CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Chemistry Review(s)

NDA 21-572

CUBICIN®
(daptomycin for injection)

Cubist Pharmaceuticals, Incorporated

Reviewed by

Zi-Qiang Gu, Ph.D.
Division of Antiviral Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA # **21-572**

2. REVIEW # **1**

3. REVIEW DATE: **August 1, 2003**

4. REVIEWER: **Zi-Qiang Gu, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 57,627 (Original)	
IND 57,627, Serial No. 57	Sept. 2000
IND 57,627, Amendment 031	1999 Annual Report
IND 57,627, Amendment 074	2000 Annual Report

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-572	Dec. 20, 2002
NDA 21-572/Response for information request	March 27, 2003
NDA 21-572/BC, Stability update	March 31, 2003
NDA 21-572/Response for information request	April 11, 2003
NDA 21-572/Response for information request	May 15, 2003
NDA 21-572/Response for information request	July 3, 2003
NDA 21-572/Response for information request	August 5, 2003
NDA 21-572/Response for information request	September 3, 2003
NDA 21-572/Response for Label	September 11, 2003

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Cubist Pharmaceuticals, Inc.
Address:	65 Hayden Avenue, Lexington, MA 02421
Representative:	David H. Schubert
Telephone:	718-860-8455

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CUBUCIN® (proposed)
b) Non-Proprietary Name (USAN): Daptomycin
c) Code Name/# (ONDC only): CB-109187, LY146032
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antibiotics

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 250 mg and 500 mg

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: _X_Rx ___OTC

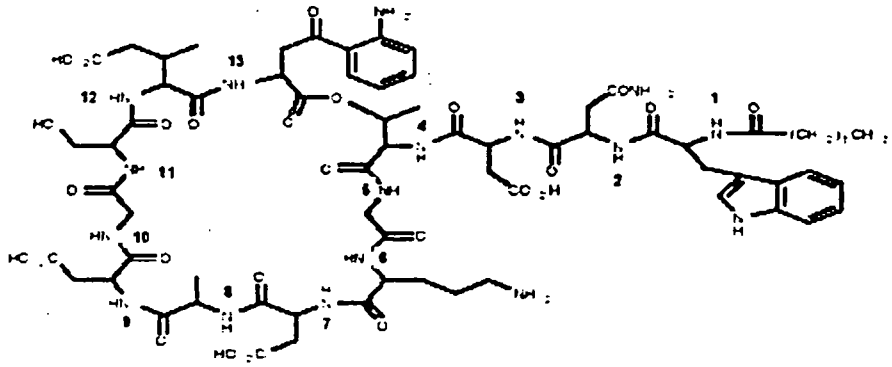
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Chemical Structure:



Molecular Formula: $C_{72}H_{101}N_{17}O_{26}$
Molecular Weight: 1620.67

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	\	USP Type I glass vials	3	Adequate	10/1/2002	Reviewed by S. C. Pope
—	III	\	\	3&4	Adequate	9//14/01 4/14/2003	Reviewed by Y. Yang and S. P. Peri
—	Type II	\	\	3&4	Adequate	2/7/2000	Reviewed by S. Simek

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approval	9/12/03	Joel Jiang
EES	Approval	9/12/03	Office of Compliance
Pharm/Tox	Approval	9/12/03	Wendelyn Schmidt
Biopharm	Approval	9/12/03	Charles Bonapace
LNC	N/A		
Methods Validation	Pending		
ODS	Not recommended	9/12/03	CUBICIN is recommended by DAIDP
EA	Exclusion Acceptable	9/12/03	Zi-Qiang Gu
Microbiology	Approval	9/12/03	Bryan Riley

The Chemistry Review for NDA 21-245

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing and Controls information provided for the drug substance and the drug product (CUBICIN™, daptomycin for injection) are adequate. Therefore, this NDA is recommended for approval for CUBICIN™ (daptomycin) for injection, with recommendation of an expiration dating period of 24 months when stored at 2-8°C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance (DS), deptomycin (LY146032) is reportedly a novel bactericidal lipopeptide that represents a new class of natural product antibiotics. Daptomycin is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains); *Streptococcus pyogenes*, *Streptococcus agalactiae*; *Enterococcus faecalis* (vancomycin-susceptible strains only); —
— . The mechanism of action appears to involve calcium-dependent insertion of the decanoyl side chain into the bacterial membrane followed by depolarization of the membrane with concomitant release of K^+ ions. These events are tied to rapid, concentration dependent killing of Gram-positive organisms.

Daptomycin, as a new chemical entity, is unique among current antibiotics due to the presence of both lipophilic (ie, decanoyl side chain) and hydrophilic (ie, peptide) regions in the molecule.

The manufacturing process for the drug substance is difficult, —
— procedures . The purified drug substance is .

Specification for the starting materials and reagents are properly specified, and parameters for in-process controls are adequately identified and monitored. The structural characteristics of daptomycin have been evaluated by using different spectroscopic and analytic techniques, and are in good agreement with literature's original assessment. Specification of the drug substance includes appearance, identification — concentration and purity — related degradants and impurities (specified, unspecified and total), specific rotation, residue on ignition, heavy metals, residual solvents, bacterial endotoxins and microbial limits.

The drug substance stability data were generated on batches manufactured at — using the — process (24 months at $-15°C \pm 5°C$ and at $-5°C \pm 3°C$, 3 months at $5\pm3°C$). The results conformed to the final specification. There are no significant time-dependent variation and trend observed. The retest period of — months for drug substance is justified when stored at recommended storage condition of —

Drug product, CUBICIN™ (daptomycin for injection), is supplied as a sterile, lyophilized powder (250 mg and 500 mg) for reconstitution with 0.9% sodium chloride injection, USP. There is no excipient used in the manufacture of the drug product. The manufacturing process for the drug product includes

labeling and packaging.

The regulatory specification for CUBICIN™ (daptomycin for injection) is adequately established. The primary stability data is provided on six representative batches (3 in the 250 mg/vial and 3 in the 500 mg/vial) at $5°C \pm 3°C$ (24 months), at $25°C\pm 2°C$ (24 months) and at $40°C \pm 2°C/75\%RH$ (6 months). Statistical evaluation of the primary stability data appears to support a shelf-life of — for CUBUCIN® (daptomycin for injection) in a glass vial with a rubber closure and aluminum seal when stored at the recommended storage condition of $2°C$ - $8°C$. However, a shelf-life of 24 months stored at 2-$8°C$ is recommended for CUBICIN™ (daptomycin for injection) based on overall review of the information provided.

B. Description of How the Drug Product is Intended to be Used

The drug product, CUBICIN™ (daptomycin for injection), is supplied in single-use vials containing either 250 or 500 mg daptomycin as a sterile, lyophilized powder. The contents of daptomycin 250 mg vial and 500 mg vial should be reconstituted with 5 mL and 10 mL of 0.9% sodium chloride injection, USP, respectively. Reconstituted daptomycin should be further diluted with 0.9% sodium chloride injection, USP to be administered by intravenous infusion over a period of 30 minutes. The final concentration of the solution for infusion should not exceed 20 mg daptomycin/mL. The intended clinical dose regimen is 4 mg/kg every 24 hours by 30-minute intravenous (i.v.) infusion to hospitalized patients for 7 to 14

days. A shelf-life of 24 months for CUBICIN™ (daptomycin for injection) is recommended when stored at 2-8°C.

C. Basis for Approval, Approvable or Not-Approval Recommendation

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the production of CUBICIN™ (daptomycin for injection), 250 mg per vial and 500 mg per vial.

After discussion and negotiation with the applicant, acceptable levels for related substances in the drug substance specification were established in conjunction with the Pharmacology/Toxicology reviewer, based on the pre-clinical and clinical data, as well as the history data on manufacturing. The analytical methods and validations for the drug substance and the drug product are properly documented and appear adequate from regulatory perspective.

Pre-approval inspection concluded that all manufacturing, testing and packaging facilities were acceptable in CGMP compliance.

The proposed trade name CIDECIN™ was concerned for mistaking with the name of a currently marketed product (CLEOCIN®) by the Agency. Therefore, the applicant has proposed five candidate names (CUBICIN, ——— and ——— for evaluation. CUBICIN™ is recommended for the trade name for daptomycin by DAIDP.

III. Administrative

A. Reviewer's Signature

Chemist:
Zi-Qiang Gu, Ph.D. {Signed electronically in DFS}

B. Endorsement Block

Chemistry Team Leader:
James Vidra, Ph.D. {Signed electronically in DFS}

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pages of trade

secret and/or

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commercial

information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zi-Qiang Gu
9/12/03 01:04:34 PM
CHEMIST

Jim Vidra
9/12/03 01:09:19 PM
CHEMIST