CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Clinical Pharmacology and Biopharmaceutics Review

NDA#	21-572
PRODUCT	Daptomycin (Cubicin™)
FORMULATION	Sterile powder for injection
DOSAGE STRENGTH	250 mg and 500 mg vials
SUBMISSION DATES	12/19/02, 3/17/03, 3/26/03, 3/27/03, 4/11/03, 5/19/03, 5/20/03, 5/28/03, 5/29/03, 6/19/03, 8/8/03, 9/3/03
SUBMISSION TYPE	New Molecular Entity, 1P
SPONSOR	Cubist Pharmaceuticals, Inc., Lexington, MA 02421
OCPB DIVISION	Division of Pharmaceutical Evaluation III
MEDICAL DIVISION	Division of Anti-Infective Drug Products
REVIEWER	Charles R. Bonapace, Pharm.D.
PM REVIEWER	Jenny J. Zheng, Ph.D.
TEAM LEADER	Philip M. Colangelo, Pharm.D., Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

I: EXECUTIVE SUMMARY

Cubist Pharmaceuticals, Inc. submitted a priority review New Drug Application for Cubicin™ (daptomycin for injection) on December 19, 2002. Daptomycin is a cyclic lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus* that demonstrates *in vitro* activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. The proposed dosing regimen of daptomycin is 4 mg/kg intravenously administered over 30 min q24h for 7 to 14 days. The sponsor is seeking an indication for complicated skin and skin structure infections — — caused by susceptible strains of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, *Enterococcus faecalis* (vancomycin-susceptible strains only), —.

Daptomycin represents a new class of antibacterial agents with a novel mechanism of action that involves binding to the bacterial cell membrane followed by membrane depolarization and cell death. Since the mechanism of action of daptomycin is different from other antimicrobial agents, it may offer a therapeutic alternative in select cases of antimicrobial resistance. The goal of Cubist continues to be focused on delivering daptomycin to the market as quickly as possible to address the pressing public health need for new classes of antibiotics effective in treating serious and life-threatening infections caused by Gram-positive pathogens, particularly *Staphylococcus aureus* (including methicillin-resistant strains).

Several review issues have been identified that impact the quality of data submitted for review. These issues consist of the analytical methodology in the renal impairment study, the impact of using estimated creatinine clearance (Cockcroft and Gault equation) vs. measured creatinine clearance, the unusually large degree of inter-study variability among studies with healthy adult subjects, and the impact of this variability in assessing a dosage recommendation in elderly subjects.

In the renal impairment study (Study DAP-00-01), plasma concentrations of daptomycin were initially determined by a validated — method for all subjects (controls and renal impairment). Since plasma concentrations of daptomycin were greater than other phase 1 studies with the same once-daily dose, the sponsor determined the concentration of daptomycin in subjects with normal renal function using a validated — assay. The — method overestimated the plasma concentrations of

daptomycin by an average of 46% (accuracy ranged from 73% to 187%). Thus, the sponsor converted plasma concentrations of daptomycin determined by — to the — for all subjects in study DAP-00-01 using the equation derived from the linear relationship between samples determined by — The accuracy of daptomycin concentrations exceeded 100 ± 15% in 34% of plasma samples as determined by the reviewer. The sponsor re-assayed all plasma samples from Study DAP-00-01 (subjects with normal and impaired renal function) using the validated — assay.

Also in Study DAP-00-01, the sponsor assigned subjects for the pharmacokinetic analysis to treatment groups based on estimated creatinine clearance (CL_{CR}) using the Cockcroft & Gault equation and ideal body weight (IBW). However, many of the subjects were obese based on a mean body mass index of 31.1 kg/m^2 that ranged from — kg/m^2. The reviewer assigned subjects to treatment groups based on their measured creatinine clearance. Due to differences between the estimated CL_{CR} using Cockcroft & Gault and the measured CL_{CR}, only one subject remained in the 30-50 mL/min treatment group.

In a second renal impairment study (Study DAP-MDRI-01-09), the sponsor enrolled eight subjects with moderate renal impairment (CL_{CR} 30-50 mL/min). The sponsor did not enroll a control group. All subjects had a CL_{CR} of 30-50 mL/min using IBW, three subjects had a CL_{CR} of 30-50 mL/min using actual body weight, and one subject had a CL_{CR} of 30-50 mL/min based on a measured creatinine clearance. This study was unable to provide information about the pharmacokinetics of daptomycin in subjects with CL_{CR} 30-50 mL/min.

The mean daptomycin C_{max} ranged from 42.3 to 62.4 µg/mL (1.48-fold) and the $AUC_{0-\infty}$ ranged from 301 to 517 µg*hr/mL (1.72-fold) from Phase 1 studies in which healthy volunteers received a single 4 mg/kg dose of daptomycin. The inter-subject variability of C_{max} and $AUC_{0-\infty}$ within a study was generally <20%. The source of variability between studies is unknown.

In the geriatric study (Study DAP-GER-01-11), the mean $AUC_{0-\infty}$ from healthy elderly subjects was within the range of values for healthy subjects from previous Phase 1 studies, although the $AUC_{0-\infty}$ from the control group (healthy young subjects) was less than previously observed from healthy subjects. The mean $AUC_{0-\infty}$ for elderly subjects was 58% greater than the control group of young subjects. Based on these findings and safety data from Phase 3 clinical studies, no dosage adjustment of daptomycin is warranted for elderly subjects with normal (for their age) renal function.

In skin blister study (DAP-00-04), the sponsor used a microbiological assay validated with serum to determine the concentration of daptomycin from plasma. No data were submitted to demonstrate the cross-validation of the microbiological assay in serum and plasma. It is known that anticoagulants can alter the *in vitro* protein binding of highly protein bound drugs (M. Klassen, S.C. Edberg. 1996. Measurement of antibiotics in human body fluids: Techniques and significance, p. 230-294. *In* V. Lorian (ed.), Antibiotics in laboratory medicine, Fourth edition, Williams and Wilkins, Baltimore) and thus, impact the results of a microbiological assay. Since the plasma concentrations of daptomycin from study DAP-00-04 were greater than any previous Phase 1 study in which healthy subjects received the same dose, the results of this study were deemed unacceptable for labeling purposes.

COMMENTS:

1. Although the sponsor used cryopreserved hepatocytes to assess the potential of daptomycin to act as an inhibitor and inducer of cytochrome P450 isoforms, the sponsor has not assessed the potential of daptomycin to act as a substrate. The sponsor is encouraged to evaluate the potential of daptomycin to act as a substrate of the predominant cytochrome P450 isoforms.

2. The reviewer recommends a dosage adjustment for patients with renal impairment, beginning at moderate renal impairment (CL_{CR} 30-50 mL/min). However, there was only one subject with a CL_{CR} of 30-50 mL/min in the renal impairment study (Study DAP-00-01) based on measured creatinine clearance. Although the relationship between CL_{CR} and CL_T is linear with increasing renal impairment, additional data are necessary to characterize the pharmacokinetics of daptomycin in subjects with moderate renal impairment.

A. RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE-III) has reviewed NDA . The submission is acceptable from a Clinical Pharmacology point of view provided that the sponsor agrees with the Agency's label recommendations.

The Phase IV Commitment recommendations and labeling comments outlined in the annotated label should be conveyed to the sponsor.

B. PHASE IV COMMITMENTS:

1. [redacted]

2. It is recommended that the sponsor perform a clinical study to assess the safety, efficacy, and pharmacokinetics of daptomycin in renal impairment patients with complicated skin and skin structure infections. The sponsor is encouraged to include patients with foot and decubitus ulcers complicated by diabetes. Enrollment into the study should be limited to patients with an estimated (via the Cockcroft and Gault equation using ABW) creatinine clearance ≤50 mL/min and an attempt should be made to enroll an equal number of patients into the following categories: CL_{CR} 30-50 mL/min, CL_{CR} <30 mL/min, hemodialysis patients, and CAPD patients.

/S/

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Philip M. Colangelo, Pharm.D., Ph.D., /S/
Team Leader

cc:
Division File: NDA 21-572
HFD-520 (CSO/Peat)
HFD-520 (MO/Ross, Thompson, Nambiar, Sorbello)
HFD-520 (Microbiology/Sheldon, Coderre)
HFD-880 (Division File, Lazor, Selen, Colangelo, Bonapace)
CDR (Clin. Pharm./Biopharm.)

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