CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-227

MEDICAL REVIEW

Medical Officer Review of NDA 21-227

Cancidas ® (caspofungin acetate for intravenous injection) for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Date Submitted:	28 July 2000
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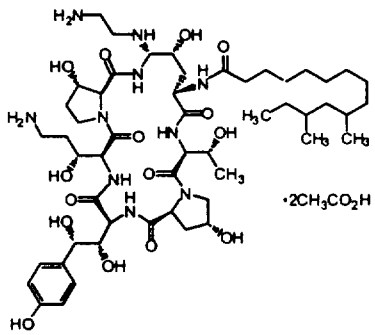
Applicant: Merck & Co., Incorporated
P.O. Box 4, BLA-20
West Point, PA 19486-0004
Telephone number: 610.397.3051
Contact person: Tamra L Goodrow, Ph.D.
Associate Director, Regulatory Affairs

Drug:

Proprietary name:	Cancidas ®
Generic name:	caspofungin acetate for intravenous injection
Chemical name:	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 B0 diacetate (salt)
Molecular formula:	$C_{52}H_{88}N_{10}O_{15} \cdot 2C_2H_4O_2$
Molecular weight:	1213.42
Molecular structure:	

Drug class:	antifungal
Formulation:	50-mg vial, 70-mg vial for intravenous injection
Route of Administration:	intravenous
Related INDs:	[redacted]

TABLE OF CONTENTS

APPEARS THIS WAY ON ORIGINAL

Executive Summary of NDA 21-227:

Proposed Indication and Usage:

This new drug application seeks approval for the following indication, reproduced from the original proposed label contained in the NDA: "Cancidas® is indicated for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies."

Proposed Dosage and Administration:

"A single 70 mg loading dose should be administered on Day 1, followed by 50 mg daily..... Although there is no information to demonstrate an increase in efficacy with higher doses, available safety data suggests that an increase in dose to 70mg daily may be considered in patients without evidence of clinical response.....In patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), after the initial 70 mg loading dose, Cancidas® 35mg daily is recommended."

Recommendations:

a. It is recommended that this NDA be approved for the treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies.

b. The following are recommendations for the drug label:

2. The following clause should be added as a modifier in the Indications section: "Cancidas® *has not been studied as initial therapy for invasive aspergillosis.*"
3. The following clause should be added in the Precautions section: " *General precautions: The efficacy of the 70 mg dose*

Summary of Clinical Findings:

a. Summary of Efficacy:

The applicant submitted data from one pivotal multi-center, international study (Study 019) to support the efficacy of Cancidas® in the treatment of patients with invasive aspergillosis who were refractory to or intolerant of other therapies. This was an estimation study designed to demonstrate that at least 30% of patients refractory to or intolerant of other therapies will respond to Cancidas®. The efficacy of Cancidas® from this study is compared to the outcomes in a multi-center derived historical control consisting of patients with in invasive aspergillosis with similarly limited therapeutic options. To be eligible for both studies, patients had to have definite or probable invasive aspergillosis as defined by the Mycoses Study Group Criteria. A successful

outcome included complete resolution or improvement of baseline parameters, whereas stabilization or progression of disease were unsuccessful outcomes. An independent expert panel consisting of three mycology experts evaluated outcome at end of treatment in the Study 019. Similar criteria for diagnosis and outcome were applied to a historical control (Study 028/029), identified from a chart review of patients diagnosed in the four years preceding the study. The limitations of the historical control study preclude a statistical comparison of the clinical status of patients in Study 019 to those in Study 028/029. The differences between the Cancidas® treated patients and the historical control, and the potential biases that limit this comparison, are summarized in the review of Dr. Cheryl Dixon, Biostatistical Reviewer, and in the body of this review. The discussion in this summary is therefore limited to the efficacy in Study 019.

Sixty-three of 69 patients enrolled in Study 019 were evaluable at end of treatment. The majority of patients in the Cancidas® study were refractory to at least 7 days of conventional therapy (84%). The mean age of the patients in the pivotal study was 47 years old. There were more males than females (42/63 or 66.7%), and a minority of patients came from US sites (29/63 or 46%) compared to the European sites. The majority of infections were definitively established on the basis of histopathological parameters, in either the pulmonary or the extrapulmonary sites. Cases of probable pulmonary aspergillosis utilizing less stringent criteria comprised only 28.6% of all cases. Hematologic malignancies were the majority of the underlying immunocompromising conditions predisposing to aspergillosis (41/63 or 65.1%). Twenty patients also underwent a bone marrow transplant (20/63 or 31.7%). Three patients had no defined risk for invasive aspergillosis. At baseline, 22.2 % of the population was neutropenic and a greater proportion (36.5%) was receiving immunocompromising doses of steroids.

Study 019 found the Clinical Response at the follow-up assessment (test of cure) to have a success rate of 41% (includes complete and partial responses). The Division concurred with this analysis of efficacy performed by a panel of 3 experts employed by the applicant. The expert panel analysis excluded patients from the analytic population where confirmation of the diagnosis was based on microbiologic information obtained after inclusion, as well as information obtained postmortem. The Division's efficacy analysis in patients who received 1 dose (intent-to-treat, ITT) or who received 7 days of treatment (clinically evaluable, CE), confirmed the overall efficacy of Cancidas®. Cancidas® achieved clinical success rates between 38.5% and 50% in the ITT and between 44.6% and 54% in the CE analysis in the Division analysis, depending on the subpopulation studied (refractory, intolerant or both). There were successful outcomes in patients with traditionally poor responses to therapy for invasive aspergillosis, including patients with baseline neutropenia, acute leukemia, patients undergoing bone marrow transplantation, and patients with graft versus host disease. A successful outcome was common in patients with less severe underlying immunocompromise (two patients with CNS infection who were diabetic or had a stable renal transplant) or with successfully treated underlying disease (54.5% success rate in the hematologic patients whose disease was in remission). Two of four patients considered complete cures had surgical extirpation of the involved sites, one patient received itraconazole together with Cancidas®. Twenty patients were evaluable 4 weeks after the end of therapy, one of these patients relapsed. There were no successes in persistently neutropenic patients. Two of six patients with suspected or proven CNS infections were treated successfully, whereas CNS aspergillosis developed despite treatment in 2 additional patients.

Study 019 provided a microbiological evaluation in support of the invasive aspergillosis indication, although methodological difficulties unique to the indication limit the utility of this information. Of 22 patients with a successful clinical outcome, 6 patients had microbiologic persistence, whereas all 18 microbiologically evaluable clinical failures had persistently positive cultures. Sufficient clinical evidence of activity against *Aspergillus fumigatus* (8/33 or 24.2%) was demonstrated. There was insufficient evidence of activity to support efficacy against *A. flavus* (5/9) and *A. niger* (1/4). There was no correlation between microbiological susceptibility to Cancidas® and clinical outcome. Treatment did not alter the MICs of subsequent clinical isolates.

In this single pivotal study of efficacy of Cancidas® clinical success at end of therapy was ~40%. This success rate is comparable to the success rates of other agents reviewed and approved by the Division for this indication, and is similar to the 30% efficacy ascribed to amphotericin B treatment reported in the medical literature (see Review). The efficacy from this study, buttressed by the *in vitro* evidence of susceptibility, the efficacy in clinically analogous animal models, as well demonstrated antifungal activity in the supportive studies are the basis for approval of Cancidas® for invasive aspergillosis in patients with limited therapeutic

options. Nevertheless, the limitations in information regarding the drug's activity for patients with aspergillus infections that have not been studied must also be pointed out. The efficacy attributable to Cancidas® alone is difficult to evaluate in patients that received prior intensive therapy. Cancidas® has been shown to be efficacious only in patients previously treated with other antifungals and its efficacy, when given as a single agent as initial therapy, is not known. The efficacy of Cancidas® alone or in combination with another antifungal agent needs to be studied in patients refractory to or intolerant of amphotericin B, as well as in initial therapy. Cerebral aspergillosis developed in 2 patients in the study despite Cancidas® treatment, suggesting a limitation to the drug's efficacy in cerebral aspergillosis. In addition, other CNS mycoses such as Histoplasmosis and Cryptococcal meningitis developed despite Cancidas® in the HIV patients enrolled in the mucosal candidiasis trials. It is unclear whether this is attributable to limited activity against other mycoses, or whether it is due to lack of CNS distribution. Nevertheless, clinicians should remain aware of the possible development of CNS infections despite Cancidas® therapy, until the distribution of the drug in the central nervous system is better understood. The efficacy of higher doses of the drug against aspergillus must also be addressed.

The impact of a drug's ability to kill the organism (fungistatic vs. fungicidal effect) on eventual outcome (relapse) has not been addressed in clinical studies. Future studies describing the relapse rates of invasive aspergillosis in patients treated with Cancidas® compared to polyenes, will allow an evaluation of the impact of the "cidal" activity of an antifungal agent. In the population of patients whose aspergillus infection has an accelerated progression rate, or in the persistently neutropenic patient with traditionally poor outcomes from invasive aspergillosis, the difference in cidal or static activity may be amplified, particularly when therapy is given alone or as initial therapy. The label currently emphasizes that Cancidas® not be used as initial therapy, until its efficacy can be compared to the fungicidal agents in this clinical setting.

b. Summary of Safety:

The safety database for this indication consisted of the 69 patients in Study 019, supplemented by data from the clinical pharmacology trials and studies in mucosal candidiasis. The efficacy results in the candidiasis studies however, were not reviewed as part of this application. Of 612 subjects that received single or multiple doses of Cancidas® over half (n=338) were patients with fungal infections, while the rest consisted of 274 healthy subjects in clinical pharmacology trials. The majority of patients received a loading dose of 70 mg on day one, followed by 50-mg doses on subsequent days. Two hundred seventy seven (82%) patients in the mucosal candidiasis trials received 10-14 days exposures, whereas 61 (18%) patients in the invasive aspergillosis trials received mean drug exposures of about 30 days. Forty-five patients (19%) who received the label dose of 50 mg had exposures greater than 14 days; a minority of these patients received the drug for 21 days or more. Seventy one (21%) of patients with fungal infections received the highest recommended therapeutic dose (70 mg), whereas in clinical pharmacology trials, 57% of healthy subjects received the highest dose strata (>50 mg), consisting of single doses in 48%. Only one patient on cyclosporine received Cancidas® concomitantly; women comprised 21% of patients with Cancidas® exposures, and there was one pediatric patient (a 15 year old with hematologic malignancy and invasive aspergillosis). Two patients received repeated exposures of the drug.

Patients with fungal infections reported more adverse events than healthy subjects and of these adverse events, patients with HIV infections had more adverse events attributed to Cancidas® (48.3% drug-related adverse events in patients with mucosal candidiasis vs. 24.8% for healthy subjects and 14.5% for patients with invasive aspergillosis). There were more deaths in the invasive aspergillosis patients and their adverse events were more likely attributed to the underlying disease. Only one patient in the invasive aspergillosis study had a serious drug-related adverse event; that of a patient post-allogeneic bone marrow transplant for non-Hodgkin's lymphoma who developed hypercalcemia and renal insufficiency for which an alternative etiology could not be found. One other patient enrolled after the study cut-off date developed an anaphylactic adverse event that responded to diphenhydramine and corticosteroids. More patients with invasive aspergillosis had drug discontinuations generally for progression of underlying disease and for events unrelated to drug. Fever and infusional toxicities constituted the most frequent adverse events, occurring at a frequency generally lower than for amphotericin B (16.75 and 18.6 % respectively for Cancidas® compared to 69.7 and 23.6% for amphotericin B, respectively). While respiratory adverse events in general were more frequent for amphotericin B, more patients who received Cancidas® had bronchitis symptoms and symptoms resembling upper respiratory tract

infections, including "colds" as compared to amphotericin. Twenty-one patients developed pulmonary infiltrates. Only one of these events was considered drug related. Seven of these twenty-one adverse events occurred in the invasive aspergillosis studies, 14 were reported in the mucosal candida studies. These adverse events were indistinguishable from PCP in the latter and from progression of invasive aspergillosis in the former. Other drug related rare adverse events that may be important include hypercalcemia and renal insufficiency (1 case) and histamine mediated responses, including anaphylaxis. These adverse events are known to occur more frequently with amphotericin B.

Elevations of serum transaminases and signs of histamine release were identified in pre-clinical studies and were specifically sought for in the clinical studies. There was one case of anaphylaxis, whereas other patients showed local and systemic signs of histamine release despite the frequent co-administration of corticosteroids in the invasive aspergillosis patients and antihistamines in the mucosal candidiasis blinded studies. Clinically significant transaminase elevations (>5X the ULN) with bilirubin elevations appeared to occur at a frequency (2%) similar to that of fluconazole.

The concomitant use of Cancidas® and cyclosporine is currently not recommended in the label. Single doses of cyclosporine administered to healthy subjects in interaction studies appeared to accentuate the hepatotoxic potential of Cancidas®. It is unclear whether the elevations in transaminases occurred as a consequence of increased exposure to Cancidas® (Cancidas® AUCs increased by 35% with cyclosporine co-administration). Cyclosporine is the most frequently used transplant immunosuppressive and this lack of information will likely be a limitation to the safe use of the drug. The clinical significance of this interaction in patients receiving multiple doses of both drugs should be addressed by the applicant in future studies as a phase IV commitment.

Tacrolimus levels are reduced in patients receiving concurrent Cancidas®. This interaction is particularly important since invasive aspergillosis can develop well beyond the initial post-transplantation period, when tacrolimus monitoring may be measured less frequently, and when target levels are lower than in the initial post transplantation period. However, given that Cancidas® is an intravenous drug, and given the known drug-drug interaction profile for tacrolimus, it is likely that severely ill patients receiving both drugs intravenously, will have tacrolimus levels monitored more frequently. Co-administration of caspofungin with tacrolimus did not appear to increase the baseline hepatotoxic potential of Cancidas®.

No interactions have been noted with amphotericin B and itraconazole, as well as mycophenolate mofetil. Cancidas® is neither an inhibitor of nor a substrate for cytochrome P450 isoenzymes and interaction with other drugs utilizing this enzyme is therefore not anticipated. Initial population pharmacokinetic studies in patients that concomitantly received nelfinavir and cytochrome 3A4 inducers, however, indicate enhanced clearing of Cancidas® independent of the cytochrome P450 interaction. These include the antiretroviral nelfinavir, and a broad array of other drugs such as dexamethasone, phenobarbital, carbamazepine, phenytoin, rifampicin, and other cytochrome 3A4 inducers. These initial studies indicate that reduced levels of Cancidas® may occur with their concomitant use, although the mechanism appears to be unclear. The magnitude of these initial observations should be studied as phase IV commitments, to allow better dosing recommendation with their concomitant use.

The supportive safety information in the studies presented compares the safety of Cancidas® to the desoxycholate formulation of amphotericin B and fluconazole. There is no comparative information against the lipid formulations of amphotericin B and of itraconazole, currently the drugs more often employed for invasive aspergillosis. Nevertheless, against amphotericin B, Cancidas® appears to have a favorable safety profile, as do the other drugs approved for this indication.

The safety database contains limited information on the longer (>14 days) drug exposures and at the higher (≥ 70 mg) doses. Since it is likely that higher dose and longer durations will be seen in the context of clinical use of the drug, additional safety data is needed for both higher doses and longer treatment durations. The exclusionary criteria in the studies eliminated patients who received cyclosporine and had used a broad range of metabolic inducers. Characterization of the safety of Cancidas®, in addition to a description of the pharmacokinetic interaction studies described above, in these areas of limited information needs to be addressed in the applicant's phase IV study commitments.

Based on the above information, the label should contain the following information: the precaution section should include information on the limited dose exposures for the highest dose and the longer treatment durations. It should also warn of lower drug concentration with the concomitant use of nelfinavir and other metabolic inducers, as well as warn about low drug levels in patients on tacrolimus. The precautions section should also include a statement regarding the possibility of histamine mediated reactions, as well as a statement about the development of pulmonary infiltrates. The warning section of the proposed label contains information on the possible interaction with cyclosporine.

Risk -Benefit Assessment:

The aggregate of information supporting the efficacy of Cancidas® in invasive aspergillosis includes the efficacy of caspofungin demonstrated in the open label study (Study 019), the *in vitro* studies and efficacy in animal models of invasive aspergillosis, the reported antifungal activity in supportive studies, a comparison of this information to the known efficacy of other antifungals from the clinical reviews of NDAs submitted to the Agency, and the reported efficacy of alternative antifungal agents in the literature. The drug was established to be active *in vitro* using NCCLS modified methods, prolonged survival in mice and rabbits and was reported to have antifungal efficacy in mucosal candidiasis. In Study 019, strict criteria were utilized to define disease as well as outcome. In addition, this information was independently reviewed by an expert panel, which had full access to source data. The expert panel efficacy rate of 41% for Cancidas® approximates the range of 25% complete response to amphotericin B to 57% for the lipid complex of amphotericin B recently reported in the literature (15, 16). In addition the 41% caspofungin response rate is within the range of 27 to 62% established efficacy of the lipid formulations of amphotericin B, as well as of itraconazole, reported in the FDA clinical reviews of the NDAs of these alternative antifungal agents (18-21).

Cancidas®'s most prominent adverse events observed were fever and infusional toxicities. These occurred with less frequency, and were generally less severe than those seen with amphotericin B. Further, they are potentially amenable to pharmacological procedures (e.g. antihistamines and/or corticosteroids), as currently employed with amphotericin B. Additional preliminary safety data from clinical trials in patients with candida infections indicate a hepatotoxic potential comparable to fluconazole. In addition, rare adverse events such as hypercalcemia, pulmonary infiltrates, and renal insufficiency were also reported, although their drug-relatedness could not be established in this sick population.

The outcome of patients with invasive aspergillosis who are refractory to or intolerant of treatment remains dismal. The historical control outcome in this NDA describes a success rate of 16.9%, and an even more miniscule 4.5% in hematologic patients with poorly controlled underlying disease. In other historical controls submitted to the agency, the response to amphotericin B, varied from 10% to 43%, and the Cancidas® outcomes in the prospectively treated patients was clearly similar to these success rates. Nonetheless, untreated invasive aspergillosis is a fatal disease. A review of the efficacy and safety of Cancidas® in this NDA favors the approval of this agent for a severe disease such as invasive aspergillosis in patients refractory to or intolerant of other therapies.

Dosing:

The proposed dose is a single 70-mg loading dose on day 1 followed by daily 50-mg doses, the duration of therapy to be determined by the treating physician. For patients without evidence of a clinical response, the applicant proposes a higher dose of 70 mg based on available safety information. The convention of increasing doses of currently available antifungals in patients with invasive aspergillosis who do not respond to initial therapy is not well supported by evidence of improved efficacy. Nevertheless, at the advisory committee discussing the efficacy and safety of Cancidas®, the invited experts predicted that escalated doses of the drug would likely be used in the same manner as the other antifungals. To provide some guidance for the clinician who may be inclined to escalate the dose in the face of clinical failure in the patient with limited therapeutic alternatives, the option to increase the daily dose to 70 mg is described in the label.

The minimum lethal dose of caspofungin in preclinical studies was 50 mg/kg in rats; this is approximately 8-10 times the recommended human daily dose. There is no reported overdose experience in the clinical studies submitted to the NDA. In these studies, the highest dose exposure was 100 mg, administered as a single dose to 5 patients. This dose was well tolerated.

There is little safety information for exposures at the highest proposed dose (70 mg) and for longer durations (>14 days). Compared to candidiasis, invasive aspergillosis is conventionally treated with higher doses of all available agents, for much longer durations than 2 weeks. In addition, drug combinations and repeated courses of therapy are patterns of use of antifungals for invasive aspergillosis. It is anticipated therefore, that Cancidas® will be used in similar ways when the drug is marketed for this indication, and additional safety information on the higher dose when used for longer periods will help guide dosing for this indication.

There is insufficient evidence to exclude a dose relationship for transaminase elevations, because of the confounding influence of cyclosporine and tacrolimus co-administration in the clinical pharmacology studies, and the limited number of patient's exposures and doses studied in the clinical studies. While the anticipated adverse reactions from the higher dose may not offset the anticipated benefit for a severe disease such as invasive aspergillosis, they may offset the benefit for conditions such as mucosal candidiasis where treatment alternatives are available and outcome not as dire.

In patients with mucosal candidiasis, the lower dose (35 mg) is associated with less efficacy compared to the efficacy achieved with the 50-mg dose. There is no similar evidence presented from dose ranging studies for invasive aspergillosis to suggest that higher dose levels are more efficacious. Limited animal data suggests that higher doses do not translate into improved survival for invasive aspergillosis. Because of the severity of this infection, the efficacy achieved with the 50-mg daily dose, and the favorable safety profile, and the anticipated clinical use of the drug, the efficacy of higher doses of caspofungin should be established in phase IV studies to provide better dosing guidance. The limited information regarding the safety of the increased 70-mg dose, as well as the absence of efficacy information to support such a modification in patients with no clinical response, is in the proposed label.

Special Populations:

1) Pediatrics: Pediatric patients constitute a great proportion of the population at risk for fungal infections, including invasive aspergillosis in children with hematologic malignancies, which behaves similarly as it does in adults. Information on Cancidas®'s pharmacokinetics and safety in children could extend the benefits of its efficacy to this population.

2) Gender: Because pharmacokinetic studies indicate a 20% increase in AUC for caspofungin in women compared to men and since the toxicity profiles appears to show an increase of drug related reactions in subjects with a lighter frame, women may have a higher incidence of adverse events. There were a few females in the studies of patients with infections and it is not possible to make an assessment of the influence of gender on toxicity.

3) Race: The populations studied in the international trial showed a balance in terms of racial representation. There appeared to be no difference in outcome based on racial characteristics.

4) Renal: the effect of renal impairment on Cancidas®exposure is similar in subjects with moderate, advanced (severe) and end-stage renal impairment. Cancidas® clearance is approximately 30% less in these subjects compared to the control group, a change that is considered to be clinically insignificant, and no dosage adjustment is recommended.

5) Hepatic impairment: Clearance of Cancidas® is reduced in subjects with moderate hepatic insufficiency as compared to controls, requiring dosage reduction to 35 mg daily after 70-mg loading dose, in moderate hepatic insufficiency patients. Ongoing studies are designed to address whether dose reductions are also warranted for patients with severe hepatic insufficiency.

Review:

Introduction and Background:

Introduction:

This is the Medical Officer review of the new drug application (NDA) for Cancidas® for the treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies. Following the presentation of the regulatory background for Cancidas® the clinical studies demonstrating efficacy on invasive aspergillosis will be presented. A brief overview of the available agents, a history of their approval and the efficacy rates of the approved drugs for invasive aspergillosis will follow the discussion of the historical control limitations and the biases that preclude a statistical comparison between the Cancidas® treated patients in Study 019 and the historical control. The safety of Cancidas® will then be discussed followed by a summary of the risk benefits of Cancidas® for invasive aspergillosis. A brief summary of the advisory committee discussion and the final committee advice will be presented in the appendix.

Background:

Cancidas® is the first member of a new class of antifungal drugs (echinocandins) submitted for approval as an antifungal agent. Cancidas® reduces the synthesis of B (1,3) glucan, an essential structural cell wall component of fungi, whereas available antifungal agents including the polyenes (such as amphotericin B), and the azoles (such as itraconazole), are active against fungal cell membranes. Loss of cell wall glucan results in osmotic fragility of the fungal organism. The activity of the drug on the cell wall is accomplished indirectly, by non-competitive inhibition of a gene whose product is a cell membrane protein responsible for glucan synthesis. Cancidas® is currently manufactured as a semi-synthetic lipopeptide (echinocandin) compound for IV infusion.

The new drug application is for the sole indication of the treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies. The proposed dose requires a 70-mg loading dose on day 1 followed by daily doses of 50 mg for the duration determined by the treating physician. The drug is intended for use in adults, a deferment of the pediatric program was initially granted. A pediatric written request letter has recently been drafted by the Division in response to a proposal made by the applicant.

Cancidas® is not approved nor marketed outside of the United States. Other pharmacologically related products under development and therefore currently not approved for the same indication includes [redacted] both of the same class of agents. The agents that are currently approved for the indication of treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies include itraconazole and the lipid formulations of amphotericin B. Amphotericin B is the only antifungal approved for initial treatment of invasive aspergillosis. Amphotericin acts by damaging cell membranes and altering their permeability, leading to cell death. This direct action on cell membranes is also the main reason for its numerous well-known toxicities to mammalian cells. The lipid amphotericin products mitigate this toxicity to some degree by nature of their differential affinity for fungal rather than human cell membranes, and their targeted distribution to certain organs of the reticuloendothelial system rather than the plasma or the kidney.

Itraconazole, which is available as a cyclodextrin intravenous formulation as well as an oral formulation belongs to the class of antifungals that inhibit sterol synthesis and are therefore more inhibitory rather than actively fungicidal. Its main toxicity is a reversible idiosyncratic hepatitis. Further, the drug has significant cytochrome P450 interactions with many important pharmacological agents, and maintenance of drug levels is challenging with the oral formulation. The availability of an intravenous formulation overcomes

this limitation for the severely ill patient, but the association of the cyclodextrin excipient with pancreatic adenocarcinomas in rats tempers the prolonged and widespread use of the agent.

> MO comment: Alternative agents with a favorable safety profile compared to amphotericin B and less pharmacokinetic interactions than itraconazole will provide an important alternative that will expand the therapeutic options for a invasive aspergillosis, particularly when these agents have been shown to fail. The echinocandins have the potential of filling the gaps in the limited therapeutic options for the population of sick patients who succumb to this pathogen. The indication sought in this NDA targets this select group of patients.

Regulatory History:

In August of 1995, Merck Company, Inc. filed the original IND application for Cancidas® [redacted] to the Division. The Division of Antiviral Drug Products initially held regulatory responsibility for this product; this was transferred to the Division of Special Pathogen and Immunologic Drug Products in 1998.

On March 10, 1997 at an end-of-Phase 2 meeting, the Division noted that a safety database of at least 300 patients treated with 70 mg, the highest recommended treatment dose, would be adequate to assess safety for this dose. Further, the Division noted that 50 patients would be insufficient to support a claim for the treatment of invasive aspergillosis in those refractory to or intolerant of other therapies. The Division recommended evaluation of efficacy by an independent expert panel and further noted that the studies to support a salvage indication for invasive aspergillosis and candidiasis should be active controlled comparative studies. Dr. Feigal, Acting Director, noted that because of the approvals of alternative agents to amphotericin B, studies in patients with invasive aspergillosis should be comparative and should not use historical controls, particularly for a new compound. The concurrent control design was subsequently abandoned due to the difficulty of enrollment into the study.

On May 12, 1999, Cancidas® was granted fast track designation by the Division due to the evidence presented supporting both its potential to address an unmet medical need and to treat a serious or life threatening condition. It was at this time that the Division recommended an epidemiological study to determine the prevalence of invasive aspergillosis as well as to provide a comparator for the active treatment study. The Division further recommended concurrent assessment of outcome in the Cancidas® treated and historical control by an independent expert panel.

On October 21, 1999, the Office of Post Marketing Drug-Risk (OPDRA) concluded that the trade name Cancidas® was unlikely to be confused for other existing drug names.

On November 22, 1999 at a Pre NDA meeting, the Division reminded the applicant that the adequacy of the size of the safety and efficacy database might be a review issue. The Division proposed that a study consisting of at least 100 evaluable patients could be adequate to assess drug efficacy. The Division further stated that the efficacy demonstrated (overall response rate and partial versus complete response) and the breakdown of entry diagnosis (refractory versus intolerant) would be considered in the final analysis. Although the Division preferred that the expert panel review the entire historical control, the Division agreed to have a random sample of the historical control be reviewed instead. Further acknowledging that the historical control group does not allow for a direct comparison of efficacy in patients with Cancidas® vs. standard antifungal therapy for invasive aspergillosis, the Division requested a detailed data analysis and interpretation plan to describe a range of trial results the applicant would consider positive evidence of efficacy, specifying primary and sensitivity analysis. The Division expressed concern about the size of the safety database for patients on therapy greater than 14 days. The Division agreed to allow a rolling submission of the NDA, as well as deferment of the applicant's Pediatric Development Program.

On March 2, 2000, the Division concluded that the data analysis plan submitted by the applicant on March 2, 2000 was reasonable. The Division indicated that no one particular analysis will be considered primary to the exclusion of others, rather the overall pattern of results will be the basis for efficacy conclusion. The

Division further concurred with the statement that Cancidas® will be evaluated as being as good as standard antifungal therapy if the 95% confidence interval for the adjusted ratio of efficacy contains 1 and the lower limit of the confidence interval is $\geq$ 0.70.

Clinically relevant findings from chemistry, toxicology, microbiology, and biopharmaceutics reviews:

Chemistry:

(see review by Dr. Dorota Matecka for discussion of chemistry issues)

There are no relevant issues from a clinical perspective.

Toxicology:

(See review of Dr. Owen Mc Master for a more comprehensive discussion.)

Cancidas® is the first of its class to reach human development, and its toxicity profile could not be predicted based on others in its class. The development of cilofungin [redacted] an earlier echinocandin with strong antifungal activity *in vitro*, was discontinued due to metabolic acidosis. This adverse event was attributed to the drug's [redacted] vehicle, and does not appear to be attributable to this class of antifungals. Cancidas® is water-soluble and obviates the need for a similar vehicle. another investigational echinocandin that is currently unapproved, shows evidence of hepatotoxicity at the highest studied dose, as well as hemolysis and injection site adverse events when dosed chronically over 4 weeks. Preclinical toxicity reveals hypertrophy of hepatocytes and enlargement of the liver with cilofungin.

Acute toxicity studies in animals reveal that the minimum lethal doses of Cancidas® ranged from 2-8.4 mg/kg (equivalent human doses, based on body surface area conversions) across various species. The more sensitive murine species, for which the maximum non-lethal dose was 1 mg/kg, were not used in repeat dose studies. The most common findings on repeat-dose studies in rats and rabbits were allergic-type reactions consisting of signs of histamine release, injection site damage/thrombosis and liver toxicity.

Cancidas® injection was associated with signs of histamine release in rodents, manifesting as hyperemia of the ears and feet, swelling of snout and feet, bradypnea, decreased activity and sternal recumbency. These signs were transient and occurred within one hour of dosing, and were usually gone before dosing the following day. (See Dr. Owen Mc Master's review for more detail.) Liver toxicity consisted of increases in hepatic enzymes in rats, rabbits and monkeys. Although rare, and not definitely dose- related, subcapsular necrosis was also seen in animals that received 5 but not 27 week drug exposures, to doses approximately 4-6 times the approved human dose. Injection site damage ranged from discoloration, to thrombosis, and hemorrhage.

Cancidas® passes through the placenta and is secreted in breast milk. Incomplete ossification of the skull, torso and talus, as well as increased resorptions, peri-implantation losses and dead fetuses/pups were seen in the offspring of pregnant rodents who received the drug at doses equivalent to 1mg/kg in humans, based on body surface area comparisons. Carcinogenicity studies were not performed with Cancidas®. In the animal studies, there was no evidence of mutagenicity or impairment of fertility at doses equivalent to 1mg/kg in humans, based on body surface area comparisons.

> MO comment: The current label lists this drug as Pregnancy category C. Since invasive aspergillosis is more frequent in men, and since immunocompromised women often have impaired fertility, it is unlikely that information on safe use in pregnancy will accrue quickly to enable a change in this classification. The practical implications of these preclinical findings however, are not expected to significantly alter the use of the drug for the female patient of childbearing potential. It is unlikely that a possible potential risk to the developing fetus would inhibit the use of the drug to save the mother's life, since the drug is approved for a highly fatal infection, in

patients with limited therapeutic alternatives. Further, it is unlikely that contraception will be needed for the critically ill patient with invasive aspergillosis, and that even if it does, that the severity of preclinical embryotoxicity would cause a decision between delivery and abortion. These risk/benefit relationships may change if the drug is utilized for less severe infections, which is also less likely to occur given that the drug is available only as an intravenous formulation.

Because the drug acts on cell wall composition, the applicant suggests that toxicity may be limited in humans, as mammalian cells do not possess cell walls. Nevertheless, because the reduced cell wall glucan is a consequence of Cancidas® activity on a cell membrane enzyme, it is at least theoretically possible that there could be a structural or functional homologue for the cell membrane enzyme that is amenable to responding to the drug's activity and therefore might be a mechanism for the drug's potential toxicity.

Incubation of *C. albicans* with cilofungin (an analogue of echinocandin) for 18 hours decreased the ergosterol content by 55 – 60 % and glucan content by >70% (2), whereas chitin and mannan content were increased. It is unclear whether the changes in chitin, mannan and ergosterol are a direct effect of cilofungin or a consequence of an alteration in glucan content leading to dysregulation of carbohydrate synthesis that leads to changes in the integrity of the cell membrane. Nevertheless, while this class of antifungals act against a cell wall target, they appear to have a broader activity against cell sterols and could therefore likewise have some effects on mammalian cell membrane as well.

On February 12, 1999, Dr. David Stevens, Professor of Medicine of Stanford University informed the Division regarding mortality findings in mice that received [redacted] another echinocandin under development by [redacted] and glucocorticoids together. The findings from these studies were subsequently published in the February, 2000 issue of Antimicrobial Agents and Chemotherapy (1). In this paper, Dr. Stevens further explores the interaction between the echinocandin [redacted] with glucocorticoids in mice, after earlier unpublished observations that DBA/2 mice pretreated with cortisone acetate died following intraperitoneal treatment with the echinocandin. In the new studies, Dr. Stevens reports that concomitant use of cortisone, hydrocortisone or triamcinolone with [redacted] but not [redacted] or the steroid alone, resulted in early deaths occurring from Day 3 of treatment with [redacted] 25 mg/kg IP, QD. These findings were limited to one strain of mice and to cortisone, hydrocortisone and triamcinolone, but not to dexamethasone. Histological observations revealed acute infarcts in the kidney, intravascular calcific material and embolic materials in arterioles in lung, and myocardium. The proposed mechanism for this effect, however, was not explored by Dr. Stevens in the report (details in safety review).

In the NDA submitted, pre-clinical toxicology information in mice consisted of 2 studies with 33 ICR mice that received IV Cancidas®, and another study of oral Cancidas® administered to 3 ICR mice. None of these mice were concomitantly receiving corticosteroids. After these initial 3 murine studies, rats, rabbits and monkeys were used to characterize the toxicological profile of Cancidas®, because mice were found to be four times more sensitive to Cancidas® than these other animal species (see review by Dr. Owen Mc Master). Nevertheless, in the microbiologic efficacy studies, no signal for early deaths were noted in Cancidas® treated mice who received conditioning corticosteroid treatment, although these studies utilized different strains of mice than those used by Dr. Stevens (See review by Dr. Shukal Bala).

A review of the clinical studies does not appear to show an increase in embolic or vascular events in the Cancidas® treated patients on steroids compared to those patients not on steroids. In addition, the rate of vascular events (excluding phlebitis) appears to be similar between Cancidas®and fluconazole in the comparative mucosal candidiasis studies. The influence of corticosteroids could not be evaluated in the aspergillus trials since most patients were on corticosteroids. The applicant further submitted an updated analysis comparing deaths in patients on corticosteroids and deaths in patients not receiving corticosteroids, and did not find any relationship of mortality to concomitant caspofungin and corticosteroid use.

Microbiology:

(See review of Dr. Shukal Bala for a more comprehensive discussion.)

The mechanism of action of Cancidas® results in reduced cell wall glucan and increased osmotic fragility of the fungal cell. Glucan is an important constituent of the cell wall of many fungi and the proportion of this polysaccharide in the walls of different fungi varies; this may explain the differential activity of the drug against various fungal species. The 50% inhibitory concentration (IC_{50}) value of Cancidas® for *Aspergillus fumigatus* is 9.6 *n*M compared to 0.6 *n*M and 2.5 *u*M, respectively for *Candida albicans* and *Cryptococcus neoformans.*

It is important to point out that even though Cancidas®'s ultimate activity is specific for a component of the fungal cell wall, this is accomplished by the drug's more immediate action on a cell membrane enzyme modulated by a FKS1 gene. Time kinetics in *C. albicans* studies show the rate of kill of Cancidas® to be slower compared to amphotericin B, consistent with this mechanism of action. Using traditional broth dilution testing, Cancidas® killing occurs at 7 hours compared to 1 hour with amphotericin B.

Activity against Aspergillus *in vitro:*

The echinocandins do not show complete inhibition of growth against aspergillus species and the applicant attempted to quantitate the activity of the drug against aspergillus by a visual scale using electron microscopy and [redacted] optics. The minimum effective concentration (MEC) which altered the morphology of hyphae using the above methods, varied from 0.06 to >2 *u*g/ml for various species of aspergillus.

Staining with fluorescein dyes, which differentially penetrate the cell based on viability, was performed to determine whether the drug actually affects viability compared to just inhibiting growth. The applicant demonstrated that Cancidas® at 0.3 *u*g/ml, for 6 hours was lethal at the selective areas with active cell growth i.e., the apical tips of hyphae and areas of hyphal branching. In regions of less active growth the hyphae were viable. In comparison, amphotericin B at a concentration of 0.15 *u*g/ml resulted in an almost complete loss of viability of the organism. This difference is attributed to amphotericin B's disruption of cell membrane.

As standard broth dilution methods utilized for bacteria and yeast are technically difficult to perform for filamentous fungi, the applicant further modified proposed NCCLS *in vitro* susceptibility testing (M-38P), utilizing a qualitative visual scale to quantitate growth inhibition. This was termed as MIC-2 (≥ 50% inhibition of growth) or MIC-80 (≥ 80% inhibition of growth). The *in vitro* susceptibility using these measures shows variability in activity of Cancidas® against different aspergillus species, with a range of [redacted] for the MIC-2 and MIC-80, respectively.

In vitro susceptibility testing was done on over 90 clinical isolates of Aspergillus from 36 patients in the pivotal study for invasive aspergillosis (Study 019) [*A. fumigatus* (n=80), *A. flavus* (n=11), *A. niger* (n=4) and *A. terreus* (n=3)]. The *in vitro* activity of the drug varied with the medium, the concentration of the conidial suspension, and the incubation time, but none were found resistant to Cancidas® based on the previously established MIC-2 and MIC-80. The usefulness of the MIC-2 or MIC-80 values in predicting clinical outcome has not been established. Subsequent isolates from these patients following treatment with Cancidas® were also tested for inducible resistance, based on mutation of the FSK1 gene. No subsequent isolates were found to have acquired resistance. The applicant estimates resistance based on the FSK1 gene to occur spontaneously at a rate of 1 in 10^8 organisms.

There is limited information on the *in vitro* activity of Cancidas® against other fungal pathogens such as *Fusarium, Trichosporon, Pseudoallescheria* and *Mucor spp,* which can cause infections mimicking invasive aspergillosis.

Activity against Aspergillus *in vivo;*

The *in vivo* activity of MK-0991 against aspergillus species *(A. fumigatus and A. flavus)* was assessed initially in immunocompromised rodents.

In animal models of invasive aspergillosis, Cancidas® has been shown to a) prolong survival and b) reduce mycological burden of infection. These studies utilized one strain of *A. fumigatus* (strain MF5668), in various models of immunosuppression (C'5 deficient, neutropenic, and pancytopenic mice) and initiated Cancidas® therapy at the time of challenge or 24 hours later. In these studies, Cancidas® was effective in improving the survival rate comparable to amphotericin B. The effect of Cancidas® therapy on the mycological burden of invasive aspergillosis was measured in a single experiment of persistently neutropenic (> 28 days) mice. In this study, Cancidas® initiated 24 hours post-infection for 7 days was effective in reducing mycological burden in mice kidneys (based on colony forming units i.e., CFU and histological findings) on days 4, 15, and 28, comparable to amphotericin B.

> MO comment: The murine model studies submitted to the NDA do not reflect human infection with invasive aspergillosis in terms of pathophysiology, route of infection, site of organ involvement and clinical manifestations. Furthermore, mycological burden is measured in a single organ of little relevance for the disease process in humans, in a site where drug levels in rodents are known to be higher than those achieved in the lung. The model also does not correlate mycologic activity with drug levels (PK/PD). Therefore, even if both survival and mycological burden were significantly reduced in this murine model, this information is of limited clinical relevance. Although murine models are cheaper to develop, require less logistic support and lend themselves to large, repeated testing , the model may not necessarily directly correlate with the clinical disease in humans.

In a separate submission to the IND [redacted] the applicant referenced an animal model of invasive aspergillosis in rabbits and made the preliminary results of this model available at the Division's request. Additional materials were subsequently submitted by facsimile and the results discussed with Dr. Thomas Walsh of the National Cancer Institute, who developed the model, at a teleconference held on December 28, 2000.

In this clinically analogous model of granulocytopenic rabbits with invasive pulmonary aspergillosis, amphotericin B and Cancidas® were compared to untreated controls regarding survival, burden of infection in the organ of interest for invasive aspergillosis, correlating radiographic scores from CT scans and radiographs to histology, infarction and pulmonary hemorrhage and tissue mycology. In this model, the mean duration of survival was 6.9 days for untreated controls, compared to 10.4 and 8.8 for Cancidas® and amphotericin B, respectively, at equivalent daily doses of 1 mg/kg. This increased survival paralleled an improvement in pulmonary infarct score, measured as number of infarcted lobes per lung and improved lung weights, as did amphotericin B, compared to untreated controls. Paradoxically, the improvement in survival as well as in pulmonary measures of disease did not translate into a reduced mycological tissue burden. Rather, an increase in colony counts to 1.9 CFU/g of lung was seen in Cancidas® treated rabbits, compared to untreated controls. This contrasted with the predictable reduction in colony counts seen with amphotericin B in this model (3).

> MO comment: Of note the improved mycological clearance seen with amphotericin B did not result in a survival advantage for amphotericin B, whose mean duration of survival was still less than that for Cancidas®, raising the question regarding the impact of drug toxicity on survival from invasive aspergillosis. Cancidas® whole lung levels in this model were above the target of 1 ug/gm with the 1 mg/kg dose.

Pharmacokinetics:

(See review of Dr. Houda Mahayni for a more comprehensive discussion.)

Concentration-time profile analysis indicates a triphasic decline in Cancidas® concentration after administration of a single dose. Drug levels appear to be a function of drug distribution rather than metabolism. The terminal elimination phase is attributed to slow release of drug from tissues (40-50 hours Gamma phase).

Absorption, Distribution, Metabolism and Excretion:

Cancidas®'s steady-state volume of distribution is 9.67 L. The drug is extensively bound to albumin (~97%) and is not taken up significantly by red blood cells. Cancidas® metabolism is slow, with very little biotransformation on the first 24-48 hours post-dose. The parent drug accounts for the majority of plasma and urine radioactivity at 24 to 30 hours post-dose. Cancidas® undergoes peptide hydrolysis and N-acetylation, degrading chemically to L-747969, an open-ring peptide present up to 5 days after a single dose. Two other reactive intermediates, the synthetic amino acid, dihydroxyhomotyrosine, and its N-acetyl derivative, both of which form covalent adducts to protein, are formed during the hydrolytic degradation of Cancidas® to L-747969. The 2 metabolites are seen only in urine, indicating rapid clearance relative to a slow formation and/or release rate. On the other hand, the parent drug is slowly excreted unchanged at low levels in urine (1.44% of dose). Excretion of drug, through the renal (41%) and fecal (34%) routes, peaks 6 to 7 days post-dose with 75% recovery at 27 days, consistent with the slow degradation, disposition, and excretion. The intermediate L-747969 binds avidly to liver tissues, slowing its release from liver.

Steady state was not achieved with the drug up to 28 days following initiation of dosing with the 50-mg dose. In healthy subjects, plasma levels above the target 1 ug/ml were immediately achieved with the addition of a 70-mg loading dose on day 1. Plasma levels are generally lower and more highly variable in patients than healthy subjects. In these patients, the addition of the same loading dose of 70 mg allows trough levels to be consistently maintained above the 1 ug/ml target when measured at day 9 and 14.

Levels of Cancidas® in the CNS are known to be limited in rodents and are unknown in humans.

MO comment: Twenty to 50% of cases of invasive aspergillosis are associated with cerebral infection and this pharmacokinetic limitation of the drug should be recognized when it is used for this indication.

Special Populations:

Pharmacokinetic studies were done and the following were observed:

Age – minor reductions in clearance occur with age and do not require dose reduction.

Gender - a 20% increase in AUC in women was not felt significant and dose adjustment id not required.

Renal impairment – the effect of renal impairment on Cancidas®exposure is similar in subjects with moderate, advanced (severe) and end-stage renal impairment. Cancidas® clearance is approximately 30% less in these subjects compared to the control group, is felt to be insignificant, and no dosage adjustment is recommended.

Hepatic impairment – Clearance of Cancidas®is reduced in subjects with moderate hepatic insufficiency as compared to controls, requiring dosage reduction to 35 mg daily after the 70-mg loading dose, in moderate hepatic insufficiency patients. Ongoing studies are designed to address whether dose reductions are also warranted for patients with severe hepatic insufficiency.

Drug-Drug Interaction:

The interaction of Cancidas®with the following CYP450 substrates/inhibitors was studied: cyclosporine, amphotericin B, FK-506 (tacrolimus), itraconazole, and mycophenolate mofetil. Studies indicate no significant pharmacokinetic interaction for co-administration of Cancidas®with amphotericin B, itraconazole, and mycophenolate mofetil and no dosage adjustment is therefore necessary. Additionally, no increase in cyclosporine levels was seen, rather, an increase in Cancidas® C_{min} concentrations was noted. The extent of this interaction is still being characterized. In addition, concomitant use of cyclosporine appears to enhance the transaminase elevations attributed to Cancidas® (discussed in Safety section of the review). Concomitant use of the drugs cannot be recommended until such time that the safety of the combination has been established. [redacted] concentrations are reduced with the co-administration of Cancidas®. Monitoring of tacrolimus levels should be done when these drugs are co-administered.

Cancidas®is neither an inhibitor of nor a substrate for cytochrome P450 isoenzymes. Nevertheless, initial population pharmacokinetic studies in patients that concomitantly received nelfinavir and other cytochrome 3A4 inducers, indicate enhanced clearing of Cancidas® independent of the cytochrome P450 interaction. These metabolic inducers, which include efavirenz, nevirapine, rifampin, dexamethasone, phenytoin and carbamazepine, could lead to reductions in Cancidas® concentrations through two mechanisms:

induction of transport mechanism could lead to increased drug clearance, or
induction of a minor oxidative pathway could accelerate metabolism.

The applicant indicates that although Cancidas® is not known to undergo oxidative metabolism, an unknown minor oxidative pathway could become a major pathway if induced. The inducers appear to have a variable effect on Cancidas®levels because omeprazole appeared to have no effect. Studies are currently underway to better understand the magnitude and mechanism of these interactions.

Description of clinical data and sources:

The primary source for the evaluation of clinical efficacy was the phase II trial on invasive aspergillosis (Study 019). Data for a separate phase III compassionate use study that recruited 3 patients has not been evaluated and is not covered in this review. The efficacy in Study 019 is compared to a historical control study (Study 028, also known as Study 029 in the non-US sites). Studies 019 and 028/029 (the latter referred to henceforth in the review as the historical control study) are described in tandem in the review on clinical efficacy (see Table 1 in the next page).

The primary data for the calculation of adverse event rates were from the 3 phase II comparative safety studies of Cancidas®against desoxycholate amphotericin B (003, 004) and fluconazole (020). Events that were observed in the phase II studies against invasive aspergillosis as well as in phase I studies were also considered in assessing the overall adverse event profile of Cancidas®. In addition there were several phase I studies that were conducted to specifically address particular drug-associated adverse events or drug-drug interactions (Table 2). Two patients in a dose ranging Candida esophagitis study (Study 007) received 2 courses of the drug and comprise the only repeat dosing experience. Serious drug related adverse events from the Merck WAES database (Worldwide Adverse Event System) from patients enrolled into the studies following the cut-off date for NDA submission regularly forwarded to the Division. Some of these cases are pertinent to the safety issues and have been included in the safety discussion.

In addition to the clinical trial data, the applicant also reviewed the submitted relevant literature on the efficacy of antifungal therapy for invasive aspergillosis, in the effort to perform a meta-analysis. This report was also incorporated in the NDA. The Division supplemented this report by reviewing the new guidelines on the management of invasive aspergillosis published by the Infectious Disease Society of America (22), as well as additional information on other members of the echinocandin class of antifungals for any safety related issues reported both in the published literature as well as in the FDA archives.

MO comment: The amount of data gathered for the historical control was limited in scope compared to Study 019. Although the electronic datasets contained the same variables, the amount of information contained differed from Study 019. For example, the concomitant therapy listings were limited to corticosteroids and immunomodulators, and the vital signs and physical examination data were limited to the respiratory parameters. The safety datasets did not contain an integrated dataset, and even the discussion of safety in the integrated summary of safety did not present the safety for the entire population enrolled into Study 019.

A DSI audit was conducted in the site that enrolled the highest number of patients (M.D. Anderson Cancer Center) and found no issues with data quality and procedures.

Clinical Review Methods:

The Medical Officer employed the following methods in the review:

1) review of CRTs and case summaries of efficacy studies for adherence to inclusion/exclusion criteria, case and outcome definition
2) review of random CRTs of safety studies for adherence to inclusion/exclusion criteria, case and outcome definition
3) comparison of efficacy between the ITT and CE population in 019 to an analogous population in the historical control
4) characterization of historical control vs. other historical controls utilized in the comparison of efficacy for agents reviewed in the Division
5) assessment of the comparative safety of Cancidas® (in clinical trials vs. other therapies), based on the electronic data set, as well as review of the deaths and serious drug related adverse event summaries that accompanied the electronic dataset
6) review of previous advisory committee transcripts relevant to the discussion of design plans for invasive aspergillosis studies

CLINICAL STUDIES

The primary source data for this application derives from three studies on Invasive Aspergillosis (IA):

Protocol	Major Entry Criteria	Primary (Secondary) Efficacy Endpoint	Note
(019) non-comparative international, phase IIb	Definite/Probable IA Refractory to or Intolerant of "standard Rx"	Resolution or improvement of clinical, radiologic/bronchoscopic findings at EOT (Mycologic response, Relapse at 4 wk FU infusion AEs, discontinue due to AE)	Independent panel assessed, 70 mg load D1, 50 mg variable duration
(024/025) compassionate use, international, phase III	Definite/Probable IA Refractory to or Intolerant of an AmB formulation	Resolution or improvement of clinical, radiologic/bronchoscopic findings at EOT	Independent panel assessed 70 mg load D1 50 mg variable duration
(028/029) historical control, US, (1995-1998)	Definite/Probable IA treated for 7 days with "standard Rx"	Resolution or improvement of clinical, radiologic or bronchoscopic abnormalities	(?) assessed Minimum of 7 days of standard Rx.

Efficacy in Candida Esophagitis (CE) was considered supportive of antifungal activity:

Protocol	Major Entry Criteria	Primary (Secondary) Efficacy Endpoint	Daily Doses
(003) comparative, Phase IIa	Microbiologically Documented candida Esophagitis	Evaluation of symptoms and endoscopy (Mycologic response)	70 mg and 50 mg vs. dAmB 0.5 mg/kg x14 d
(004) comparative, OPC and CE, phase IIb	Microbiologically Documented oropharyngeal and esophageal candidiasis	Evaluation of symptoms and oropharyngeal exam or endoscopy	30, 50, 70 mg vs. dAmB 0.5 mg/kg x10-14 d
(007) non-comparative, CE pharmacokinetic, phase IIa	Microbiologically documented CE	Pharmacokinetics in patients with CE (symptoms, endoscopy)	70 mg and 50 mg for 14 days

Review of Efficacy:

Clinical Studies:

Sixty-nine patients with invasive aspergillosis who were refractory to or intolerant of other antifungals were enrolled in the open label Study 019. The clinical efficacy of Cancidas® in this single pivotal trial was compared to a retrospectively reviewed historical cohort (Study 028) of patients who received any antifungal therapy for invasive aspergillosis. An additional 3 patients with invasive aspergillosis were enrolled in a separate compassionate use study. The Division has not reviewed the data from this study.

Three comparative (Study 003, 004, 020) and 1 non-comparative study (Study 007) in mucosal candidiasis provide supportive evidence of the antifungal activity of Cancidas®.

> MO comment: The efficacy data from the mucosal candidiasis studies have not been extensively reviewed and the efficacy of Cancidas® in this indication will not be discussed. However, these studies are important from the safety standpoint and have been reviewed in that context.

The protocol summary highlights for Study 019 and Study 028/029 will be presented in tandem, covering study procedures including exclusion criteria, disease definition, response to prior therapy, timing of assessments, outcome definitions and study design and analysis.

Study Procedures:

Study 019:
Prospective, timed evaluations of the clinical, laboratory, microbiologic radiographic parameters were employed for Study 019. Patient enrollment for Study 019 was from May 1998 to April 2000.

Study 019 Procedures				
Timed Assessment	Day 0	On Treatment,	EOT	4 wk FU
History/Physical examination	X	X	X	X
Laboratory safety	X	X	X	X
Non-invasive cultures	X	X	X	X
Radiographic studies	X	X	X	X
Adverse experience monitoring		X	X	X

In the historical control study, conventions of clinical care dictated the timing of similar procedures.

Historical Control:
Cases diagnosed from January1995 to March 1999 were enrolled into the study. Case finding was based on a review of hospital discharge registries, as well as listings in the pathology, microbiology, and subspecialty consultation departments in 10 investigator sites. The majority of patients in both Study 019 and 028 were identified in 4 sites common to both studies. Trained abstractors (other than the principal investigator) reviewed records and abstracted information onto the case report forms. Outcome assessments were made by the site investigator based on data obtained by the trained abstractors.

> MO comment: The limits of retrospective studies precluded a comparison between adverse events in Study 019 and the agents used for treatment of invasive aspergillosis in the historical control. Reliability of clinical information is similarly influenced by the retrospective nature of the study.

Investigators:

Study 019:

The following investigators entered patients in Study 019. Drs. Greenberg and Raad were US investigators that also participated in the historical control study.

Investigators for Study 019	
Investigator (Code)	Institution
Adam, R. (001)	University of Arizona Microbiology Department
Greenberg,R (004)	University of Kentucky Medical Center
Raad, I. (008)	MD Anderson Cancer Center
Miller, K. (021)	New England Medical Center
Petersen, F. (025)	University of Utah Medical Center
Betts, R. (030)	University of Rochester
Bloomberg, E (078)	University of Pennsylvania
Sjolin, J.	Sweden
Boogaerts, M.	Belgium
Jacobs, F.	Belgium
Sellesslag, D.	Belgium
Dupont, B.	France
Ozier, Y.	France
Oppenheim, B.	UK
Gobernado, S.	Spain
Petrikkos, G.	Greece
Colombo, A.	Brazil
Severo, L.	Brazil
Eisen, D .	Australia
Dobb,G.	Australia

Historical Control:

The following US sites enrolled patients into the historical control:

Investigator	Institution	Enrolled
US:		199 (87%)
Carroll, K.	ARUP Laboratories**	7
Dominguez, E.	University of Nebraska Medical Center	26
Finberg R. / Hibberd, P.	Children's Hospital /Dana Farber Cancer Institute	14
Greenberg, R.	University of Kentucky Medical Center	14
Hiemenz, J.	Walt Disney Memorial Cancer Institute	12
Marr, K.	Fred Hutchinson Cancer Research Center	40
Polish, L.	Washington University School of Medicine	08
Raad, I.	M.D. Anderson Cancer Center	67
Tucker, P.	Johns Hopkins University	11
Non-US :		
J Maertens	UZ-Gasthuisberg – KUL	30 (13%)
Total		229

** This was a laboratory research unit that was affiliated with the University of Utah.

MO comment: These US centers are recognized to be among the leading cancer and transplantation units in the country.

Exclusion Criteria:

Study 019:

The following table lists the exclusion criteria for Study 019 and the historical control study. The exclusion criteria between the two studies differed substantially, with patients in Study 019 excluded on the basis of baseline abnormal laboratory values possibly indicating severe underlying disease such as low hemoglobin, hematocrits, platelet counts and INR, bilirubin or liver function test abnormalities.

MO comment: Some of these criteria (Criteria 4,5,6,9,11,13) could not be applied to the historical control for practical reasons, but certain criteria, such as the exclusion of patients with abnormal baseline laboratory values, acute hepatitis or cirrhosis, could have been applied. More important, was the exclusion of patients not expected to survive at least 5 days from the time they are identified as refractory of intolerant of antifungal therapy in the Cancidas® treated study group.

Cancidas® (Study 019)	**Historical Controls (Study 028)**
1.Disease limited to allergic bronchopulmonary aspergillosis, aspergilloma, or ocular disease	Disease limited to allergic bronchopulmonary aspergillosis, aspergilloma, or ocular disease
2. Disease limited to sinusitis or external otitis unless histopathological evidence of tissue invasion with Aspergillus	Disease limited to sinusitis or external otitis unless histopathological evidence of tissue invasion with Aspergillus
3. Abnormal Lab values **Hemoglobin <8 gm/dl** **Platelet count < 25,000/muL** **INR > 1.6** **Bilirubin >3 times the ULN** **AST or ALT >5 time the ULN** **Alkaline phosphatase >3 times the ULN**	
4.Unwillingness to stop current treatment	
5.Need for other sys. Antifungal therapy	
6.History of allergy, hypersensitivity to echinocandin	
7. Not refractory or intolerant	
8. Patients who are not expected to survive at least 5 days	
9. Pregnant or breast feeding	
10. Diagnosis of acute hepatitis or cirrhosis	
11.Previous participation in this study	
12. Any condition or illness which might confuse the results of the study or pose additional risk to the patient	
13. Patients who are taking rifampin, ritonavir, cyclosporine A or tacrolimus	

Historical control:

The exclusionary criteria for the historical control is limited to the following:
disease limited to allergic bronchopulmonary aspergillosis, aspergilloma, or ocular disease, and
disease limited to sinusitis or external otitis unless histopathological evidence of aspergillus tissue invasion.

MO comment: The difference in exclusionary criteria, particularly those that relate to abnormal laboratory values and the exclusion of patients not expected to survive, could have resulted in a sicker patient population for the historical control.

Inclusion Criteria:

Disease definitions of invasive aspergillosis are modeled after recognized Mycoses Study Groups criteria. Definite pulmonary and extrapulmonary infections required histopathological or tissue mycology obtained through invasive procedures. These criteria were consistently applied between Studies 029 and 028.

Study 019:
Patients met the following definitions of definite or probable aspergillus infection.

Pulmonary Aspergillosis
a) Definite: Tissue histopathology showing septate, acute branching hyphae with or without a positive culture for *Aspergillus spp.* from the same site or, in the absence of histopathology, a positive culture from tissue obtained by an invasive procedure, such as transbronchial biopsy or percutaneous needle aspiration.
b) Probable:

Radiology	Additional Criteria
CXR (nodules with cavities) PLUS	2 sputum CULTURES **OR**
	1 bronchoalveolar lavage or bronchial brush CULTURE **AND** CYTOLOGY examination
CT scan (halo, crescent, pleural based wedge infiltrates) PLUS	CULTURE OR CYTOLOGICAL examination from either 1 sputum or bronchoalveolar lavage OR bronchial brush specimen
	OR
	2 galactomannan ELISA OR PCR from serum OR BAL

MO comment: Because certain radiological features of invasive aspergillosis are known to be predictive of true disease, for pulmonary aspergillosis, these criteria, together with other less invasive cultures or newer diagnostic tests, were employed in the category of probable pulmonary disease. Chest radiographs showing cavitating nodules and 2 sputum or 1 BAL culture, with positive direct examination fulfilled the criteria for probable infection. Whereas in the presence of more distinctive CT features of the halo or crescent sign, or pleural based wedge infiltrates, a positive direct exam or a single respiratory culture from either sputum or BAL or 2 consecutive galactomannan ELISA or PCR fulfilled this criteria [4,17].

Historical control:

Inclusion criteria varied slightly for Study 028, where only one sputum culture (compared to 2 in Study 019), was needed when a chest radiograph was suggestive of aspergillosis. One study site (Patricia Hibberd, Principal Investigator for Children's Hospital, Boston) in the historical control, however, required 2 cultures as in Study 019, and excluded 228 patients from the review of the historical control.

MO comment: When the applicant excluded the patients enrolled from this center in its analysis, there was no change to the overall conclusions derived from the study. To determine whether the outcome would change when the 228 patients are included in the study, the Division requested the applicant to submit a the data from a randomly selected sample of these patients. However, the applicant was unable to provide the information, and the true impact of this change in inclusion criteria can not be assessed fully.

Patients enrolled as probable disease were upgraded to definite if, at a later surgical procedure or autopsy, they were found to have aspergillosis by histopathology.

MO comment: The difficulty of utilizing these criteria to diagnose cerebral aspergillosis is recognized and therefore all cases of CNS aspergillosis were based on investigator's assessment and to which the MO concurred. Only 2 cases of cerebral aspergillosis are definitely established, both were clinically evident on treatment and were diagnosed by autopsy cultures.

Extrapulmonary infections were all definite: Patients needed to have histopathological evidence of invasion by aspergillus in the sinus mucosa or bone to qualify for inclusion.

Response to prior therapy:

Study 019:

Refractory disease was progression or failure to improve despite 7 days of therapy with desoxycholate amphotericin B, any lipid formulation of amphotericin B, itraconazole, or other investigational azoles.

Intolerance was defined as renal intolerance (doubling or creatinine >2.5 mg/dL) as well as infusional and other toxicities.

Patients were either refractory to or intolerant of the standard therapy used in the institution. Standard therapy included amphotericin B, lipid formulations of amphotericin B, or itraconazole. Patients who failed or were intolerant of investigational azoles with activity against aspergillus were also permitted to enroll into this study. The current label of the lipid formulations of amphotericin B and itraconazole indicates their use for patients refractory to or intolerant of desoxycholate amphotericin B.

Historical Control:

Infusional or other toxicities qualified for the definition of intolerance in Study 019. In the historical control study, the single criteria defining intolerance was a creatinine value of greater than or equal to 2.5 mg/dl. Additionally, for Study 019, a doubling of baseline creatinine or any level greater than 2.5 ug/dL on treatment or at baseline, defined renal toxicity. For Study 019, therefore, a patient with a baseline creatinine of 0.5, who had a subsequent creatinine of 1.0, qualifies for inclusion.

> MO comment: Intolerant patients in Study 028, therefore, may have had more significant reductions in renal function based on this difference in criteria. This is particularly important as renal insufficiency is identified as an independent predictor for poor outcome for these patients (5, 12).

Refractory response to prior therapy was assessed in both studies after 7 days of initial treatment. Intolerance could occur at any point in time, including at baseline.

> MO comment: Patients with a baseline creatinine of 2.5 ug/dL, could therefore, based on this definition of intolerance, receive Cancidas® as initial therapy, without the need to receive other alternative therapies.

Outcome assessment:

Outcome assessment for Cancidas® therapy was at end of therapy, whereas relapse was measured 4 weeks post end of therapy.

Strict definitions of outcome were applied to both Studies 019 and 028, based on clinical, radiological and bronchoscopic findings when present at baseline. Favorable outcomes include both complete and partial responses whereas stable disease and clinical progression were considered unfavorable outcomes.

Mechanics of Outcome Assessment:

Study 019

An expert panel of mycologists, consisting of Dr. David Denning, Dr. Thomas Walsh and Dr. Tom Patterson, who had not participated as investigators for Study 019, reviewed study 019. The expert panel

members independently applied the criteria for diagnosis and outcome following review of case summaries, radiographic, culture and pathology reports. Discrepancies in assessment between the experts were resolved at face to face meeting, at which time actual radiographs were reviewed and outcome adjudicated. A majority decision served as the final panel assessment.

The expert panel disagreed with the investigator's assessment of outcome in 15 patients, resulting in a downgraded assessment in 13 of these 15 cases. However, since the change in assessment fell within the category of favorable or unfavorable (i.e. a downgrading of complete to partial response, for example), the dichotomous outcome of success vs. failure was retained in all but one patient.

Disparities in outcome assessment between the expert panel and the investigators:	
Diagnosis:	1 patient excluded by the expert panel based on a low titer + galactomannan. 1 patient's diagnosis changed from probable to definite.
Response to prior treatment :	1 patient excluded based on refractoriness to prophylaxis rather than therapy 1 patient changed from intolerant to refractory.
Outcome assessment:	panel and investigators disagreed on 15 patients (15/69 = 21.73%). 1 considered unevaluable at end of therapy 7 downgraded to partial from complete responses* 2 upgraded responses [stable to partial in 1**, failure to stable in another 1]

* all remained successful outcomes ** resulted in a change in overall outcome, from success to failure in 1 patient, the other upgraded response remained a failure

Historical control:

For the historical control study, one of the investigators, Dr. John Hiemenz, reviewed the cases blinded as to site. He reviewed 20 data tables per patient, abstracted from case report forms, and analyzed tabular displays while blinded to site. Any discrepancy between the site investigator and the expert review was noted on a separate form. This review was recently submitted to the Division on December 22, 2000. The expert reviewers' overall conclusions approximate the site investigator's assessment.

> MO comment: The degree of concordance for outcome assessment between the expert panel and the site investigators was 54/69 or 72.3% for Study 019 compared to 200/214 of 93.45% between the expert and the rest of his colleagues for the historical control. Independent of the potential biases in secular trends and patient selection in the historical control study, the expert assessment significantly differed between the two studies, limiting the comparability of both studies. These differences could have been minimized even though the historical control was not designed at the inception of the active treatment study. The same expert panel, blinded as to treatment of invasive aspergillosis could have evaluated a sample of the historical control. In addition, the same amount of information for the historical controls could have been gathered and the same exclusionary laboratory criteria could have been applied.

Study Design and Analysis: Efficacy

Study 019:

Study 019 was an estimation study assuming an efficacy rate of at least 30% for Cancidas®treated patients. The primary objective of the study was to estimate in patients with invasive aspergillus infection, who are treated with Cancidas®as salvage therapy, the proportion of patients with a complete or partial clinical response at the time of discontinuing intravenous antifungal therapy. The secondary efficacy objective was to determine the proportion of patients with a relapse at 4 weeks post intravenous therapy. Ninety-five percent exact confidence intervals were calculated for the overall group proportions. The primary analytic population was the MITT or modified intent to treat population, which consisted of all patients who received 1 dose of Cancidas®. The Expert Panel MITT population superceded the sponsor's MITT analysis, as requested by the Division.

Historical control:

In comparing the efficacy of 019 to the historical control, the applicant's primary analysis was the proportion of success at end of treatment. The applicant additionally performed a secondary analysis using a logistic regression model adjusted for baseline risk variables predictive of outcome, comparing the probability of a successful outcome in Study 019 compared to historical controls. Cancidas® was evaluated as being as good as standard antifungal therapy if the 95% confidence interval for the adjusted efficacy ratios contained 1 and the lower limit of the confidence interval is ≥ 0.70.

> MO comment: Given the reservations about the adequacy of the historical control study as comparator for Study 019, the Division did not perform this analysis.

Study Design and Analysis: Safety

Study 019:

In estimating safety, the sample size of 50 patients with invasive aspergillosis has a 95% probability of detecting at least 1 drug-related adverse event (DRAE) if the incidence of the adverse event in the entire population is $\geq 5.8\%$.

The safety in the clinical pharmacology and mucosal candidiasis studies comprised the bulk of the safety analyses. The inclusion of the patients in the safety analysis allowed the detection of at least 1 DRAE if the incidence of the adverse event in an analogous population with similar drug exposures, was at least 1%. Further, the mucosal candidiasis safety database allowed a comparison of the adverse events between Cancidas® and the antifungal amphotericin B and fluconazole.

> MO comment: Because of the significant differences in terms of underlying disease, concomitant medications, and durations of therapy the conclusions that can be drawn from the integrated safety assessment are limited. However the indication being sought is one for which there are limited therapeutic options and where untreated disease is almost universally fatal.

Results:

Patient Accounting:

Study 019:

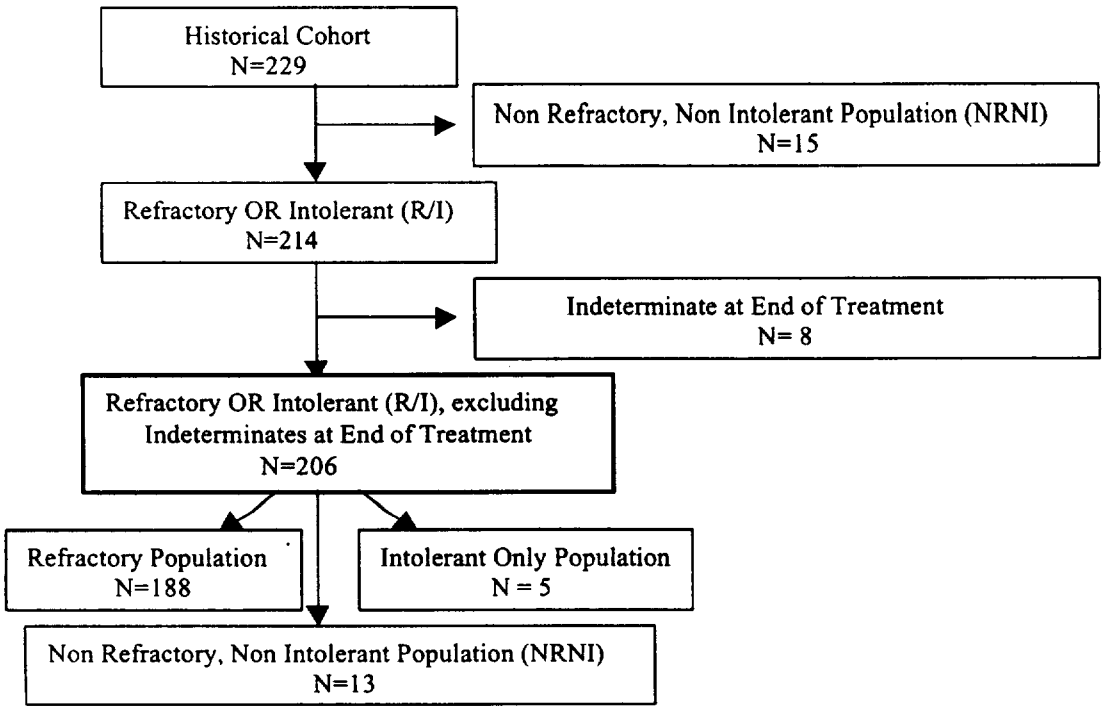
The applicant initially presented efficacy and safety results for the first 58 patients reviewed by the expert panel at the time of NDA submission. The safety and efficacy of an additional 11 patients was subsequently submitted and are discussed separately by the applicant. The information presented in this review is that of the composite data from both submissions.

Sixty-nine patients were enrolled in 019, of whom the expert panel excluded 6 patients, one for protocol violation, 2 because they were inevaluable at end of therapy and 3 because a pathogen other than aspergillus was subsequently identified. The evaluable population therefore consisted of 63 patients.

Study 028/029:

For the historical control study, over 1,200 records were reviewed for possible inclusion into the study. One site excluded 228 records from review based on the availability of only one positive respiratory sputum. The Historical cohort, consisting of all patients who fulfilled the diagnostic criteria and were evaluable on day 7, finally consisted of 229 patients.

The following flow chart, obtained from the NDA, shows the disposition of these 229 patients.



The refractory and intolerant subset (shown in the bolded box) is the Division's historical control subset for purposes of describing the study in relation to the 63 evaluable cases in Study 019. The applicant further partitioned this category into 5 patients who were intolerant only, 13 indeterminate at 7 days and 188 refractory patients.

> MO comment: The basis for this partitioning was difficult to glean from the data provided. The Division, in an attempt to determine the efficacy of currently available salvage therapies, reviewed the applicant's historical control database to characterize the antifungal agents employed as initial treatment of IA, and the response to prior therapy as refractory or intolerant of at least 7 days of treatment. By excluding patients who received only one antifungal or multiple concurrent antifungals without significant modifications throughout their treatment course, the Division assembled a population requiring salvage therapy, analogous to that in the open label study. These 96 cases are assumed to have had treatment for invasive aspergillosis modified because they were refractory to or intolerant of the initial treatment. This analysis was undertaken to ascertain the outcome in patients refractory to or intolerant of currently available treatment alternatives for invasive aspergillosis.

Demographics and Baseline Characteristics:

The mean age and sex of patients were similar between Study 019 and the historical control. A minority of patients in the historical control was from non-domestic sites, compared to over half of the patients in Study 019. There was one pediatric patient enrolled (18 years) and one patient on cyclosporine.

Baseline Demographic Characteristics between the populations in Study 019 and the Historical Control:

	Study 019 N = 63		Study 028/029 N = 206	
	n	(%)	n	(%)
Mean Age (yrs)	47		48	
Sex = Male	42	(66.7)	108	(52.4)
Study Site = US	29	(46.0)	183	(88.8)
Probable pulmonary	18	(28.6)	75	(36.4)
Definite Diagnosis	45	(71.4)	131*	(63.6)
Pulmonary	27	(42.9)	79	(38.3)
Extrapulmonary+	18	(28.6)	52	(25.2)

+includes single organ involvement *>50% confirmed at autopsy

Diagnosis:

A definite diagnosis was established in similar numbers between the two studies, as shown in the above table. While a diagnosis of aspergillosis was established at autopsy only in 17 cases for the historical control, autopsy cultures also confirmed a definite diagnosis in 55% and 65% of pulmonary and extrapulmonary cases, respectively, even if the clinical diagnosis was made in life. For Study 019, (9/63) 12.5% of the patients had autopsy confirmation of invasive aspergillosis by culture. Of the 10 patients for whom autopsy cultures were done in Study 019, one was negative (511), whereas the 9 patients (018, 219, 252, 301, 386, 472, 506, 510, 512) provided confirmatory evidence for definite invasive aspergillosis.

A diagnosis of aspergillosis was based on 2 positive galactomannan ELISA for 13 patients [326, 386,411, 426, 427,471, 502,503,505,506,508,509,512] and by PCR in 2 patients [251and 417] in Study 019. The electronic database reports one positive galactomannan ELISA for an additional 9 patients [327,328,412,426,476,501,507,511, and 512]. Four patients had a negative galactomannan ELISA [329,330, 417,446]. Patient 329 had a positive BAL culture and definite disease by autopsy, Patient 330 had a positive BAL culture, patient 417 had a positive PCR on 2 separate occasions, and patient 446 had positive BAL cultures, as well as a direct exam suggestive of aspergillosis on a resected lobe. In Study 019, galactomannan ELISA was performed on various specimens, including serum, CSF, BAL fluids etc. For the historical control study, galactomannan ELISA was performed at baseline and on treatment in only 6/206 patients [5.6, 516, 518 519, 522, 524], whereas an additional 10 patients had a test done after baseline. Furthermore, only serum ELISAs were done, with no studies performed on other clinical material obtained during establishment of diagnosis (e.g BAL, sputum, and sterile body fluids).

> MO comment: For the historical control study, it is possible that the galactomannan assays were performed retrospectively, rather than integrated in the case finding process, given the highly investigational nature of these tests at the time early patients in the historical control studies were treated. While the utility of these tests in predicting response to therapy is unclear, the diagnostic value of two positive assays appears to be established, particularly in Europe (6,7,8,9).

Underlying disease:

The proportion of patients with various underlying diseases was generally similar, between Study 019 and the historical control except for a higher proportion of bone marrow transplant recipients in Study 028.

> MO comment: The risk factors for invasive aspergillosis are well described, and the similarity on proportions of underlying risk between the two studies is not surprising.

Risk Factors for Invasive Aspergillosis in Study 019 and the Historical Control:

	Study 019 N = 63		Study 028/029 N = 206	
Underlying disease:	n	(%)	n	(%)
Hematologic malignancy+	41	(65.1)	144	(69.9)
bone marrow transplant	20	(--)	85	(---)
Organ transplant	8	(12.7)	32	(15.5)
Solid tumor	3	(4.8)	10	(4.9)
Other risk factors	8	(12.7)	20	(9.7)
None	3	(4.8)	0	(0)
ANC < 500 cells/mm^3	14	(22.2)	57	(27.7)
prednisone >20mg/day	23	(36.5)	74	(35.9)

+ includes all other patients with underlying risk factors

The proportion that was neutropenic at baseline and on immunocompromising levels of corticosteroids was also similar between study 019 and the historical control study. Three patients (4.8%) in Study 019 had no underlying immunocompromise, whereas all patients in the historical control were immunocompromised. At day 7 of antifungal therapy, 57% of patients were refractory only and 27 % of patients were both refractory and intolerant in Study 019, with an overall rate of refractory of 84%. There were no analogous populations in the historical control, where 91.3 % of patients were considered refractory OR refractory and intolerant to prior therapy. In the historical control study, where intolerance is defined by a creatinine >2.5 mg/dL, a review of the creatinine at 7(± 2) days showed that 42 patients had a creatinine > 2.5 mg/dL in the first week of study entry.

> MO comment: Since only 5 patients in the historical control study were identified as only intolerant of antifungal therapy, the rest of the 37 patients with an elevated creatinine must be in the category of both refractory and intolerant, leaving 151/206 (73.3%) as refractory only, and 37 (17.96%) as both refractory and intolerant. This shows a disproportion of patients in the refractory only category for the historical controls study over that of Study 019. A reconciliation of evaluability and outcome assessments by the Applicant, Expert Panel and Medical Officer, based on patient summaries and tables submitted to the agencies is presented in the Appendix.

Response to prior antifungal therapy:

	Study 019 N = 63		Study 028/029 N = 206	
	n	(%)	n	(%)
Refractory only	36	(57.1)	188	(91.3)
Refractory and intolerant	17	(27.0)	N/A	--
Intolerant only	10	(15.9)	5	(2.4)
Creatinine > 2.5 mg/dL	10	(15.9)	42	(20.4)

For Study 019, 38 of 69 patients had a baseline creatinine greater than the upper limit of normal, whereas only 10 of these had a creatinine greater than 2.5 mg/dL. In study 028/029, a creatinine was available for only 18 patients at baseline. On treatment, however 180 of the 229 had a creatinine greater than the upper limit of normal, and of these, 42 had a level greater than2.5 mg/dL by day 7. The proportion of patients with renal insufficiency between the two studies was therefore 10 of 63 (15.9%) patients in Study 019 and 42 of 206 (20.4%) in the historical control.

The applicant presented the prior therapy of the patients in both historical control and Study 019 based on a complicated decisional analysis attributing treatment effect to any one of the antifungals taken for more than 60% of the entire treatment duration, as well as other analytic criteria forwarded to the Division. The Division was unable to confirm these analyses using the analytic criteria provided. To simplify the definition of prior therapy, the Division presents the proportion of patients in Study 019 and the historical

control who received any antifungal for any duration, in sequence or in any combination in the following table.

Prior antifungal therapy in Study019 and Historical Control:

Prior treatment	Study 019 N = 63		Study 028/029 N = 206	
	n	(%)	n	(%)
Itraconazole	39	(61.9)	94	(45.9)
Amphotericin B	37	(58.7)	123	(61.1)
Abelcet®	24	(38.1)	107	(49.3)
Ambisome®	21	(33.3)	11	(4.8)
[redacted]				
Amphotec®	2	(3.2)	13	(6.1)

*3 patients: (057, 019, 412) plus one patient who received post Cancidas®treatment (536)
** Patients 103, 256, 263, 383 received the drug concomitantly, another received the drug post therapy

A greater proportion of patients in the historical control received desoxycholate amphotericin B, and Abelcet® as prior therapy, whereas more patients in Study 019 received Ambisome® and Itraconazole®. Although none of the patients in the historical control is listed as having received an [redacted] 4 patients [103, 256, 263 and 383] received this drug as concomitant therapy, and one other patient received the drug on follow up.

> MO comment: The distribution of antifungal agents between the two studies is probably a reflection of the market availability of the agents, as Abelcet® was the first marketed lipid formulation and was used with greater frequency in the historical control. On the other hand, the intravenous formulation of Itraconazole® and the small unilamellar vesicle formulation of amphotericin B (Ambisome®) have only been recently approved for use and are more likely to have been utilized in greater frequency in Study 019.

Duration of therapy: TOTAL THERAPY:

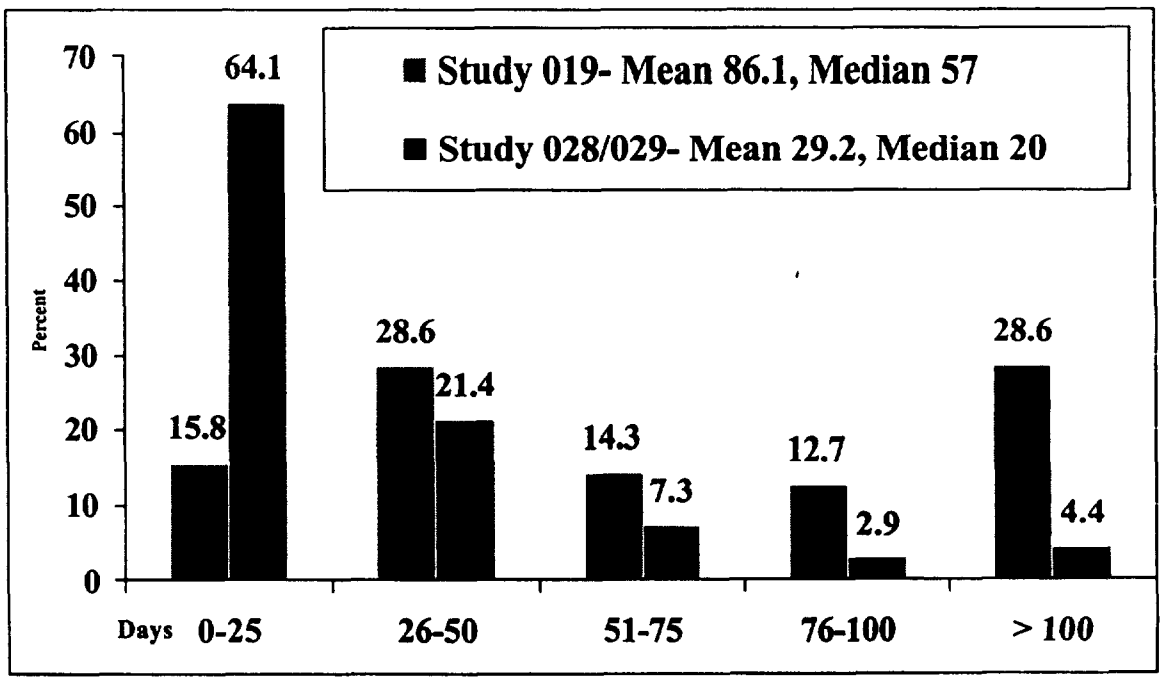


Figure 2. Duration of total therapy (in days) for Study 019 and the Historical control.

The total duration of therapy, which includes the prior therapy and Cancidas® therapy for Study 019 and the standard therapy for 028/029 is shown in this graph. The mean duration of total treatment for the Cancidas® treated patients was 86.1 days compared to 29.2 days for the historical controls. The largest difference was accounted for in the first three weeks of total therapy.

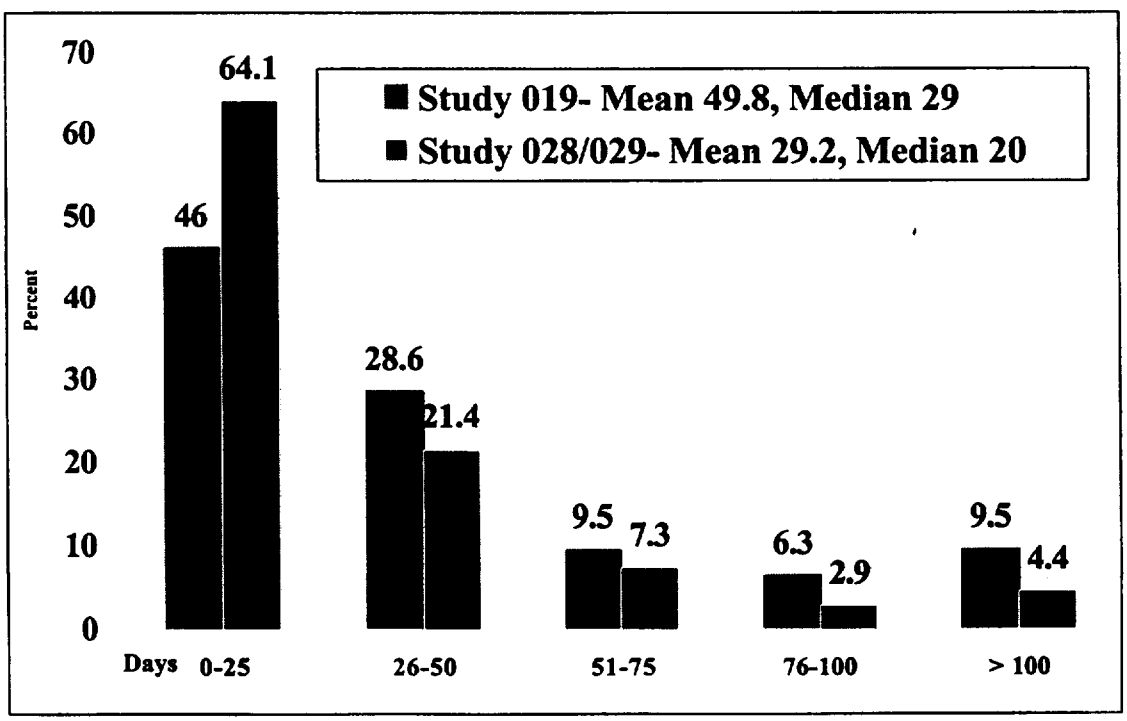
> MO comment:- While it is known that patients with invasive aspergillosis who receive short courses of therapy are less likely to respond(10), we cannot discount the possibility that the shorter duration of treatment in the historical control is due to the fact that less aggressive therapy may have been pursued for severely ill patients or that the patients may have died early. The difference in duration of total treatment between the two studies also brings into question whether the test of cure date used in 019 is comparable to the test of cure date used in the historical control. Because patients in the prospective Study 019 could receive intravenous therapy on an outpatient basis, and since information in the historical control was limited to in-hospital days, the test of cure dates may not necessarily be analogous in both studies. This limits our ability to compare the efficacy rates between both studies with confidence.

The distributions of the total length of therapy are different for the two groups. The point may be raised that the reason Cancidas® patients were on therapy longer than the historical controls was due to the fact that they were responding to Cancidas® therapy. This, however, does not seem to be the case. The next table shows how long the Cancidas® subjects were on their prior therapy versus the total duration of treatment of the historical controls.

Duration of Therapy: PRIOR THERAPY:

The distribution of the durations of the prior therapy for 019 (represented as the light bars in figure 3 in the next page) and the standard therapy for the historical bars (dark bars) are shown above. The shapes of the distributions appear to be fairly similar at first glance. However, there were far more patients in the historical control in the first category of 0-25 days, whereas the proportion of patients who received Cancidas® were more than the historical control at all later time points. This resulted in the fact that patients in Study 019 were on their prior therapy longer than the historical controls were on their total therapy, as illustrated by the difference in the means durations of 49.8 prior therapy days for Cancidas® versus 29.2 days standard therapy for historical controls.

Figure 3 Duration of PRIOR Therapy for Study 019 vs. TOTAL standard therapy for Study 028/029.



MO comment: The historical controls may be more comparable to the population of patients eligible to enroll into the Cancidas® trial (mean duration of therapy 49.8 days at the time they were identified as refractory to or intolerant of PRIOR therapy), rather than to the group of patients at the end of Cancidas® therapy (mean duration of 86.1 days TOTAL therapy, which include PRIOR therapy and Cancidas®).

Efficacy at end of therapy:

Efficacy at end of therapy for Study 019 and the Historical Control:

	Study 019 Expert Panel		Study 028/029 Investigator	
Population	n/N	(%)	n/N	(%)
All patients	26/63	(41.3)	35/206	(17.0)
Response to prior therapy				
Refractory	19/53	(35.8)	27/188	(14.4)
Intolerant Only	7/10	(70.0)	3/5	(60.0)
Site of infection				
Pulmonary	21/45	(46.7)	32/154	(20.8)
All other sites	5/18	(27.8)	3/52	(5.8)

The overall efficacy of standard therapy at end of intravenous therapy in the historical control was 17%, compared to 41 % in Study 019. The same dramatic difference in efficacy was seen in the population of refractory patients. On the other hand, the intolerant only patients did well overall regardless of which study they were a part of. Successful outcomes in the patients with pulmonary infection in Study 019 were greater than patients with pulmonary infections in the historical control, as well as those with extrapulmonary infections in both studies.

The Division reviewed the Expert Panel assessments of Study 019 and agreed with their evaluations. Additionally, the Division performed two efficacy analyses in Study 019, to achieve the following objectives:

1) To determine the overall efficacy of Cancidas® in patients who fulfill the clinical criteria of definite and probable IA at the time the decision to treat is made, excluding autopsy or culture information available subsequent to completion or discontinuation of therapy (efficacy analysis in the intent to treat population [ITT]).

2) To determine the efficacy of Cancidas® in patients who receive at least 7 days of therapy, in the same manner that the historical control population was determined to be refractory to or intolerant of 7 days of antifungal therapy (efficacy analysis in the clinically evaluable population [CE]).

The Division excluded indeterminates (n = 2) at the end-of-therapy analysis to parallel the expert panel analysis in Study 019.

Divisions' additional efficacy analyses at end of therapy for Study 019 and the Historical Control:

	Study 019 ITT		Study 019 CE		Study 028/029 MITT*	
Population	N	[%]	N	[%]	N	[%]
All patients	65	(38.5)	56	(44.6)	96	(19.8)
Refractory	54	(35.3)	45	(42.2)	90	(17.7)
Intolerant only	12	(50.0)	11	(54.0)	2	(100)
Pulmonary	51	(41.2)	46	(45.7)	76	(22.4)
All other sites	10	(40.0)	8	(50.0)	20	(10.0)

*MITT- patients with data to support inclusion in refractory or intolerant category

The analysis performed by the Division in all patients, as well as in those patients that received 7 days of therapy confirmed the overall efficacy of Cancidas® in Study 019, except for lower efficacy rates in the ITT

analysis. In the Division analysis, Cancidas®achieved clinical success rates between 38.5% to 50% in the ITT and between 44.6% and 54% in the CE analysis. The same efficacy analyses with the experts' comparative analyses is presented in the Table in page 40. The efficacy rates in the Historical Control are based on all 96 patients in the data base who had information that allowed a determination of their being either refractory or intolerant to therapy.

> MO comment: The decision to initiate treatment for invasive aspergillosis is based on a clinical syndrome, which often does not fulfill the strict criteria applied in Study 019. Thus, the ITT analysis may be more representative of the anticipated successes in patients treated outside the clinical trial setting.

Efficacy by baseline risk:

Compared to historical controls, Cancidas®was efficacious in patients with traditionally poor outcomes from invasive aspergillosis, such as acute leukemia, bone marrow transplantation, baseline neutropenia and corticosteroid use. The applicant's logistic regression analysis presented confirms the odds of a successful outcome when these predictive factors are adjusted in both populations.

Efficacy rates by Baseline Risk:

	Study 019		Study 028/029	
Population	n/N	(%)	n/N	(%)
Acute leukemia	8/17	(47.1)	9/69	(13.0)
Chronic leukemia	1/9	(11.1)	5/33	(15.2)
Lymphoma	4/8	(50.0)	1/22	(4.5)
Baseline prednisone >20 mg	8/23	(34.8)	8/74	(10.8)
Baseline neutropenia	2/14	(14.3)	4/57	(7.0)
Persistent neutropenia	0/8	(0)	0/38	(0)

Efficacy by status of underlying disease:

The Division attempted to analyze the influence of the status of the underlying disease on efficacy of treatment for invasive aspergillosis, limited to patients with hematologic malignancies. The status of the underlying disease at baseline was obtained from the electronic data sets provided. Status of the underlying disease at end of therapy was unavailable, limiting the impact of this analysis. Nevertheless, some insights may be gleaned regarding the relationship of underlying disease and treatment outcome for invasive aspergillosis. As expected, patients whose underlying disease was generally uncontrolled, based on a diagnosis of relapsed disease or the development of a graft versus host response, also failed treatment of invasive aspergillosis, whereas patients whose underlying disease was in remission, fared better in the treatment of their invasive aspergillosis.

OUTCOME OF THERAPY FOR INVASIVE ASPERGILLOSIS							
STATUS OF MALIGNANCY	Study 019 Success	Failure	%IA Success	Study 028/029 Success	Failure	%IA Success	Difference(019-HC) in IA Success
Remission	6	5	(54.5)	7	18	(28)	(29.3)
Relapse / GVHD	9	14	(39.1)	2	43	(4.4)	(34.7)
TOTAL	15(44%)	19		9(13%)	61		
IA Success			(15.4)			(23.6)	

Of note, the difference in success rates between Study 019 and the historical control narrows when the underlying disease was under control, with improvement in success rates in both Study 019 and the historical control over patients in relapse. The success rate of 54.5% in Study 019 in patients whose leukemia is in remission, approximates the success rates in patients with invasive aspergillosis whose underlying disease is other than a hematologic malignancy (11), whereas the success rate in the historical

control is still lower than that reported in the literature, suggesting that in this population of patients, other factors in addition to the status of the underlying disease may be influencing outcome of treatment. The difference in successful outcome between patients in relapse vs. patients in remission was greater in the historical control study compared to Study 019. This suggests further that for the historical control, factors other than the status of the underlying disease itself were contributing to the outcome.

> MO Comment: The dynamic interplay of underlying disease, aggressiveness of therapy for underlying disease and the independent influence of such treatment on the hosts' changing status could only be studied if the analyses accounted for these changes over time. This is particularly important as some of the patients in the Cancidas® arm were treated for up to 160 days.

Complete Response, Relapse and Death:

While the proportion of patients with successful outcomes in Study 019 were numerically higher than those for the historical control, more of the historical responses were considered completely successful outcomes, using the same criteria of clinical and radiologic clearing of baseline abnormalities. For Study 019, three patients in the original 58 cases and one additional patient in the 11 subsequent patients had complete responses to Cancidas®, for an overall complete response of 15% compared to 14/35 or 40% in the historical control study.

	Study 019		Historical Control	
	n/N	(%)	n/N	(%)
Successful outcome	26/63	(41.3)	35/206	(16.9)
Complete responses	4/26	(15.4)	14/35	(40)
Relapses	2/23	(8.6)	?/12	N/A

The completely successful outcomes in Study 019 were in three patients with pulmonary aspergillosis and one patient with a skull infection and possible CNS extension. Adjunctive therapies in three of these 4 patients consisted of lobectomy prior to 8 days of Cancidas® in one patient, resection of the skull in another, and concomitant itraconazole therapy in the third. One patient successfully underwent re-induction therapy and neutropenia with continued successful outcome of his aspergillus infection. For the historical control, comparative information on relapses is limited by the fact that follow-up information was available only for 12 of the 35 successful outcome patients (34%).

> MO comment: The expert panel did not evaluate relapse limiting the utility of this information. Furthermore, the patients in whom 4-week post end of treatment follow-up is a minority of the entire study population, with a quarter of the patients evaluable at the 4 week post treatment follow-up. Of the 26 patients in Study 019 with successful outcomes, 23 (88.5%) were evaluable at this late endpoint. One of these patients had a documented relapse, and another was suspected to have had a relapse.

There were 31 deaths (49.2%) in Study 019. Two of these deaths occurred in patients considered to have a successful outcome. Thirteen of the 17 had postmortem examination suggestive of aspergillosis on postmortem exams (9 by culture, the rest by direct examination.)

Efficacy rate by geographic site:

Success rates differed between the patients treated at the US and European investigator sites. The European patients appear to have had a higher success rate than the US patients in Study 019 study, whereas this was not evident in the historical control, where the majority of patient were obtained from US sites. This raises the question as to whether factors such as differences in the practice of patient care, different treatment regimens, or different methods of ascertaining diagnosis or outcome may influence the results of the study.