CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-227

ADMINISTRATIVE DOCUMENTS

NDA 21-227: CANCIDAS™
(Caspofungin Acetate I.V.)
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1.	Active Ingredient	caspofungin acetate
2.	Strength	50 mg vial and 70 mg vial
3.	Trade Name	CANCIDAS™
4.	Dosage Form Route of Administration	Vial i.v.
5.	Applicant Firm Name	Merck Research Laboratories
6.	NDA Number	21-227
7.	Approval Date	— — —
8.	Exclusivity-Date First ANDA Could Be Submitted	to be determined
9.	Applicable Patent Number *	5,378,804 Expiration Date: March 16, 2013 5,514,650 Expiration Date: March 16, 2013 5,952,300 Expiration Date: March 28, 2017

NDA: 21-227				
Trade Name: Cancidas				
Generic Name: caspofungin acetate				
Applicant Name: Merck Research Laboratories				
Division: 590 (Division of Special Pathogen and Immunologic Drug Product)				
Project Manager: Leo Chan				
Approval Date: January 26, 2001				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes		No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	X	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	5 years			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:				
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1				
Investigation #2				
Investigation #3				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

Signature of PM/CSO Leo Chan /S/ 1/26/01
Date: January 26, 2001
Signature of Division Director /S/ 1/26/01
Date: January 26, 2001

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	021227	**Trade Name:**	CANCIDAS (CASPOFUNGIN ACETATE) INJ
Supplement Number:	000	**Generic Name:**	CASPOFUNGIN ACETATE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF INVASIVE ASPERGILLOSIS FOR PATIENTS WHO ARE REFRACTORY TO/OR INTOLERANT OF/OTHER THERAPIES
Action Date:	~~1/28/00~~ 1/26/01 FC		

Indication # 1 Treatment of invasive aspergillosis in patients who are refractory to, or intolerant of, standard therapies.

Label Adequacy: Inadequate for ALL pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any): There is no oral formulation available for adult patients due to chemical incompatiblities. It is doubtful that an oral formualtion (i.e., suspension) would be possible.

Lower Range	Upper Range	Status	Date
0 months	18 years	Deferred	

Comments: The applicant has submitted a pediatric development program that is currently under review.

This page was last edited on 1/26/01

/S/ — Signature

1/26/01 — Date

Caspofungin Acetate - Aspergillus
Item 16 – Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21227/000
Stamp: 28-JUL-2000 Regulatory Due: 28-JAN-2001
Applicant: MERCK RES
SUMNEYTOWN PIKE BLA 25
WEST POINT, PA 19486

Priority: P Org Code: 590
Action Goal: District Goal: 29-MAY-2001
Brand Name: CANCIDAS (CASPOFUNGIN ACETATE) INJ
Established Name:
Generic Name: CASPOFUNGIN ACETATE
Dosage Form: INJ (INJECTION)
Strength: 50 MG/VIAL, 70 MG/VIAL

FDA Contacts:
L. CHAN (HFD-590) 301-827-2155 , Project Manager
D. MATECKA (HFD-590) 301-827-2398 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation:

ACCEPTABLE on 19-DEC-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-MAY-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: 1112271
MERCK AND CO INC
RT 340
ELKTON, VA 22827

DMF No:
AADA No:

Profile: CFS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-DEC-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 2211017
MERCK AND CO INC
126 EAST LINCOLN AVE
RAHWAY, NJ 07065

DMF No:
AADA No:

Profile: CFS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-OCT-2000

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

DRUG SUBSTANCE STABILITY TESTER

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2510592**
MERCK AND CO INC
SUMNEYTOWN PIKE BLA20
WEST POINT, PA 19486

DMF No:
AADA No:

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-AUG-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STERILIZER

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-SEP-2000**
Decision: **WITHHOLD**
Reason: **FACILITY NOT DOING FUNCTION**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: October 21, 1999	**DUE DATE:** February 10, 2000	**OPDRA CONSULT#:** 99-037

TO : Mark Goldberger, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

TROUGH: Leo Chan
Consumer Safety Officer, Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

PRODUCT NAMES: Cancidas (caspofungin acetate) [redacted]	**MANUFACTURER:** Merck & Co., Inc.

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

OPDRA does not object to the use of the proprietary name, Cancidas.

/S/ 2/8/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 2/8/00

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Table D-1 (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study See Table D-1 for (*Name of clinical study*) Caspofingin Acetate, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☑ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☑ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Richard N. Kender	TITLE Vice President, Financial Eval. & Analysis/Business Development
FIRM/ORGANIZATION Merck & Co., Inc.	
SIGNATURE Richard N. Kender	DATE 5/2/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	"Caspofungin Acetate"	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Richard N. Kender	Vice President, Financial Eval. & Analysis / Business Development
FIRM/ORGANIZATION: Merck & Co., Inc.	
SIGNATURE: Richard N. Kender	DATE: 5/2/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

MEMORANDUM
Jan. 26, 2001

TO: Mark Goldberger, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
FROM: Kenneth L. Hastings, Dr.P.H.
Pharmacology/Toxicology Team Leader, DSPIDP
SUBJECT: NDA 21-227 (Caspofungin acetate; CANCIDAS®)

I have read the Pharmacology/Toxicology review of this NDA written by Dr. Owen McMaster, DSPIDP, and concur with his conclusion that the application is approvable. I have also read the final version of the product label and concur with the pharmacology/toxicology sections (*Carcinogenesis, mutagenesis, and impairment of fertility; Pregnancy category; Overdosage; Animal pharmacology and toxicology).* The information contained in the label accurately reflects data supplied by the Sponsor to support the safety of caspofungin acetate.

Kenneth L. Hastings, Dr.P.H.

APPEARS THIS WAY
ON ORIGINAL

Division Director Memo

NDA 21-227: caspofungin; trade name Cancidas (Merck)

Mark J Goldberger MD MPH

Jan 23, 2001

Overview: Cancidas is the first of a new class of antifungal drugs the echinocandins. The drug is available only in an intravenous formulation. In the initial application Merck has requested an indication for treatment of refractory or intolerant aspergillosis that has not responded to standard therapy. A supplemental NDA for serious candida infections is expected within the next several months. This application was reviewed by the AntiViral AC on Jan 10, 2001. The AC voted 8-0 to recommend approval.

Patients with aspergillosis refractory and/or intolerant to standard antifungal therapy have few therapeutic alternatives and a high mortality rate. To support this indication Merck has submitted data from a non-randomized trial of patients. The details of this trial that included the review of cases conducted by an independent group of experts are in the medical officer review. At the request of the FDA Merck developed and submitted a historical control for this trial. This control group included both patients receiving initial therapy as well as those who were refractory and/or intolerant to other approved therapies. The medical review, the statistical review and a consultative review from OPDRA discuss in great detail the issues of comparability of the historical control with the Cancidas group. Noteworthy problems include differences in duration of therapy prior to entry into the Cancidas and historical group, and a progressive improvement in historical control response rates from 1995 to 1998, the years for which data was collected. The AntiViral Committee also expressed concerns as to the usefulness of the historical controls.

The safety database the applicant included not only the aspergillosis trial noted above, but data from their clinical pharmacology program and data from randomized trials vs amphotericin B and fluconazole in patients with esophageal and invasive candidiasis. Monkeys dosed for 5 weeks showed hepatic necrosis at a dose with 4-6 times the human exposure of from a 70mg daily dose. This finding was not observed in a longer study at a similar dose. Although increased LFTs were observed in the setting of concomitant use of cyclosporine, no evidence of hepatic necrosis was reported. There was also some indication of histamine/infusion related reactions in both pre-clinical studies as well as in the clinical data. These latter reactions are discussed in greater detail in the MO review. An important benefit of this product is the lack of nephrotoxicity that is a major dose limiting toxicity with amphotericin B. Although present infusion related toxicity may in fact be less of an issue as compared to at least some amphotericin products.

Basis for approval: The overall response rate in the aspergillosis trial was 41% as opposed to 17% in the historical control. However due to issues of comparability a formal statistical comparison between the two groups is not appropriate. We believe that

it is likely that the 17% rate underestimates the "true" response rate in such a group. Some of the differences between the groups are noted above and discussed in greater detail in the reviews. Given these concerns I nevertheless believe the following pieces of information when taken together support approval.

A wide variety of data from in vivo animal models demonstrates the antifungal activity of this product in infections due to aspergillus.

The response rate of 41% seen in the open label trial is comparable with recent experience with other products approved for treatment of refractory/intolerant infections due to aspergillus.

The response rate seen in the historical control group is on the lower side of what has been observed in such control groups but is still within the range of previous observations. A comparison between Cancidas and control patients after either eliminating all patients who received prior treatment for a short time or by using the response rate seen in the control group during the last year of inclusion demonstrates the response rates in the two groups to be at least comparable.

Cancidas offers a different and potentially more favorable safety profile as compared to other products currently available for treatment of aspergillus infections. In particular its lack of nephrotoxicity provides an important advantage in the management of patients who are being treated simultaneously with multiple medications.

The proposed indication is for patients with systemic aspergillus infections who are refractory or intolerant to standard therapies. This is a group with almost no therapeutic alternatives and a high mortality rate.

On balance therefore although the available information would not support a claim that Cancidas is superior to available alternative therapies the likelihood that it is worse is quite small, it is accompanied by an advantageous safety profile and patients for whom it is indicated have few if any alternatives.

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID NUMBER: #D000688

DATE: January 17, 2001

FROM: Judy A. Staffa, Ph.D., R.Ph., Epidemiologist
Division of Drug Risk Evaluation II (DDRE II)
HFD-440

THROUGH: Kathleen Uhl, M.D., Acting Director
DDRE II, HFD-440

TO: Mark Goldberger, M.D., Director
Division of Special Pathogens, HFD-590

SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW
Consult – Use of historical controls as comparator group in submission of NDA-21-227 for Cancidas (caspofungin)

Executive Summary

Cancidas™ (caspofungin acetate) is a new antifungal agent, an echinocandin, which is being tested for efficacy and safety in treating invasive *Aspergillus* infections. The data submitted to the Agency (NDA-21-227) under Protocol 019 represent the first efficacy study of this drug for treatment of invasive aspergillosis in humans. Protocol 028 was designed to create a group of historical controls, with which to compare the experience of patients in P019. OPDRA was asked by the reviewing statisticians in HFD-590 to review protocols 019 and 028 to provide some epidemiological insight into the appropriateness of the sponsor's use of non-randomized, non-concurrent historical controls.

A brief review of the medical literature identified three major biases – information bias, bias from secular trends in diagnosis and treatment, and selection bias – that frequently affect comparisons using historical controls. A review of the study protocols 019 and 028 suggests that, despite substantial efforts by the sponsor, these potential biases were not adequately controlled. As a result, these two study populations are not comparable, which is actually a common situation in studies using historical controls. In general, studies with historical controls are considered to generate hypotheses for subsequent confirmation using more rigorous, randomized studies. The persistence of these biases, and the resulting differences between study populations, could act to predispose the historical control group to have a lower success rate and the Cancidas™-treated group to have a higher success rate, independent of treatment with Cancidas™.

I. Introduction

Cancidas (caspofungin acetate) is a new antifungal agent, an echinocandin, which is being tested for efficacy and safety in treating invasive *Aspergillus* infections. The data submitted to the Agency (NDA-21-227) under Protocol 019 represent the first efficacy study of this drug for treatment of invasive aspergillosis in humans. Protocol 028 was designed to create a group of historical controls, with which to compare the experience of patients in P019.

OPDRA was asked by the reviewing statisticians in HFD-590 to review protocols 019 and 028 to provide some epidemiological insight into the appropriateness of the sponsor's use of historical controls. Three questions were detailed as key for OPDRA's focus.

II. Questions raised by HFD-590 statisticians

1. *As a general question, what are the major biases associated with the use of historical controls and what are the implications of these biases?*

   Historical controls are defined as non-randomized, non-concurrent comparators to the current study treatment of interest. The major biases associated with the use of historical controls are as follows:

a. Information bias

This bias can occur if the data collected for the current, treated group is not comparable to that collected for the historical controls with regard to either quality or completeness. For example, if information for the current, treated group is collected prospectively, using research instruments, but the information for the historical controls is collected from abstracting medical records that were not designed for study data collection, bias could result. Most often, information is more accurate and complete for the current, treated group than for the historical controls. This better information could lead to an apparent treatment effect that in actuality is due to differences in the quality of information available.

b. Bias from secular trends in diagnosis and treatment

The difference in calendar time between the experience of the current, treated group and that of the historical controls can also make observed differences difficult to interpret. Changes in other factors, unrelated to the treatment of interest, that occur over time could produce effects that are falsely attributed to the studied treatment. Such factors include:

- Improvements in supportive patient care over time, leading to differences in characteristics of the patient population and their management;
- Temporal trends in mortality in the affected patient population. A valid comparison with the current, treated group would be the baseline mortality of the current patient population, rather than that of a past patient population. This is particularly true if there have been major changes in mortality from the disease over time;
- Different methods of evaluation or assessment of diagnosis or outcome for the same disease over time. These can lead to differences in the severity of disease between the current, treated group and historical controls and/or changes in the ability to assess outcome. Changes in diagnostic technology or standard medical practice are often the reasons for these differences.

c. Selection bias

Selection bias occurs when certain types of patients are selected into the treatment group but not into the control group, or vice versa. For example, if patients who are less severely ill are more likely to be in the current, treated group than in the historical controls group then better survival in the current, treated group could be falsely attributed to the treatment. Randomization is designed to minimize this type of bias, by increasing the probability that the treated and control groups are similar with regard to factors known to affect outcome, as well as unknown or unmeasured factors.

The major implication of these types of biases is to produce an apparent treatment effect when in actuality there is none. There are numerous examples in the medical literature, particularly from the field of oncology, in which treatments believed to be effective based upon comparisons with historical controls were later proven false when evaluated through randomized trials[ii,iii]. The effect size must be large enough to overcome the effects of random error and bias introduced by the design – but since it is hard to quantify the effects of all the biases, it is hard to know how large an effect size would be considered "large enough" to overcome them.

2. *Specific to this application, have the usual biases associated with historical controls been adequately addressed in the design and conduct of Protocol 028?*

A review of the protocol with regard to the biases of concern produced the following observations:

a. Information bias

- Less clear information is available on outcome from the historical controls than from the treated group. For example, the expert panel assessment was conducted very differently, with a panel of three independent experts reviewing extensive materials for the treated group, but only one of the site investigators reviewing limited records-based information for the controls. These differences could bias the success rates down in the historical control group, as evidenced by an overall success rate of 16-17%. Background information from the medical literature suggests that amphotericin B has ~40% success rate.
- Different criteria were used to assess safety information in the treated and control groups – but this should bias toward finding more problems in the treated group. Fewer safety issues might be recorded in the medical records.
- The patients in 019 were followed out of the hospital; for 028 patients, follow up ended at discharge due to lack of availability of further records.
- Difficult to ascertain which patients are refractory to treatment, as opposed to intolerant, based on retrospective information collection.

b. Bias from secular trends in diagnosis and treatment

- This bias was clearly demonstrated in HFD-590 biostatistician's table of increasing success rates in the historical control group by year. This implies that the success rate, had concurrent control patients been recruited in 1999 and 2000, would have been somewhat higher.
- The inclusion criteria were slightly different – in the treated group, patients could have had prior therapy with an investigational azole. In the historical control group, it is likely that this drug was not available at that time. Only one treated patient was listed as having taken this drug, but it may have been included in the "multiple drug" category as well, and if so, it could explain some of the observed effects.

- All of the P-019 patients received prior therapy with anti-infectives; only about 50% of 028 were recorded as receiving them because only information regarding nephrotoxic anti-infectives was abstracted from the medical record. There may have been other differences between the populations, based on changes in management and treatment of underlying conditions due to the availability of newer immunosuppressive agents and other diagnostic advances.

c. Selection bias

- In the historical control group, 282 patients were incorrectly screened out of one study site, based upon having < 2 sputum samples. The sponsor has tried to address this issue by excluding all patients from this site from the analysis and found a very small decrease in the response rate. They determined, however, that it is not feasible to review these patients' records to determine these patients' eligibility.
- There were differences in the distribution of domestic and foreign patients between treated and control groups, which could impact on the success rate of treatment if standards of patient care and support differ across countries. The European patients also seemed to have a higher response rate than the U.S. patients, supporting potential differences in care and/or diagnosis.
- There were substantial differences in total days of treatment, with the treated group having a much longer duration of therapy with any antifungal therapy (see biostatistician's analysis). The observed effect could be due to longer antifungal therapy, rather than therapy with caspofungin. The length of antifungal therapy prior to study enrollment (at 7 days after treatment initiation for historical control group, but at 7 days or longer for treated group) was also much longer for the Cancidas ™-treated patients, perhaps contributing to their higher success rates.
- The exclusion criteria were different between the two studies and more relaxed for the historical control group. For example, there were no exclusions of patients from the historical control group based on abnormal laboratory values. This may have allowed sicker patients into the control group, whose outcomes would be worse. Particularly troublesome is the exclusion criterion in the treated group of "Patients not expected to survive at least 5 days", which was not applied to the historical control group.
- Patients had to be alive to be treated with Cancidas in P-019. Patients in 028, however, could be included after death, based on autopsy samples providing confirmation of *Aspergillosis*. This could imply a lesser severity of illness in 019, with patients recruited at an earlier phase of illness – particularly in light of the exclusion criteria in the previous bullet.

These observations suggest that the potential biases associated with historical control studies were not adequately controlled in Protocol 019 and 028.

3. *Are the two study populations, Protocol 019 and Protocol 028, comparable? If so, what conclusions can be drawn?*

- No, these two study populations are not comparable, which is actually a common situation in studies using historical controls. In general, studies with historical controls are considered to generate hypotheses for subsequent confirmation using more rigorous, randomized studies [iv].
- The notable differences between the treated group and the historical control group provide alternative explanations for the effects seen, rather than being due to the tested treatment. These alternative explanations need to be ruled out before the effects can be reasonably attributed to the drug. It can be hard to do that, particularly since there are likely effects due to variables we don't know about or can't measure – this is why randomization is so important.
- It is difficult to draw conclusions about safety, given no concurrent comparator. However, it seems that safety information is better ascertained in the treated group than from the medical record. Since the safety of this product relative to current therapy appears to be an important issue, it needs to be considered, but in the context of an often-fatal illness it may not be the primary issue of interest. The small sample size of the treated group (n<70) also makes the detection of safety concerns very difficult and limited only to the most commonly occurring in a very complex patient population.

III. Conclusions

A review of the study protocols 019 and 028 suggests that, despite substantial efforts by the sponsor, several potential biases were not adequately controlled. As a result, these two study populations are not comparable, which is actually a common situation in studies using historical controls. The persistence of these biases, and the resulting differences between study populations, could act to predispose the historical control group to have a lower success rate and the Cancidas™-treated group to have a higher success rate, independent of treatment with Cancidas™.

Signed 1/17/01
Judy A. Staffa, Ph.D., R.Ph.
Epidemiologist

Cc:

NDA 21-227
HFD-590 Division file
HFD-590 Goldberger/Roca/Navarro/Higgins/Dixon/Chan
HFD-440 Uhl/Piazza-Hepp/Staffa/Singer/Dempsey

References

[i] Gordis L. *Epidemiology.* W.B. Saunders Co, Philadelphia; 1996: p.222.

[ii] Moertel CG. Improving the Efficiency of Clinical Trials: A Medical Perspective*Statistics in Medicine* 1984;3:455-65.

[iii] Pinsky CM. Experience with Historical Control Studies in Cancer Immunotherapy*Statistics in Medicine* 1984;3:325-29.

[iv] Gehan EA. The Evaluation of Therapies: Historical Control Studies*Statistics in Medicine* 1984;3:315-24.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: January 12, 2001

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

ADDRESS: Merck Research Laboratories
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West Point, PA 19486
Phone (610) 397-3051
Fax (610) 397-2516

FROM: Leo Chan, R.Ph.

IND: [redacted]

SUBJECT: CANCIDAS™ OPDRA Review

Please refer to Merck's correspondence dated September 29, 2000, received October 2, 2000, which provides hard copies of certain draft primary packaging components for CANCIDAS™ for use by the Office of Post Marketing Drug Risk Assessment (OPDRA) in their second review of the CANCIDAS trademark.

After consultation with OPDRA, the Division has the following comments on the submitted carton labeling:

1. The Division requires a labeling change from 0.9% Sterile Saline for Injection to 0.9% Sodium Chloride Injection.
2. The Division requires a USUAL DOSAGE statement. The Division's recommendation include adding "Usual Dosage: See package insert" to the carton and vial labels.
3. The Division recommends changing the red band (indicating the strength on the primary display panel) to another color to provide better contrast on both the 50mg vial and 50mg carton labels.
4. The Division recommends moving the colored band to the area above the "Rx Only" statement as on the vial labels for both cartons described in 3. This move would make the strength more prominent.
5. The Division recommends providing the resultant concentration per mL when providing reconstitution directions.

The Division does not object to Merck's proposed use of the CANCIDAS tradename.

If you have any further questions, please contact me at (301) 827-2127.

/S/

Leo Chan, R.Ph.
Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: January 23, 2001

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

ADDRESS: Merck Research Laboratories
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Phone (610) 397-3051
Fax (610) 397-2516

FROM: Leo Chan, R.Ph.

NDA: 21-227

SUBJECT: Phase 4 Commitments for CANCIDAS™

Please refer to your correspondence dated January 18, 2001, received January 18, 2001, which outlines Merck Research Laboratories' proposed Phase IV commitments. In preparation for our teleconference, the Division is providing the following comments below.

1. **Evaluate the safety and pharmacokinetics of higher doses of caspofungin in healthy subjects and patients with aspergillosis who are refractory or intolerant of standard therapies.**

   The Division believes it would be beneficial to obtain efficacy information on the above-defined patient population. The Division would also like additional safety information on treatment regimens equal to, or longer than, 28 days. This would be particularly important for the 50-mg dose treatment regimen.

   The three goals (your proposal and our two additional requests) could potentially be accomplished with a dose-ranging study.

2. **Obtain additional clinical safety information on patients receiving concomitant caspofungin and cyclosporin.**

   In addition to the clinical safety information, the Division would like Merck to obtain trough concentrations from patients receiving concomitant caspofungin and cyclosporine.

3. **Evaluate use of combination therapy of caspofungin and other antifungal agents in the treatment of invasive aspergillosis using animal models and clinical studies in patients refractory or intolerant of standard therapies.**

   The Division agrees in principle to Merck's proposal.

4. **Continue to evaluate population pharmacokinetics for all ongoing caspofungin in Phase III studies.**

   In addition to continuing the evaluation of the population pharmacokinetics of caspofungin in all ongoing caspofungin Phase III studies, the Division would like Merck to obtain trough samples for establishing attainment of steady state.

5. **Continue to monitor for resistance of caspofungin in clinical trials and characterize the resistance, where possible.**

   The Division agrees in principle to Merck's proposal.

6. **Submit final clinical study reports for protocols 030, 032, and 035.**

   The Division would like Merck to propose a timeline for the submission of these study reports.

The Division would like to introduce two additional Phase 4 commitments for discussion:

A. The Division would like annual updates on the status of the progress of Merck's discussions with recognized experts in the fungal community (such as the Mycoses Study Group and the EORTC) regarding the definition and prioritization of research issues surrounding the clinical use of caspofungin.
B. The Division would like Merck to provide descriptive information on the patient population that is treated with caspofungin, including the number of patients that have been treated, demographics, indication for use, underlying disease, concomitant medications and duration of therapy. This descriptive information would provide a needed context in which to evaluate any safety concerns. These data may be collected in a variety of ways, for example, through the use of large inpatient databases that contain medical and pharmacy information and/or use of automated databases which capture hospitalization data for special populations (AIDS patients, transplant patients) for reimbursement purposes. This can be done initially on a quarterly basis, with the intent to re-evaluate in a year's time to determine if a another time interval would be more appropriate.

If you have any further questions, please contact me at (301) 827-2127.

/S/

Leo Chan, R.Ph.
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: December 22, 2000

TO: Tamra L. Goodrow, Ph.D.
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Fax (610) 397-2516

FROM: Leo Chan, R.Ph.

NDA: 21-227

SUBJECT: Use of Historical Controls as a Comparator Group

After consultations with our biostatisticians and the Office of Post-Marketing Drug Risk Assessment, the Division has outlined some concerns associated with Protocol 028 as a comparator to Protocol 019.

1. **Information Bias** - We have concerns that the data collected for the historical controls may not be comparable to that collected for the current, treated group, with regard to either quality or completeness.
   a. Assessment of outcome associated with the historical controls is not as rigorous as for the treatment group (no data received yet on an expert panel assessment for this group). This could bias the success rates down in this group, as evidenced by the overall rate of 16-17%. Of note, the background information for amphotericin B suggests an approximate baseline success rate of 40%.
   b. Different criteria were used to assess safety information in the treated and control groups. As a result, there exists the potential of recording fewer safety issues from medical records in the historical control group.
   c. There exists a potential difficulty in differentiating refractory from intolerant patients in the historical control group, making it difficult to assure appropriate comparison to the refractory patients identified more clearly in the 019 protocol.
   d. The follow-up time period was different between the historical control and treatment groups. The patients in 019 were followed out of the hospital while patients in 028 were followed-up only to the time of discharge. This clearly impacts on the information available for each group.

2. **Bias from secular trends in diagnosis and treatment** - The difference in calendar time between the experience of the current, treated group, and that of the historical controls can make observed differences difficult to interpret due to potential differences in supportive patient care

over time. Our main concern is that these changes in other factors could be producing some of the observed effect rather than the studied treatment.

a. Historical control success rate by year of enrollment increases from 1995 (17%) to 1998 (28%). It is uncertain, but possible that the rates for 1999 and 2000 would be even higher if concurrent controls were used.
b. The difference in the inclusion criteria between the two study groups allowed for the possibility of patients having prior therapy with an investigational azole in the treatment group, which was likely unavailable at the time of the historical control group.
c. Potentially, there exist differences in drug therapy baseline and/or concomitant therapy between patients of P019 and P028. For example, it appeared more 028 patients received corticosteroids than 019 patients did, but it is difficult to determine this because of different classification systems used in the tables. One hundred percent of 019 patients received anti-infectives, whereas only 50% of 028 patients did.
d. We are also concerned about potential differences over time in the ability to manage and treat the underlying disease of these patients, which could differentially affect the outcome of these studies.

3. **Selection Bias** - Certain types of patients are selected into the treatment group but not into the control group, or vice versa.
   a. In the historical control group, 282 patients were incorrectly screened out of the study based upon having < 2 sputum samples. It appears that it is not feasible to sample these patients' records to determine their eligibility so the impact cannot be assessed.
   b. There were differences in the distribution of domestic and foreign patients between the treatment and control groups. The success rate of treatment could be influenced if standards of patient care and support varied greatly between countries.
   c. The duration of therapy between the two studies was substantially different (patients in 019 received longer anti-fungal therapy in total).
   d. The exclusion criteria were somewhat different for the two studies. The control group appeared to allow sicker patient enrollment, which would affect the outcome.
   e. Deceased patients in P028 could be potentially included in the study based on autopsy samples providing confirmation of *Aspergillosis*. This could imply a lesser severity of illness in P019.

The Division believes these issues will be potential topics of discussion at the January 10, 2001 Advisory Committee meeting. The Division believes it would be beneficial to address these issues at our January 2, 2001 meeting.

If you have any further questions, please contact me at (301) 827-2127.

/S/

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Division of Special Pathogen and Immunologic Drug Products