Minutes of the AntiInfective Drugs Advisory Committee Meeting (68th)
Center for Drug Evaluation and Research
March 24, 2000

Committee Members
L. Barth Reller, M.D.
Robert L. Danner, M.D.
Keith A. Rovold, Pharm.D.
P. Joan Chesney, M.D.
Celia D. C. Christe-Samuels, M.D.
David E. Soper, M.D.
Barbara E. Murray, M.D.
Judith R. O'Fallon, Ph.D.

Consultants
Carl Norden, M.D.
James Leggett, Jr., M.D.

Executive Secretary
Kimberly Littleton Topper

Guest Experts
Joyce Drayton, M.D.
Matthew J. Kuehnert, M.D.
Franklin David Lowy, M.D.
Janet Wittes, Ph.D.

FDA
Gary Chickami, M.D.
Janice Soreth, M.D.
David Ross, M.D., Ph.D.
Diane Murphy, M.D.

These summary minutes for the March 24, 2000, meeting of the AntiInfective Drugs Advisory Committee were approved on _____.

I certify that I attended the March 24, 2000, meeting of the AntiInfective Drugs Advisory Committee and that these minutes accurately reflect what occurred.

_____//S//_____
Kimberly L. Topper
Executive Secretary

_____//S//_____
L. Barth Reller, M.D.
Chairman

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The meeting was called to order at 8:30 and Dr Reller welcomed the members. The Executive Secretary read the conflict of interest statement. Dr. Reller asked all the members at the table to introduce themselves.

Dr. Chickami, Director of Division of AntiInfective Drug Products provided organizational comments and set the stage for the presentations and discussions.

Dr. Tarpley, Discovery Research at Pharmacia and Upjohn, introduced Linezolid as a new anti-bacterial from an entirely new structure class. The drug was coming for discussion and approval for the following indications: nosocomial pneumonia, community acquired pneumonia, complicated and uncomplicated skin and skin structure infections and vancomycin-resistant enterococcus faecalis and e. faecium infections. He stated that they expected that linezolid therapy will be initiated in a hospital or the institutional care setting.

Dr. Hafkin, P&U, spoke on the pharmacokinetic profile of linezolid and it's oral bioavailability and the time concentration curve data. Testing has shown that drug exposure is equal whether the drug is given intravenously or orally so no dose adjustments are required for route of administration changes. Gender and age do not affect the AUC or exposure to the drug because the concentration of the active drug doesn't change with severe, minimal or no renal insufficiency.

Dr. Ross, Medical Reviewer, Division of AntiInfective Drug Products presented the agency's analysis of Linezolid and discussed the studies one by one. He provided a review of the clinical pharmacology, clinical/statistical analyses of efficacy, clinical/statistical analyses of safety and the development of resistance.

The committee questioned many aspects of the presentations and clarified issues prior to addressing the following questions.

1) Community-acquired pneumonia (CAP)

a) Do the data support the efficacy and safety of linezolid in the treatment of adult patients with CAP? ***10 YES*** ***0 NO***
No additional comments

b) Include in your discussion whether there are sufficient data to support the efficacy of linezolid for the treatment of CAP due to: ***5 YES*** ***5 NO***

Methicillin-resistant *Staphylococcus aureus* (MRSA)
YES: based on aggregate data in other sites and in hospital acquired pneumonia

Penicillin-resistant *Streptococcus pneumoniae* (PRSP) ***3 YES 7 NO***
YES: more evaluation on numbers already collected and based on pathogens.
NO: Need more data and patient numbers are too small
Despite the sponsors efforts there were not enough cases overall with penicillin resistant isolates

2) Hospital-acquired pneumonia (HAP)

a) Do the data support the efficacy and safety of linezolid in the treatment of adult patients with HAP? ***9 YES 1 NO***
NO: Confidence intervals are a concern

b) Include in your discussion whether there are sufficient data to support the efficacy of linezolid for the treatment of HAP due to:
I) MRSA ***10 YES 0 NO***
ii) PRSP ***2 YES 8 NO***
NO: More experience needed and higher numbers needed for resistant stains

3) Uncomplicated skin and skin structure infections (uSSSI)

a) Do the data support the efficacy and safety of linezolid in the treatment of adult patients with uSSSI? ***10 YES 0 NO***

b) Include in your discussion whether there are sufficient data to support the efficacy of linezolid for the treatment of uSSSI due to: ***2 YES 8 NO***
I) MRSA
YES: overall information shows - if it will work in CAP it will work in SSSI because of pathogen site.
NO: be sure to address dosage issue, it may be a concern with lower dose, i.e., higher dose may be required for efficacy

4) Complicated skin and skin structure infections (cSSSI)

a) Do the data support the efficacy and safety of linezolid in the treatment of adult patients with cSSSI? ***9 YES 1 NO***

b) Include in your discussion whether there are sufficient data to support the efficacy of linezolid for the treatment of cSSSI due to: ***5 YES 5 NO***
I) MRSA

5) Infections due to vancomycin-resistant enterococci (VRE)

a) Do the data support the efficacy and safety of linezolid in the treatment of adult patients with infections due to VRE? ***9 YES 1 NO***
Look for more data

b) What additional study(ies), if any, would the committee recommend?

1) more information on metabolism of drug to assist in use of drug
2) more absorption rates of drug (gastric tube, IV, pill, etc.,)
3) more post marketing e. faecalis data and have information in data sheet
4) break out bacteremia data
5) collect more data using compassionate use data
6) need more population pharmacokinetics
7) put in the labeling how many isolates of e. faecalis have been treated and indicate the comfortability factor
8) breakout the bacteremia data because it is most convincing for new drugs
9)test in osteomyelitis