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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Medical Review(s)

Clinical Review

NDA 21-572

Cubicin (daptomycin for injection)

Original New Drug Application for marketing approval for treatment of complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*

Sponsor: Cubist Pharmaceuticals, Inc.
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Date of Submission: December 19, 2002

Date Assigned: December 19, 2002

Date Review Begun: December 19, 2002

Date Review to Supervisor: August 31, 2002

PDUFA Deadline: September 19, 2002

Integrated Review of Safety and Efficacy

This document is the integrated review of safety and efficacy for NDA 21-572. Appendices describing the individual protocols, safety and efficacy, and a detailed analysis of CPK are appended to this review.

I. Recommendations

A. Recommendation on Approvability

Cubicin™ (daptomycin for injection; Cubist Pharmaceuticals) is the lead investigational antibiotic in a new class of drugs known as cyclic lipopeptides. Based on evidence from two randomized, active-controlled clinical trials submitted by the sponsor, there is adequate efficacy and safety data to recommend approval of daptomycin 4 mg/kg/day intravenously for 7-14 days, in patients 18-85 years of age, with complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria including *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*. In combined cSSSI studies, a total of 534 patients were treated with daptomycin. The safety database comprised data on 602 daptomycin-treated patients in Phase I studies, 349 daptomycin-treated patients in Phase II studies, and 989 patients in Phase III studies.

The two clinical studies conducted by Cubist in cSSSI were similar in trial design, but differed in certain baseline patient characteristics, such as underlying diabetes and peripheral vascular disease. Such differences in baseline characteristics may have had a significant effect on wound healing. Observed success rates were in fact quite different in the two studies. In both trials, daptomycin was demonstrated to be non-inferior to the comparator (vancomycin/semi-synthetic penicillins, including nafcillin, oxacillin, cloxacillin, or flucloxacillin), using a non-inferiority margin of 10%. Concomitant aztreonam or metronidazole could be used for Gram-negative/anaerobic coverage respectively. Concomitant surgical procedures such as debridement were also permitted during the study.

Sufficient numbers of patients with complicated skin and skin structure infections such as major abscesses, infected ulcers, wound infections, and cellulitis were included in the studies to justify inclusion in the label. Data were inadequate to include patients with infected diabetic ulcers. The number of patients enrolled with infected diabetic ulcers was small, errors in classification of diabetic ulcers occurred, and the clinical success rates observed in these limited data were low.

The safety profile of daptomycin is derived from 1755 subjects exposed to daptomycin in clinical studies conducted by Cubist and Lilly; limited 120-day safety data are available for an additional 52 patients enrolled in ongoing studies, most of whom received a higher dose of daptomycin at 6 mg/kg IV given once daily. Overall, the MedDRA system organ class (SOC) with the greatest percentages of reported adverse events was gastrointestinal disorders, most frequently nausea, constipation, diarrhea, and vomiting. The rates of overall adverse events, deaths, serious adverse events (SAEs) other than death, and adverse events (AEs) leading to discontinuation were similar in both treatment groups. Preclinical studies had predicted that the primary target of daptomycin toxicity was skeletal muscle. This prediction was confirmed in Phase I studies by the observed elevation of CPK with muscle-related symptoms in 2/5 subjects given 4 mg/kg IV q12h and 2/4 subjects administered daptomycin at 4 mg/kg IV q24h. In Phase III cSSSI trials, elevations in serum CPK were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 10/58 (1.8%) comparator-treated patients. Symptoms consistent with muscle injury were observed in 1/534 (0.2%) of daptomycin- treated patients.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The Agency and Cubist have agreed that Cubist will conduct two Phase 4 studies.

- The first study will consist of a safety and efficacy study in patients with cSSSI. This study is scheduled to start in the first quarter of 2004 and has an estimated 18-month study duration. The study will be open-label, randomized, multicenter, non-comparative study. The patient population for this study will consist of 72 patients with renal insufficiency in the following categories: Clcr 30-50 mL/min an Clcr <30 mL/min. Patients in the latter category may be on hemodialysis, continuous ambulatory peritoneal dialysis, or may not be maintained on dialysis. Pharmacokinetic data will also be collected in this study.
- [redacted]

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Daptomycin [Cubicin®] is a cyclic lipopeptide antibiotic that is administered intravenously.

Phase I and II studies

The Cubist Phase I studies enrolled 240 subjects who received daptomycin. The Cubist human pharmacology studies included single- and repeat-dose pharmacokinetic studies in normal healthy subjects and in special populations. Repeat-dose studies were conducted in healthy subjects and in subjects with various degrees of renal impairment, including end-stage renal disease (ESRD). Single-dose studies were conducted in subjects with moderate hepatic impairment (Child-Pugh Classification B), in geriatric subjects, and in obese subjects, and in healthy subjects. Drug interaction studies with aztreonam, probenecid, warfarin, and simvastatin were conducted in healthy subjects. Studies on daptomycin protein binding were conducted in healthy subjects and in subjects with various degrees of renal impairment, including ESRD. A placebo-controlled study was conducted to examine the effect of daptomycin given to healthy subjects at 6 mg/kg q24h for 14 days on cardiac repolarization (QT interval) and peripheral nerve conduction. Cubist also studied the penetration of daptomycin into inflammatory exudate from cantharides-induced skin blisters. *In vitro* studies were conducted to assess the influence of daptomycin on induction or inhibition of cytochrome P450 enzymes in human hepatocytes.

The Lilly Phase I studies enrolled 362 subjects who received daptomycin. These human pharmacology studies included single- and multiple-dose safety and pharmacokinetic studies in healthy subjects. Multiple-dose studies examined various doses and regimens up to 4 mg/kg q 12h x 14 days. Also included are *in vivo* protein binding studies; a metabolism and excretion study using radiolabeled daptomycin, a study in subjects with various degrees of renal impairment and drug interaction studies with tobramycin and amikacin.

Cubist conducted two Phase II studies; a third study was discontinued due to slow enrollment. DAP-BAC-9803, is an open-label, Phase II, dose-ranging trial in subjects with culture-confirmed Gram-positive bacteremia or presumed bacteremia. The study compared three doses of daptomycin (4 mg/kg q24h, 6 mg/kg q24h, or 3 mg/kg q12h with a 6 mg/kg loading dose) with standard therapy (vancomycin 1 g every 12 hours or nafcillin or oxacillin 4-12 g daily in equally divided doses) and enrollment was 3:1 daptomycin:comparator. The second Phase II study, DAP-RRC-9804, is an open-label, non-comparative, multicenter study utilizing three dose regimens of daptomycin in hospitalized subjects with bacteremia (4 mg/kg q24h, 6 mg/kg q24h, 3 mg/kg q12h following a 6 mg/kg loading dose), complicated skin and skin structure infections (cSSSI) (4 mg/kg q24h), lower respiratory tract infections (LRTI) (6 mg/kg q24h), intra-abdominal infections (IAI) (6 mg/kg q24h), or complicated urinary tract infections (UTI) (4 mg/kg q24h potentially adjusted according to MIC level) caused by Gram-positive pathogens that were resistant to vancomycin or whose infection was otherwise refractory to currently available therapy or for whom currently available therapy was contraindicated. Study DAP-RRC-

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