacteremia and endocarditis? Please include in your discussion study design issues such as case definition, specificity of diagnosis at baseline, inclusion and exclusion criteria, and endpoints.

**Comments from the Committee included:**

- **A recommendation was made for a study to prospectively define what PRSA is, as opposed to leaving this determination up to the discretion of the individual investigator.**
- **It would be useful to have data on what type of metastatic infections we do have with bacteremia, as suggested in the FDA efficacy presentation, to help clinicians determine how long to treat these infections.**
- **The Committee encouraged more investigation into toxicity. Given the reversible nature of the toxicity exhibited in this study, it is important for clinicians to predict who is at risk for toxicity.**
- **The suggestion was made that it may be of interest to investigate how the failures who had increasing MICs were treated to obtain more information on treating those types of failures.**
- **Insights were added about the overall increases of MICs with respect to all anti-infectives; considering daptomycin relative to others may be worth studying.**
- **Future studies should look more closely at some of the subgroups in this trial; more should be done to investigate who the candidates are for success rather than assuming a 65% response rate in the controls and then getting something a lot closer to 45%. If the margin is going to be based on the end of therapy endpoint, then that is a different margin than should be used for the test of cure endpoint.**
- **It was suggested that a smaller trial be considered for those patients who had a positive echocardiogram, in order to thoroughly study that patient population.**
- **Setting up a registry versus investing in another randomized trial, which is difficult in this area, may provide more real-world information about the relation of clinical outcome to the MICs with this drug and to the isolate genotype. Such a registry could be useful in improving the label and informing the clinicians.**
- **In designing future trials, diagnostic groups should be made using baseline data [possibly waiting a few days for echocardiogram on everyone], in order to get better diagnostic groups at baseline.**
- **Additional suggestions about trial design included using a fixed time of evaluation of success, rather than different evaluation times in this study, which may have caused a bias. For example, a right-sided endocarditis treatment time of 14-28 days versus comparator arm, which was 14-42 days, which may result in one group being studied longer. There needs to be a fair endpoint such as 12 weeks past randomization versus defined at therapy.**
- **Intention to treat should be the primary analysis and would have included the failures that were excluded in this study for various reasons.**
- **An additional study design suggestion was made to perform a blinded study, citing some of the biases that may have been present in this study, including the investigator's knowledge about toxicity of the antibiotic, which may cause him to interpret the threshold for toxicity differently for the study drug.**
- **The Committee commented that it would be helpful to know whether there is any difference between two weeks versus four weeks of therapy, emphasizing that outcomes studying the length of therapy should be an important consideration.**

- **A consideration should be made to study a patient population of those excluded from this trial for reasons such as having prosthetic valves and intravascular foreign materials. This information could be useful for clinicians.**
- **Additional study design suggestions included the need for a clear differentiation between MSSA and MRSA.**

***(See transcripts for detailed discussion)***

The committee adjourned at approximately 4:00 P.M.
***(See transcripts for detailed discussion)***