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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Microbiology Review(s)

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 1

NDA: 21-572 **Dates Completed: September 5, 2003**

Applicant (NDA):
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421
781-860-8660

Therapeutic Type: Daptomycin for injection

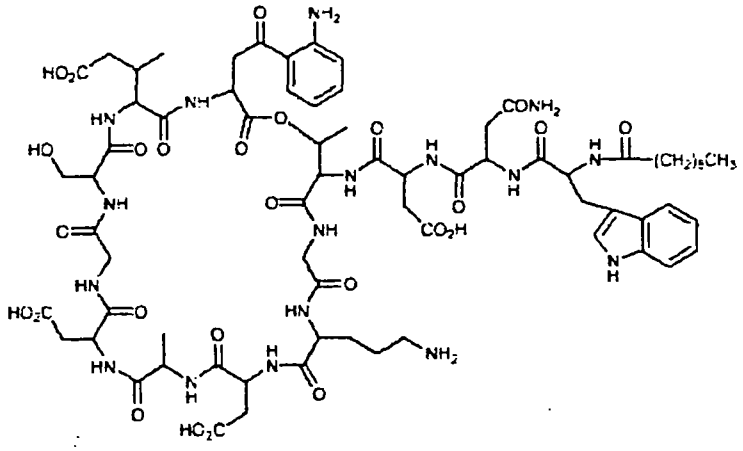
Submissions Reviewed: NDA 21,572

Providing for: Treatment of complicated skin structure infections (cSSSI)

Product Name(s):
Proprietary: Cubicin ®
Non-proprietary: Daptomycin

Chemical name: *N*-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine ε_1-lactone.

Structural formula:



Molecular formula: $C_{72}H_{101}N_{17}O_{26}$; the molecular weight is 1620.67.

Dosage form: Four mg/kg administered over a 30-minute period by intravenous infusion in 0.9% sodium chloride injection, USP once every 24 hours for 7-14 days.

Route(s) of administration: Injection

Pharmacological Category: Anti-Infective

Dispensed: Rx__X____ OTC_____

Initial Submission Dates

Received by CDER: September 12, 2003
Received by Reviewer: September 12, 2003
Review Completed: September 12, 2003

Related Documents: NDA 21,572; IND 57,693

Remarks:

This is an amendment to the original review of the clinical microbiology portion of an NDA submission from Cubist Pharmaceutical, Inc. for Cubicin. This drug is intended to treat **complicated skin and skin structure infections** caused by *S. aureus* (methicillin-susceptible and –resistant strains), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus dysgalactiae* subsp. *equisimilis*, [redacted] and *Enterococcus faecalis* (vancomycin-susceptible strains only). However, based on discussion within the review team and as negotiated with the Applicant, the [redacted] has been excluded as a pathogen for the indication.

This review addresses the modification of the breakpoints for the Streptococci species listed in the product package insert. The original susceptible breakpoint negotiated with Cubist Pharmaceuticals, Inc. of [redacted] for Streptococci have been renegotiated to ≤0.5 µg/mL, since the [redacted] is now deleted from the indications section of the package insert. It is concluded by the review team that this organism is not a pathogen for complicated skin and skin structure infections. Thus we need to change the breakpoint to reflect the susceptibility of the pathogens to be approved in the indications section of the package insert for daptomycin.

The basis of our argument rests upon the following points:

- Analysis of the in vitro spectrum of activity as presented in the original review does not support the breakpoint of — unless the — is included in the analysis.
- However, it has been determined by the review team that the — should be excluded from the analysis because they are not considered pathogens for the indication of complicated skin and skin structure infections sought by the Applicant.
- Analysis of the in vitro spectrum of activity dataset excluding — supports the breakpoint of ≤0.5 µg/mL.
- In addition to this dataset, the surveillance information clearly supports a breakpoint of ≤0.5 µg/mL. Evaluation of this data shows that the vast majority of pathogens had MICs less than 0.5 µg/mL. Thus, pathogens with MICs greater than 0.5 µg/mL are rare.
- Although pharmacokinetic/pharmacodynamic studies were performed, the majority of the studies were performed with *Streptococcus pneumoniae*, an organism not sought as a pathogen for the proposed indication. Some studies were performed with *S. pyogenes*; these data are used to provide part of the information necessary to make decisions on breakpoints. These data are not the final arbitrators of breakpoint determinations but augment existing evidence.
- Evaluation of the clinical data was also performed to determine the final breakpoint for Streptococci species. If we look at Microbiological Review #1 and specifically at Table 47 (page 59) which describes clinical and microbiological success rates by MIC, we clearly see that there are no clinical or microbiological experiences to support a breakpoint of — In fact we have little evidence to demonstrate the efficacy of daptomycin for pathogens with susceptible MICs of 0.5 µg/mL. Most of these data demonstrate clinical and microbiological efficacy for pathogens with MICs of ≤0.25 µg/mL. Since a majority of the clinical and microbiological experiences are with MICs at this dilution, and the error of the assay can be ± one tube dilution, the breakpoint supported by the data is ≤0.5 µg/mL. This is consistent with the practice of setting breakpoints that are one dilution higher than the clinical and microbiological experiences.
- These arguments were conveyed to the Applicant in a teleconference dated September 11, 2003 at which time final agreement was reached that the breakpoint of ≤0.5 µg/mL would be established for Streptococci species. They conceded the discussion and sent their final product package insert with the susceptible breakpoint of ≤0.5 µg/mL.

Conclusions/Recommendations:

The Microbiology portion of this submission is approvable but with the indicated changes to the Microbiology Section of the Package Insert. Specifically, the susceptible breakpoint of ≤0.5 µg/mL for the Streptococci species listed in the indications section of the package insert and as described in the Microbiology section should be adopted.

Peter Coderre Ph.D.
Microbiology Reviewer

Albert T. Sheldon, Jr. Ph.D.
Microbiology Team Leader

Cc: Original NDA No. 021-572
Microbiologist, HFD-520
File name: 21572-Strept BPs.doc N21572_RD#2.doc

Smicro/ATSheldon
RD#1 initialed 6/10/03, RD#2 initialed 8/27/03 ATS; Final initialed 8//03ATS

DepDir/LGavrilovich

Cc: Original NDA # 21-572
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon
HFD-520/Micro
HFD-520/MO/
HFD-520/Pharm/
HFD-520/Chem/
HFD-520/CSO/
HFD-520
HFD-502
HFD-635

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