CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-227

CHEMISTRY REVIEW(S)

DIVISION OF SPECIAL PATHOGEN
AND IMMUNOLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA #: 21-227

CHEMISTRY REVIEW #: 1P (Drug Product) **DATE REVIEWED:** January 17, 2001

SUBMISSION:	**DOCUMENT DATE:**	**CDER DATE:**	**ASSIGNED DATE:**
Original	July 28, 2000	July 28, 2000	August 28, 2000
Amendment	July 31, 2000	July 31, 2000	
Amendment	October 26, 2000	October 26, 2000	
Amendment	December 21, 2000	December 21,2000	

NAME & ADDRESS OF SPONSOR: Merck & Co., Inc.
PO Box 4
BLA-20
West Point, PA 19486-0004

REPRESENTATIVE: Tamara L. Goodrow, Ph.D.
Associate Director, Regulatory Affairs
(610) 397-3051

DRUG PRODUCT NAME:

Proprietary:	Cancidas for Injection
Nonproprietary:	Caspofungin acetate
Code Name/#:	MK-0991, l-743872-003M

PHARMACOLOLOGICAL CATEGORY: Antifungal

INDICATION: Treatment of invasive aspergillosis for patients who are refractory to, or intolerant of, other therapies

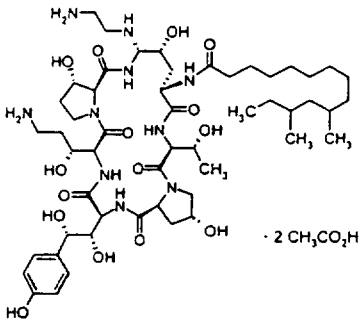
DOSAGE FORM/STRENGTH: Injection/50 and 70 mg/vial

ROUTE OF ADMINISTRATION: Intravenous

CHEMICAL NAME/STRUCTURAL FORMULA: 1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-N^2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3*R*)-3-hydroxy-L-ornithine]pneumocandin B_0 diacetate (salt)

Molecular Formula: $C_{52}H_{88}N_{10}O_{15} \cdot 2\ C_2H_4O_2$

Molecular Weight: 1213.42 **CAS #:** 179463-17-3



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:

CONCLUSIONS & RECOMMENDATIONS:

The NDA submission as amended provides adequate information on the chemistry, manufacturing and controls for CANCIDAS® (caspofungin acetate) for Injection. This application may be approved based on the review of the drug product section.

Gene W. Holbert, Ph.D., Review Chemist

Concurrence:
HFD-590: N. Schmuff

cc:

Original: NDA 21-227	HFD-590: ENavarro	HFD-590: LChan
HFD-590: NSchmuff	HFD-590: GHolbert	HFD-590: DMatecka
HFD-590: SBala	HFD-590: OMcMaster	HFD-590: HMahayni

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-227 CHEM. REVIEW #: 2S (Drug Substance) REVIEW DATE: 1/22/01

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE
Amendment (BC)	12/21/00	12/26/00

NAME & ADDRESS OF APPLICANT:

Merck & Co., Inc.
P.O. Box 4
West Point, PA 19486-0004
(610) 397-3051

CONTACT:

Tamra L. Goodrow, Ph.D.
Associate Director, Regulatory Affairs

DRUG PRODUCT NAME

Proprietary:	CANCIDAS ™
Established:	caspofungin acetate
Code #:	MK-0991
Laboratory Code #:	L-743872-003M

PHARMACOLOGICAL CATEGORY/INDICATION: Antifungal

DOSAGE FORM: Powder for injection

STRENGTHS: 50 mg/vial and 70 mg/vial

ROUTE OF ADMINISTRATION: Intravenous

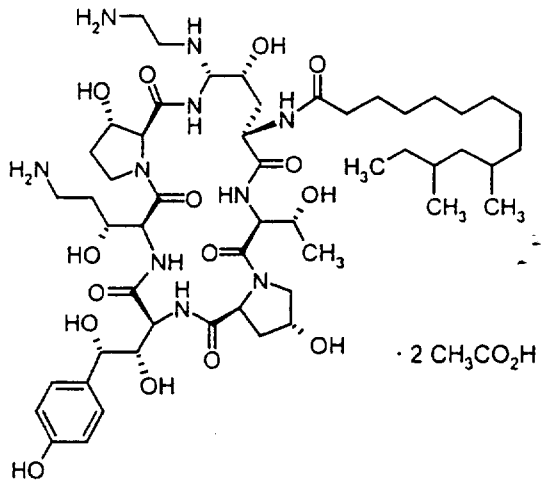
Rx/OTC: Rx

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

Caspofungin acetate; $C_{52}H_{88}N_{10}O_{15} \times 2C_2H_4O_2$; MW = 1213.42
1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-N^2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3*R*)-3-hydroxy-L-ornithine]pneumocandin B_0 acetate

Laboratory Code: L-743872-003M

CAS 179463-17-3



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review date	Letter date
			Acceptable	11/29/00	N/A

RELATED DOCUMENTS:

N/A

CONSULTS:

1. Trademark review (complete, acceptable).
2. Site inspection (complete, acceptable).
3. Environmental assessment (categorical exclusion claim, acceptable).

REMARKS/COMMENTS:

NDA 21-227 provides for caspofungin acetate for injection, which is intended for the treatment of life-threatening systemic fungal infections.

Caspofungin acetate for injection (drug product) has been developed as a sterile, lyophilized formulation for dilution prior to intravenous infusion (50 mg/vial and 70 mg/vial).

The previous (1S) and the current review (2S) are dealing with the drug substance part of the CMC (chemistry, manufacturing and controls) section of this NDA.

The drug product section was reviewed by another chemist from the Division of Special Pathogen and Immunologic Drug Products; HFD-590, Gene Holbert (see chemistry review # 1P for this NDA).

In general, the original NDA submission and the subsequent amendments have provided adequate information on the production of caspofungin acetate drug substance. The details are discussed in the review # 1S (dated November 30, 2000). Several questions and comments regarding the drug substance manufacturing were communicated to the applicant by e-mail on November 30, 2000.

The applicant responded to the Agency CMC questions and comments by e-mail on December 13, 2000 and the follow-up amendment of December 21, 2000 submitted electronically. These responses are discussed in detail in the current review.

These comments and questions dealt with the methods used for testing of the drug substance, qualification levels for the caspofungin acetate impurities, and the proposed retest date for the drug substance.

As per the Agency request, the applicant also has provided a rationale for not proposing microbial limits in the caspofungin acetate drug substance specification. The applicant's response to that request including a commitment to test a total of 25 lots of production-scale caspofungin acetate for microbial purity as part of an on-going study, was found acceptable (for details see the review notes). As per the Agency request, the applicant has provided also the relative retention time (RRT) for all impurities of the drug substance

With regard to the proposed in the original submission conditions and duration of the drug substance storage (retest after 24 months of storage at -70°C), the applicant was requested to propose an expiration date instead of a retest date for the caspofungin acetate based on the fact that

In response to this comment (Question # 8 of the Agency's e-mail on November 30, 2000), the applicant requested maintaining the retest instead of expiration date. The analysis of the provided stability data at in combination with the data at indicated that the drug substance will remain stable for at least In addition, the applicant has stated that for any caspofungin acetate that exceeds the retest period, its quality will be confirmed prior to its formulation to be equivalent to that of drug substance at time of release. Therefore, the applicant's proposal of maintaining the retest date of for caspofungin acetate drug substance stored at was found acceptable.

The December 21, 2000 amendment adequately addressed the outstanding comments and questions regarding the caspofungin acetate drug substance. Also, as per the overall recommendation made by the Office of Compliance, the GMP inspections of all facilities involved in the manufacturing of the both drug substance and drug product for this NDA were found acceptable (see the copy of the acceptable EER included in the review of the drug product section, review # 1P).

CONCLUSIONS & RECOMMENDATIONS:

The NDA submission and amendments provided adequate information on the chemistry, manufacturing and controls for the production of caspofungin acetate drug substance. The drug product was recommended for approval in Gene Holbert's review dated January 17, 2001. The related GMP and product specific inspections of the manufacturing facilities have been completed and found acceptable. From the chemistry, manufacturing and controls viewpoint, the NDA is recommended for approval.

Dorota Matecka, Ph.D.
Review Chemist, HFD-590

Norman R. Schmuff, Ph.D.
Team Leader, HFD-590

cc: Org. NDA 21-227
HFD-590/Division File
HFD-830/DD/CChen
HFD-590/TL/NSchmuff
HFD-590/Chem/DMatecka
HFD-590/MO/ENavarro
HFD-590/Pharm/OMcMaster
HFD-590/PM/LChan
HFC-130/JAllen

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-227 **CHEM-REVIEW #:** 1S (Drug Substance) **REVIEW DATE:** 11/30/00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	7/28/00	7/31/00
CMC Pre-NDA submission	3/15/00	3/17/00
Amendment (M-004)	5/24/00	5/26/00

NAME & ADDRESS OF APPLICANT:

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CONTACT:

Tamra L. Goodrow, Ph.D.
Associate Director, Regulatory Affairs

DRUG PRODUCT NAME

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Established:	caspofungin acetate
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Laboratory Code #:	L-743872-003M

PHARMACOLOGICAL CATEGORY/INDICATION: Antifungal

DOSAGE FORM: Powder for injection

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Rx/OTC: **Rx**

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

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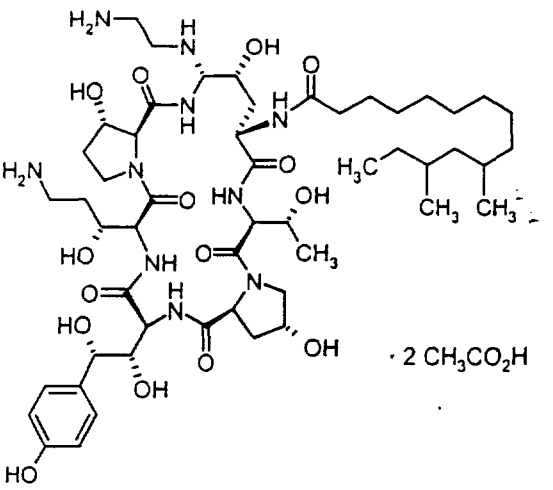
Laboratory Code: L-743872-003M

CAS 179463-17-3



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review date	Letter date
			Acceptable	11/29/00	N/A

RELATED DOCUMENTS:

N/A

CONSULTS:

1. Trademark review (complete).
2. Site inspection (pending).
3. Environmental assessment (categorical exclusion claim, acceptable).

REMARKS/COMMENTS:

NDA 21-227 provides for caspofungin acetate for injection (50 mg/vial and 70 mg/vial) which is intended for the treatment of life-threatening systemic fungal infections.

This review covers the chemistry, manufacturing, and controls (CMC) aspects of the drug substance, caspofungin acetate only. The drug product section is being reviewed by another chemist, Gene Holbert.

CONCLUSIONS & RECOMMENDATIONS:

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of caspofungin acetate drug substance. The related GMP and product specific inspections of the manufacturing facilities have not been completed at this time. From the chemistry, manufacturing and controls viewpoint (drug substance section), the NDA is recommended for approval (provided that GMP inspections are found acceptable and CMC comments and questions listed in the end of this review adequately addressed).

Dorota Matecka, Ph.D.
Review Chemist, HFD-590

Norman R. Schmuff, Ph.D.
Team Leader, HFD-590

cc: Org. NDA 21-227
HFD-590/Division File
HFD-830/DD/CChen
HFD-590/TL/NSchmuff
HFD-590/Chem/DMatecka
HFD-590/MO/ENavarro
HFD-590/Pharm/OMcMaster
HFD-590/PM/LChan
HFC-130/JAllen