Proportion of patients	Study 019		Study 028/029	
% in U.S.	37/69 (54%)		199/229 (87%)	
% in Europe	32/69 (46%)		30/229 (13%)	
	n/N	(%)	n/N	(%)
US	10/29	(34.5)	32/183	(17.5)
Europe	16/34	(47.1)	3/23	(13.0)

MO comment: This difference in outcomes between US and European sites has also been noted for other antifungals currently being evaluated in the Division. One potential source of this difference is that galactomannan assays are far more often employed for the diagnosis of patients in Europe, potentially allowing earlier institution of antifungal therapy while the diagnosis of aspergillosis is established through more traditional methods.

Efficacy rate by duration of treatment:

Clinical Efficacy rates by total duration of treatment:

Days	Cancidas 019 N = 63		Historical 028 N = 206	
	n/N	(%)	n/N	(%)
0-25	1/10	10.0	9/132	6.8
26-50	5/18	27.8	10/44	22.7
51-75	4/9	44.4	7/15	46.7
76-100	4/8	50.0	3/6	50.0
> 100	12/18	66.7	6/9	66.7
Overall efficacy	26/63	41.3	35/206	17.0

Successful outcome in Study 019 and the historical control are presented above by the duration of treatment received. The applicant has shown that the mean successes in the overall population appear to be higher for the Cancidas® treated patients (overall efficacy). Among patients who receive total treatment for equivalent durations, however, the proportions of successes appear to be similar overall between the two studies.

Clinical Efficacy by year of treatment in the Historical Control:

Year Treated	Historical Control N	(%) Success
1995	33	12.1
1996	40	12.5
1997	70	18.6
1998	63	20.6

The above table shows the clinical efficacy of standard treatment over the four-year period covered by the historical control study. There appears to be a trend to increasing efficacy over time from 17% in 1995 to 28% in the last year of enrollment.

MO comment: While improvements in transplantation or oncology may not have occurred to a significant degree in the four years covered by the historical control, the availability of new diagnostic agents, and the consequence of earlier institution of treatment because of the newer diagnostics, may have clinical significance when evaluating the impact of therapy.

Efficacy in Cerebral Aspergillosis:

In protocol 019, definition of extrapulmonary involvement was based on histopathological evidence of infection, possibly underestimating the degree of central nervous system (CNS) involvement.

Possible cerebral aspergillosis in patients with IA			
Patient #	Initial Diagnosis	Final Diagnosis	Outcome at end of therapy
Cerebral aspergillosis clinically suspected on entry into study:			
191	probable pulmonary, possible CNS		failure
251	probable pulmonary, possible CNS		partial response
366	skull osteomyelitis, possible CNS		complete response
426	probable pulmonary, possible CNS		failure
427	probable pulmonary, possible CNS		failure
506	probable pulmonary, possible CNS	disseminated#	failure
Cerebral aspergillosis developing on treatment:			
018	definite pulmonary (possible CNS)*	disseminated w/CNS	failure
507	probable pulmonary (possible CNS)**	disseminated w/CNS	failure

developed on day 16* and 58**, respectively, # no brain autopsy

Nevertheless, in Study 019, six patients were considered to have possible CNS aspergillosis on entry into study. Two of these patients responded to Cancidas®. The first was a 66 year old diabetic female (#366) diagnosed with *Aspergillus versicolor* skull osteomyelitis following a penetrating skull injury. She developed renal insufficiency following 520 mg of amphotericin B. A CT scan of the head at the start of Cancidas® therapy showed a complex brain lesion that resolved following 27 days of Cancidas® therapy. The second patient (# 251) was a 53 year old male with a successful renal transplant who was being treated for pulmonary aspergillosis with Cancidas® following clinical failure of 36 days of liposomal amphotericin B. A head MRI done 10 days into treatment with Cancidas® revealed bilateral brain abscesses that resolved after an additional 48 days of treatment. These two patients with successful outcomes at end of therapy had received significant prior therapy with amphotericin, and were less significantly immunocompromised compared to the patients who failed therapy. The Division concurred with the diagnosis of central nervous system involvement even if this did not comply with the strict case definition.

However, using the same case definition of CNS aspergillosis, two patients (018 and 507) developed CNS involvement while receiving Cancidas®on days 16 and 58 of therapy, respectively. These two patients had autopsy confirmation of their CNS involvement, and represent the only cases of definitely established cerebral aspergillosis.

> MO comment: CNS aspergillosis develops in 10-50% of patients with invasive aspergillosis and response to therapy has traditionally been dismal, although recent successes are reported with the lipid formulations of amphotericin B, and itraconazole. In murine models of disseminated candidiasis, Cancidas® has been shown to clear infection and to achieve measurable CSF levels with the alterations in blood brain barrier associated with candida meningitis. Nevertheless, invasive aspergillosis rarely causes meningitis, rather results in an infarctive process, for which the altered blood brain barrier may be of little significance therapeutically. Of note, amphotericin B similarly does not achieve levels in CSF, but because of its lipophilic nature, accumulates in brain in levels adequate to treat CNS mycoses.

Post - Cancidas® therapy:

Eleven patients with unfavorable responses to Cancidas® received further treatment of their underlying disease. This represents a subset of the patients who were treatment failures with Cancidas®, other patients having abandoned treatment due to progression of underlying disease, whereas other patients died. This subset of patients represent a group for whom treatment was considered a viable option. Many of these patients received the same drug used an initial therapy, highlighting the limited therapeutic options for this infection. Three patients had adjunctive surgery; one discontinued Cancidas®after 50 days, received suppressive itraconazole and underwent successful segmentectomy, resulting in the only successful outcome in these 11 patients. 2 other patient died, one from a blast crisis following lobectomy, whereas the other had disseminated aspergillosis not clinically evident at surgery.

MO comment: This experience underscores the limitations of medical and surgical therapy in the face of well-established disease. The availability of more treatment alternatives expands the therapeutic options for sick patients without necessarily clarifying the degree to which these drugs affect outcome. Study 019 appears to show that treatment with Cancidas® is not less efficacious than standard therapy for patients with limited therapeutic options, whereas the historical control study suggests that available drugs do not impact eventual outcomes in well-established invasive aspergillosis. With the availability of caspofungin, three lipid formulations of amphotericin B, and the intravenous and oral formulations of itraconazole as alternatives for amphotericin B in the patient refractory to or intolerant of the drug, the next challenge is to determine whether any of these new agents do influence the outcome for the patient with true refractory disease, and whether any advantage can be gained by their concomitant use.

Alternatives for patients refractory to Cancidas®:

Patient #	Initial Therapy Pre Caspofungin	Final Therapy Post Caspofungin	Outcome
0002	AmB, ABCD	Ambisome + surgery	died
0056	Ambisome	Ambisome	failure
0057	ABLC, azole	lipid AmB	failure
0059	Azole + ABLC, lipid AmB	Ambisome + surgery	failure
0186	ABLC	ABLC	failure
0187	AmB, ABLC,	ABLC	died
0246	Itra, AmB	Ambisome	died
0296	AmB, Itra	ABLC	failed
0412	azole, Itraconazole	AmB	failed
0446	lipid AmB, Itraconazole	Itraconazole + surgery	improved
0507	AmB	azole	not known

AmB=amphotericinB, ABLC=amphotericin B lipid complex, ABCD= amphotericin B colloidal dispersion

Microbiologic outcome:

Of 22 patients with a successful clinical outcome, 6 patients had microbiologic persistence in respiratory cultures, 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. Of 4 patients with *Aspergillus terreus* infections, three were complete responses and one was a partial response. There was insufficient evidence of activity to support efficacy against *Aspergillus flavus* (5/9) and *A. niger* (1/4). There was no correlation between susceptibility to Cancidas® and clinical outcome. Treatment did not alter the MICs of subsequent clinical isolates.

MO comment: Study 019 provided microbiologic data in support of the invasive aspergillosis indication, although methodological difficulties unique to the indication limit the utility of this information. The finding of *Aspergillus spp.* in repeat cultures of respiratory specimens of patients more directly relates to the drug's concentration in sputum or alveolar fluid and does not necessarily reflect its activity in tissue. The levels of Cancidas® in alveolar fluid or sputum are not known.

Limitations of the Historical Control:

The Division comparisons between Study 019 and the historical control presented above are based on one-tailed hypotheses that the difference between the efficacy in Study 019 and the historical control study are narrower than presented by the applicant's analyses. It is acknowledged that this difference could be wider or narrower than the data suggests it to be. As documented in the medical literature, the use of a historical control can lead to false conclusions of an observed effect, due to a number of biases that limit comparability. On consult with the Office of Post Marketing Drug Risk Assessment (see review by Dr.

Judy Staffa, OPDRA), the potential sources of bias the review team had identified were organized into three categories: information bias, bias from secular trends in diagnosis or treatment and selection bias.

In the historical control study, the retrospective abstracted data had limited information on concomitant medications and underlying disease, making it difficult to compare clinical severity. The information available for review by the experts differed between the two studies. More often, information is more accurate and complete for the current treated group than for historical controls. This better information could lead to an apparent treatment effect or the lack of it when there actually is one, that is in actuality due to differences in the quality of information available. There were far fewer European patients in the historical control group than in the Cancidas® treated groups and these patients appeared to have a higher success rate than the US patients. This difference in outcomes favoring patients treated in European sites has also been noted with [redacted] an as yet unapproved antifungal, raising questions about possible differences in treatment, supportive care, or susceptibility of isolates between US and European sites. Duration of therapy was different between the two studies and exclusionary criteria were more extensive for Study 019. The Cancidas® study (019) excluded patients who would not have been excluded from the historical controls. Differences in exclusion criteria between groups likely permitted sicker patients to be enrolled in Study 028/029, while excluding such patients from enrollment in 019. Poorer quality of information may have made successful outcomes more difficult to detect in the historical control group than in the treated group.

For a patient in the historical control to qualify for inclusion into Study 019, a patient must survive long enough to receive treatment. This duration on therapy prior to qualifying for treatment with the study drug can be referred to as guaranteed survival time. One potential bias in the comparison of the historical control to Study 019 is a certain amount of "guaranteed survival time" of the Cancidas® subjects. In contrast, patients only need to receive a diagnosis of invasive aspergillosis and receive 7 days of antifungal therapy to be included in the historical control group. The exclusion of patients not likely to survive 5 days of Cancidas® therapy further adds to this guaranteed survival time for Study 019. Chances are that subjects who received only 7 days of prior therapy but who were most likely to not survive for another few days would not have been enrolled into the Cancidas® trial. These subjects, however, could have been "enrolled" into the historical control trial. The result of this would be a larger percentage of failures or deaths on the historical control arm. In addition, the total duration of treatment differed between the two studies. The Cancidas® treated patients (Study 019) received treatment for longer periods than the historical control patients did. The Cancidas® patients had their prior therapy for anywhere from 2 – 90+ days, plus they would have received the additional Cancidas® therapy (1 – 163 days). While the historical control patients only received the primary therapy (again from 7 – 90+ days) and were then determined to be successes or failures.

It is possible that (based upon both secular trends and various types of selection bias) sicker patients were enrolled into the historical study but not the Cancidas® study. While market availability and not selection bias may have influenced the differential use of antifungal agents as prior therapy, the influence of the different prior therapies on outcome cannot also be discounted, even if patient were considered refractory. Given the strict criteria for improvement for a disease whose radiographic resolution of infiltrates is well described in the literature, the 7 days cut-off in describing response to prior therapy may be valid for the profoundly neutropenic patient with rapidly progressive disease, and too brief for the stable solid organ transplant recipient whose disease is more slowly progressive. The historical success rate increased by year of enrollment, with more recently treated patients having more favorable outcomes. Study 019 was completed 2 years after the historical control. The difference in efficacy between Study 019 and the historical control may therefore be a function of the temporal trends in treatment or diagnosis of the underlying disease or of invasive aspergillosis rather than due to Cancidas® alone.

All of these biases could act to predispose the historical controls to have a lower success rate and the Cancidas® treated group to have a higher success, independent of treatment with Cancidas®. Notable differences between 019 and 028 may provide alternative explanations for at least part of the treatment effects seen. Therefore, while it is not clear that all of the observed treatment effect is due to treatment with Cancidas® it is equally difficult to quantify the potential effects of these biases on the treatment difference.

MO comment: The patients enrolled into two studies required stringent definitions of disease and outcome, allowing confidence that both populations fulfilled the diagnosis and that outcomes were reliably documented. The limitations of a historical control as described above, do not negate the validity of the efficacy described in the two populations, but does call into question the ability to compare the efficacy between the two studies with full confidence. Although the historical control in this study is fraught with potential sources of bias, there has been an attempt to provide information beyond what has previously been utilized to support previous drug approvals for the indication under consideration in this NDA. The historical control for Amphotec® and Abelcet® did not attempt to define a population analogous to the actively treated study population while the Itraconazole® historical cohort consisted of patients enrolled in the compassionate study who for one reason or the other did not receive the study drug. Furthermore, the applicant attempted to present an independent assessment of outcome was attempted with the introduction of an expert reviewer blinded as to site. On the whole, however, the historical control study at best provided a perspective, which, together with efficacy data from prospectively studies from the other NDA reviews, provided an approximation of the efficacy of existing antifungal agents for patients refractory to or intolerant of amphotericin B.

Outcomes of patients in historical control patients receiving desoxycholate amphotericin B in the NDAs of antifungal agents approved for salvage therapy

Drug (Date Approved)	Design, Endpoint Outcome	Efficacy of dAmB	
		N	% success
Itraconazole (1992)	concurrent / EOT / mortality	43	10
ABELCET (1995)	historical / EOT / clinical success	(91)	23
AMPHOTEC (1996)	historical / EOT / clinical success	(60)	43
	concurrent / EOT /clinical success	37	33
AMBISOME (1997)	concurrent / EOT /clinical success	16	31

+Numbers in parenthesis refer to evaluable patients obtained from historical control studies.

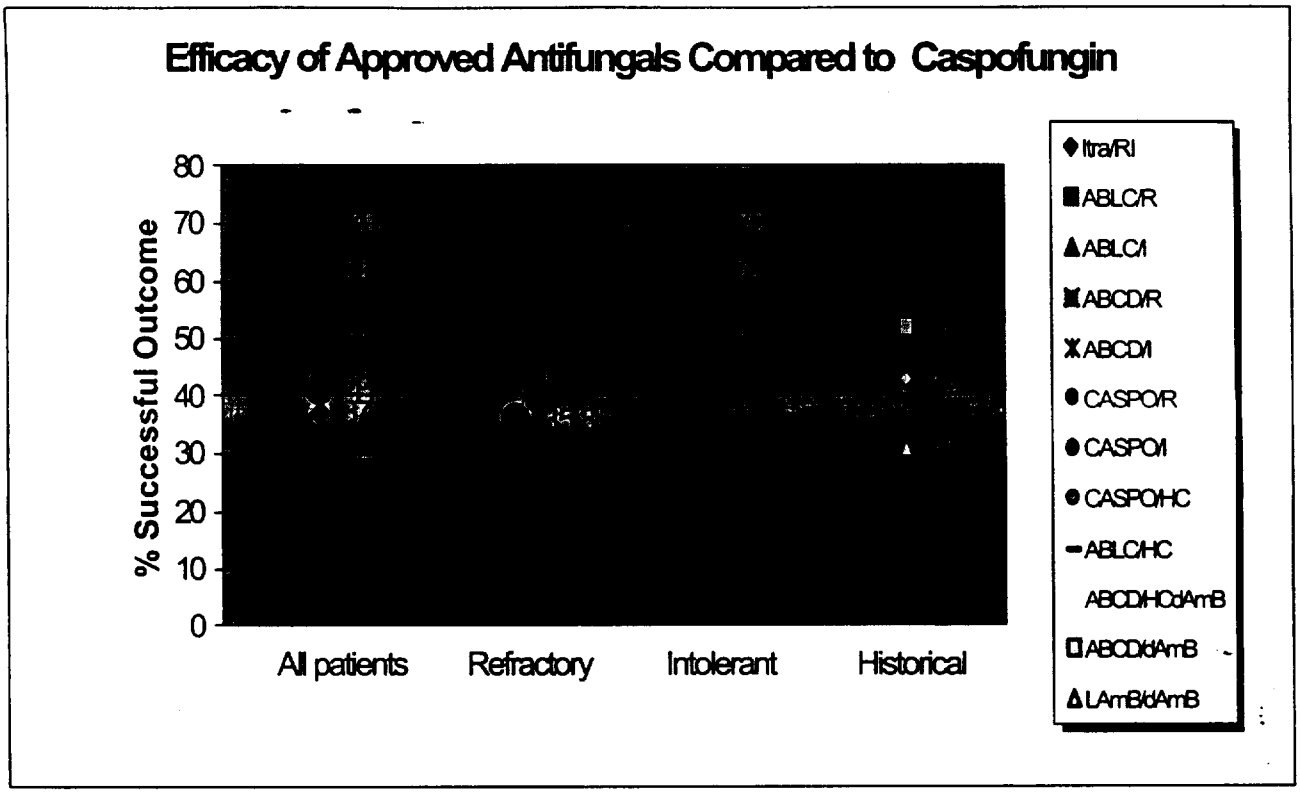
Conclusion

There are reports in the literature suggesting an early trend to improved outcomes and diminishing mortality in patients with invasive aspergillosis [12, 13, 14]. A number of factors may be contributing to this observation, including the availability of newer diagnostic tools such as PCR and galactomannan, the early and aggressive use of CT scanning, the availability of newer formulations of antifungals, and improved support for underlying disease. Nevertheless, the impact of these advances is limited for patients with established disease who are refractory to current therapy or unable to tolerate drug toxicity.

The outcome of patients who are refractory 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.

In addition, the efficacy in Study 019 is similar to the efficacy in the data that supported the approval of the existing therapies for refractory and intolerant patients with invasive aspergillosis.

The following graph illustrates the range of successes for the overall populations in the NDAs of the lipid formulations of amphotericin B, as well as the patients who were refractory to or intolerant of amphotericin B and the accompanying historical controls in those submissions. The successful outcomes in the overall population in Study 019, as well as those in the refractory and intolerant groups are similar to the efficacy of the lipid products submitted to the Agency, using similar patient populations treated under similar clinical conditions.



The efficacy rates for Cancidas® also approximate those for other antifungal agents reported in the recent literature, with response rates varying from 25% complete responses to amphotericin B to 57% for the lipid complex of amphotericin B (15, 16).

The efficacy of Cancidas® in Study 019 is well documented, with the expert panel's independent assessment based on review of radiographs and full access to clinical material not otherwise available in case report forms. The efficacy is further supported by a comparison of the efficacy in these studies to the range of responses of other therapies in the NDAs submitted to the Division, and the described efficacy of these products reported in the literature.

It is important to emphasize the limits of efficacy proven in this study. The drug's activity is proven only in patients previously intensively treated with other antifungals. Efficacy is proven only until the end of intravenous treatment. CNS infections could emerge on treatment. The efficacy of Cancidas®at higher doses, in patients that receive metabolic inducers and cyclosporine, and its use as initial treatment have not been studied. Further, the durability of successful outcomes, in terms of prevention of relapses, is also not known for this fungistatic agent.

While randomized comparative studies would allow a better evaluation of drug effect for refractory or intolerant patients, most of the concurrent controlled studies submitted thus far have been in the context of an initial treatment indication, and most of these studies have failed to complete enrollment. The increased prevalence of aspergillus, however, may account for the fact that several competing products are able to recruit patients into salvage studies, and may allow some comparative studies in the future.

Clinical Efficacy Rates for Study 019
as per the Expert Panel / FDA Analyses
compared to outcomes in the historical Controls (study 028)

	Cancidas® (Protocol 019)				Historical Control					
	Expert Panel		FDA ITT		FDA CE		Applicant MITT		FDA Subset MITT[¶]	
Population	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
All patients	26/63	(41.3)	25/65	(38.5)	25/56	(44.6)	35/214	(16.4)	19/96	(19.8)
Refractory	15/44	(34.1)	19/54	(35.3)	19/45	(42.2)	27/193	(14.0)	16/90	(17.7)
Intolerant Only	7/10	(70.0)	6/12	(50.0)	6/11	(54.0)	3/5	(60.0)	2/2	(100)
Pulmonary	21/45	(46.7)	21/51*	(41.2)	21/46	(45.7)	32/160	(20.0)	17/76	(22.4)
All other sites	5/18	(27.8)	4/10*	(40.0)	4/8	(50.0)	3/54	(5.6)	2/20	(10.0)

**6 patients with pulmonary infection suspected to have CNS aspergillosis

* 1 patient with scalp osteomyelitis developed brain abscesses that subsequently resolved with continued therapy

¶ FDA subset of the MITT= patients in the applicant's MITT who were defined in the submitted database to be either refractory to (7 days) or intolerant of (before or at 7 days) any antifungal agent(s)

APPEARS THIS WAY
ON ORIGINAL

Review of Safety:

Methods of review:

The Division reviewed the proportion of patients with adverse events occurring at least 1% in the clinical pharmacology and clinical studies. The adverse event rates for the drug were compared to the rates adverse event rates of the comparator antifungals in the mucosal candidiasis studies, and comparing rates of adverse vents between the healthy subjects and the patient populations with mucosal candidiasis and invasive aspergillosis. The Division reviewed individual cases of adverse events provided for all deaths and serious adverse events. In addition, a review of the liver function test abnormalities was performed by Dr. Leonard Sacks (see accompanying report), that looked at the mean elevations of transaminases alone and in combination with bilirubin as well as outliers with elevations greater than 5x the upper limit of normal. An analysis of the elevations of creatinine was similarly performed both in the clinical pharmacology and the clinical studies. To determine whether histamine mediated reactions developed, the Division reviewed the individual adverse events in the respiratory, skin ands skin structure and general body systems, to assemble a syndrome simulating histamine release. Cases of definite, probable and possible histamine release are presented in tabular form. Because of the pre-clinical finding of cortisone related deaths associated with infarcts and embolic phenomena reported for the [redacted] echinocandin, the adverse events database was also reviewed for the proportion of deaths in patients with corticosteroids and those in without, as well as the frequency of possible vascular embolic events.

Clinical Studies and Outline of Safety Discussion:

A general overview of the safety of Cancidas® is presented based on the pooled data from all pharmacological studies and the clinical trial studies for the indications of invasive aspergillosis and mucosal candidiasis. Safety in the pharmacological studies is presented next. The pharmacological studies are an important source of information on the safety of Cancidas® because the population consisted of relatively healthy people, some of whom had stable underlying illness and no confounding factors, as well as healthy volunteers. The limitation of the information derived from these studies, however, is that generally single doses were administered under controlled conditions.

Safety in patients with fungal infections is presented according to the indication studied. The studies in patients with fungal infections complement safety information from the pharmacological studies as they reflect the intended use of the drug, in a population of patients on multiple concomitant medications and with multiple confounding background illnesses. The studies in patients with mucosal candida infections further provide Cancidas® safety information comparative to amphotericin B and fluconazole.

The final section of the safety discussion deals with safety issues for this new class of agents identified from the preclinical studies. Other rare but important adverse events are also presented. Since Cancidas® is the first of its class to seek approval for an indication, specific consideration has been given to preclinical indicators of potential risks of the Cancidas®, as well as safety information on other echinocandins based on previous IND submissions and review of relevant literature.

Extent of Drug Exposures:

Two hundred seventy four (44.8%) of 612 individuals who received Cancidas® in clinical trials, were healthy adults who received generally single doses of Cancidas® in the clinical pharmacology studies. An additional 338 (55.2%) patients with fungal infections received multiple doses of Cancidas®. Eighty-one of the 274 subjects enrolled in 12 clinical pharmacology studies and 223 patients with fungal infections received the proposed dose of Cancidas® (50 mg, 304/612 or 50%). The patients in the clinical pharmacology subjects generally received single doses. In the clinical studies, only 45 of 233 (or 19 %) of exposures in the proposed dose represented the durations of treatment generally employed for invasive aspergillosis (>15 days). Thirty four patients received

the lower dose of 35 mg, 233 received the proposed dose of 50 mg and 71 received the highest dose of 70 mg, which represented (one fifth) 21% of all exposures in patients with fungal infections. The applicant proposes this dose in the label for patients who do not respond to the 50-mg dose.

Extent of drug exposures of Cancidas® in patients with fungal infections:

	Dose			
Duration (days)	35 mg	50 mg	70 mg	Total
1 – 7	13	72	15	100
8 – 14	21	116	54	191
15– 28	0	21	1	22
> 28	0	24	1	25
Total	34	233	71	338

Overview of Safety:

The overall safety of Cancidas® in healthy subjects and patients are shown in the following table. As expected, adverse event experiences were more common in patients with fungal infections compared to healthy subjects. Interestingly, adverse events were more often attributed to Cancidas® in the patients with mucosal candidiasis, over 90% of whom were patients with HIV infections, a population reported to be generally more sensitive to drugs.

In the generally sicker patient category of invasive aspergillosis, any event was more likely attributed to the underlying disease or accompanying therapies for underlying disease. The greater proportion of deaths in these patients supports this finding. A greater proportion of patients in the invasive aspergillosis study discontinued drug due to an adverse event. A review of these cases revealed that the decision had been made to discontinue treatment because of disseminated cancer or progressive aspergillosis, and not an adverse event directly attributable to Cancidas®.

Only one patient in the entire database was considered to have a serious drug-related adverse event - that of an allogeneic bone marrow transplant recipient who developed bilateral pulmonary infiltrates on day 24 of therapy with Cancidas®. No etiology for his infiltrates could be determined after bronchoalveolar lavage and serological studies.

Overall Cancidas® Safety:

	Healthy subjects N = 274		Mucosal candidiasis N = 263		Invasive aspergillosis N = 69	
	n	(%)	n	(%)	n	(%)
W/ an AE	127	46.4	235	89.0	64	92.8
W/ a DRAE	68	24.8	127	48.3	10	14.5
W/ a serious AE	7	2.6	49	19.8	54	78.3
W/ a serious DRAE	0		0		1	1.5
D/C due to an AE	11	4.0	7	2.7	27	39.1
D/C due to a DRAE	5	1.8	3	1.1	1	1.5
Deaths	0		15	5.7	38	55.1

Safety in Clinical Pharmacology Studies

The discussion of the safety of Cancidas® from clinical pharmacology is based on analysis of the pooled data of all single dose and multi-dose clinical pharmacology studies, given the relative small size of the individual studies. The information pertinent to individual studies as they relate to special populations and drug -drug interactions is discussed after the general safety from the pooled studies is presented.

CLINICAL ADVERSE EVENTS in the Clinical Pharmacology studies:

The most common clinical adverse experience in the clinical pharmacology studies include headache and infused-vein complication (pruritus, erythema, induration, and pain). Seven patients had a serious adverse event, none of which was considered by the investigator to be drug related. There were no deaths, or discontinuations attributed to the study drug alone or in combination.

Two subjects (0727 and 0733), had serious adverse events that required hospitalization:
1.) Subject 0727 received Cancidas® 50 mg daily on Days 1 to 10 with Tacrolimus 0.1 mg/kg every 12 hours on Days 1 and 10. On Day 17, he developed pain in his lower right leg, and three days later, he was admitted to the hospital for deep venous thrombosis. This adverse experience was moderate in intensity and continued for 15 days, and was considered by the investigator as probably not drug related.
2.) Subject 0733 received Cancidas® 50 mg daily for 4 days with [redacted] placebo on Day 1. He was admitted to the hospital for cellulitis at the injection site following his Day 4 treatment, for which he received antibiotics and improved. The investigator considered this adverse clinical experience as probably not drug related. The subject discontinued from the study due to this adverse experience.

Adverse events by body system:

Phlebitis and headaches were the most frequent adverse event. Rashes were frequent, but noted with greater frequency in patients that received itraconazole concomitantly. Drug-related rashes appeared to be more frequent (4 of 11 subjects) in the group who received itraconazole with Cancidas® compared to the group that received Cancidas® alone (0 of 28 subjects). The rate of rash with Cancidas® was not more frequent than the rate of rash in subjects that received itraconazole alone (0 of 8 subjects). Other dermatological adverse experiences in the group who received both itraconazole with Cancidas® (6 of 11 subjects) were frequent more than in the group that received Cancidas® alone (0 of 28 subjects) ($p<0.05$) but were not more frequent than the group that received itraconazole alone (3 of 8 subjects). Since rash is recognized adverse event with itraconazole, it is uncertain whether this increase is due to Cancidas®. It is unclear given the small data set of this clinical pharmacology study, whether the true incidence of dermatological adverse experiences is higher on Cancidas® plus itraconazole than on itraconazole alone. Itraconazole had no effect on the pharmacokinetics of Cancidas®, nor did Cancidas® influence the pharmacokinetics of itraconazole.

> MO comment: This small study looking at the interaction of Cancidas® with itraconazole is the only study that provides safety information for Cancidas® compared to an agent approved for the indication of refractory to or intolerant of invasive aspergillosis. There is no safety comparison to the liposomal agents in the NDA.

Laboratory Adverse Events:

Transaminase Elevations: (see also Dr. Leonard Sack's review)

The most frequent laboratory adverse event was an elevation of liver function tests. Most of these elevations were <3X the ULN. Four subjects in the clinical pharmacology studies had transaminase elevations greater than 3x the ULN. None of these patients had a concomitant elevation in bilirubin.

Subjects who received caspofungin 70 mg daily with cyclosporine mainly accounted for the increased incidence of elevated ALT and AST in the category of patients who received caspofungin with other drugs.

		Transaminase elevation *	
CaspofunginDose	Immunosuppressant Dose/Day	Any	2X ULN
70 mg x 10 days	Cycloporine 3mg/kg day 10	3/4	3/4 (2 had >3X ULN)
35 mg x 10 days	Cycloporine 3mg/kg day1	2/8	0/8 (none had >3X ULN)
70 mg x 10 days	Tacrolimus 0.1mg/kg q12 day 10	3/12	1/12 (x had >3X ULN)

*none had bilirubin elevations

MO comment: Cancidas® like other echinocandins, may cause transaminase elevations, although a dose relationship cannot be concluded based on the number of exposures at the higher dose levels (70 and 100 mg). In addition to cyclosporine, some elevation may also occur in patients that receive tacrolimus, although based on the limited information; it does not appear to be higher than that observed in the entire safety database. The extent of transaminase adverse events with tacrolimus will be difficult to understand in the aspergillus treatment study because of the severe co-morbidities in that patient population.

Elevation in Serum Creatinine:

Although infrequent, increases in serum creatinine to 1.5 times [redacted] baseline occurred even when Cancidas® was administered alone.

Creatinine increase	Cancidas® Alone	Cancidas® in combination	Total n/N	(%)
≤50 mg	0/75	0/42	0/117	0
>50 mg	4/115	1/40	5/156	3.20

(From Applicant's Table E11, Clinical safety, p E-49-51)

Most of these elevations developed in patients with baseline renal insufficiency, and were generally < 1.5 X baseline. These elevations developed only with the highest dose studied, but these patients also were part of a study of patients with underlying renal insufficiency. Only one patient had this elevation reported by the investigator as an adverse event: Subject 0384 in the Cancidas® clinical pharmacology study of patients with renal insufficiency (Study 11) had a laboratory adverse experience of increased serum creatinine from a baseline of 2.64 mg/dL [redacted] to 3.10 and 3.03 mg/d, on days 10 and 29 respectively following a 70-mg IV dose of Cancidas® One other healthy subject in Study 001, the single rising dose study, with a normal baseline creatinine of 97mmol (SI), had an elevation of creatinine to 141 *m*mol (SI) on Day 8, after a 40 mg Cancidas® dose. This elevation was 1.45X baseline and is of uncertain significance.

MO comment: The influence of higher doses of Cancidas® on patients with normal renal function cannot be predicted on the basis of single dose studies. Nevertheless in patients with baseline renal insufficiency, minor elevations in creatinine have been rarely seen after a single dose of 70 mg.

Safety conclusions from Clinical Pharmacology studies:

The most frequent infusion related adverse events were headaches, and phlebitis. The most frequent laboratory drug-related adverse event was transaminase elevations; none associated with bilirubin elevation, enhanced with cyclosporine co-administration. There appears to be a trend to dose relatedness with both transminase and creatinine elevations, but these are confounded by the study dosing that utilized the highest doses to study the interaction with cyclosporine, tacrolimus and renal insufficiency. Nevertheless, since cyclosporine is associated with an elevation of the C_{min} of Cancidas® and since the transaminase elevations were numerically more frequent with the 70-mg Cancidas® dose than the 30 mg dose when given with cyclosporine, there is basis to consider that higher doses of Cancidas® may be associated with these adverse events.

Safety in Clinical Studies:

Clinical Adverse Events in the Mucosal Candida studies:

Four hundred fifty-five patients with mucosal Candida infections received Cancidas®. None of the patients that received Cancidas® experienced a serious drug-related clinical adverse event. The incidence of drug-related clinical adverse experiences was generally similar among the Cancidas® patients that received either 35-mg, 50 -mg or 70-mg doses (45.1 to 55.4%). Discontinuations due to drug related adverse events were infrequent (6/445 or 1.3%). No deaths in these studies were attributed to drug.

Comparative Clinical Safety:

The overall safety of Cancidas® compared to amphotericin B and fluconazole are shown in the previous table. Compared to amphotericin B, systemic infusional toxicities (fever and chills), and local infusional adverse

events (pain and phlebitis) were less common with Cancidas® but more common than those observed with fluconazole.

	Cancidas® N = 263		Amphotericin B N = 89		Fluconazole N = 93	
	n	(%)	N	(%)	N	(%)
Fever (DRAE)	44	(17)	62	(70)	1	(1)
IV site AEs	49	(19)	21	(24)	16	(17)
Respiratory	5	(1.9)	7	(7.8)	0	(0)
Skin	18	(6.8)	15	(16.8)	1	(1.1)
Hypersensitivity	3	(0)	4	(4.5)	1	(1.1)
Candidiasis	27	(10)	3	(3.4)	5	(5.4)
	n/N		n/N		n/N	
Hypokalemia	14/261	(1.1)	28/89	(6.5)	0/92	(0)
Elevated creatinine	1/261	(0.4)	25/89	(28)	2/92	(2.1)

Flu-like illnesses, facial edema, and myalgia were more prominent with Cancidas® compared to amphotericin B, although hypersensitivity, dermatological and respiratory adverse events were more frequent with amphotericin B. Tachypnea or bronchitis (13 or 4.9%) were more frequently observed in the Cancidas® treated patients compared to amphotericin B or fluconazole (bronchitis: 0 and 1 patient, respectively). Twenty-seven patients developed mucosal candidiasis (10%) in the Cancidas® treated group compared to 3 in the amphotericin B (3.4%) and 5 (5.4%) in the fluconazole group. Additional adverse events identified in the Cancidas® treated group include Histoplasmosis and Cryptococcal meningitis.

Laboratory adverse events in Mucosal Candidiasis studies:

LABORATORY ADVERSE EVENTS: Creatinine elevations:

A mean increase in creatinine of 1.1 times baseline [redacted] was noted in patients who received Cancidas® compared to a mean increase of 2 times baseline [redacted] in patients who received amphotericin B, whereas eosinophilia (3.1%) was more frequently reported for Cancidas® treated patients compared to those that received amphotericin B (1.1%).

LABORATORY ADVERSE EVENTS: Transaminase elevations:

Six patients who received Cancidas® (6/263) and 2 patients who received Fluconazole had elevations of transaminases over 3 x the upper limit of normal as well elevations in total bilirubin (>20). These patients are not reflected in the table below, which only lists adverse event rates >3%, but are listed in detail in the review of Dr. Sacks. The rate of significant transaminase elevations with concomitant raised bilirubin was similar between Cancidas® (6/263, 2.3%) and fluconazole (2/93, 2.22%).

For adverse events occurring > 3%, there appeared to be no dose related trend for increased transaminases. Creatinine elevation, hypokalemia, and pyuria were more commonly seen with the 70mg dose, although the numbers of patients were small. Eosinophilia was more frequent with Cancidas® compared to the comparators

Drug-related Laboratory Abnormalities among Patients with EC/OPC (comparative studies)*
Incidence >3% (for at least one treatment dose) by Laboratory Test Category

	Cancidas® 50 mg (N=164) (percent)	Cancidas® 70 mg (N=65) (percent)	Fluconazole 200 mg (N=93) (percent)	Amphotericin 0.5 mg/Kg (N=89) (percent)

Blood Chemistry				
ALT increased	10.5*	10.8*	12.0	22.7
AST increased	13.0*	10.8*	13.0	22.7
Serum albumin decreased	8.6	4.6	5.4	14.9
Serum alkaline phosphatase increased	10.4	7.7	12.0	19.3
Serum calcium decreased	1.8	0.0	3.3	1.1
Serum creatinine increased	0.0	1.5	2.2	28.1
Serum potassium decreased	3.7	10.8	4.3	31.5
Serum sodium decreased	1.8	1.5	3.3	1.1
Total serum bilirubin increased	0.0*	0.0*	3.3	4.5
Total serum protein decreased	3.1	0.0	3.3	3.4
Hematology				
Eosinophils increased	3.1	3.1	1.1	1.1
Hematocrit decreased	11.0	1.5	5.4	32.6
Hemoglobin decreased	12.3	3.1	5.4	37.1
Platelet count decreased	3.1	1.5	2.2	3.4
WBC count decreased	6.1	4.6	8.7	7.9
Urinalysis				
Urine protein increased	1.2	0.0	3.3	4.5
Urine RBC's increased	1.1	3.8	5.1	12.0
Urine WBC's increased	0.0	7.7	0.0	24.0

Summary of Safety in Mucosal Candidiasis:

Compared to amphotericin B, Cancidas® appears to have less acute general toxicities, including fever, rigors. Symptoms suggesting hypersensitivity (myalgia, tachypnea, rash, facial edema) were noted in patients that received Cancidas®. Similar toxicities, including one case of anaphylaxis and erythema nodosum, were seen with amphotericin B. Compared to amphotericin B, there were less renal toxicities associated with Cancidas®. Similarly, electrolyte abnormalities such as hypokalemia were seen with Cancidas®, at a much lesser frequency than amphotericin B. Transaminase elevations with hyperbilirubinemia occurred at a frequency similar to that of fluconazole. Two patients who received repeated doses of the drug in Study 007 did not have any untoward events.

Clinical Adverse Events in Invasive Aspergillosis:

This section summarizes the adverse experience profile of Cancidas® from the open-label non-comparative salvage study for the treatment of invasive aspergillosis (Protocol 019). While the dose employed in this study is similar to that utilized in the mucosal Candida studies (003, 004, 0202, 007), the adverse event rates from this study are expected to be high given the nature of the predisposing underlying disease and the duration of treatment. This study evaluated Cancidas® administered intravenously at a loading dose of 70 mg on Day 1, followed by 50 mg daily for the remainder of the treatment period. These patients had complicated, severe underlying diseases requiring multiple concomitant therapies. Most patients were severely immunocompromised and received Cancidas® for more than 28 days.

Of the 69 patients enrolled in the Aspergillus study, 14 (20.3%) received Cancidas® for >7 days, 13 (18.8%) patients received 8-14 days of therapy, 13 (18.8%) received 15-28 days, 18 (26.1) received 29 to 60 days, 7 (10.1%) treated for 61 to 90 days, and 4 (5.9%) treated for >90 days. Twenty-seven patients (39%) had exposures longer than the 14-day course that was given to patients in the mucosal candidiasis studies.

As anticipated, the overall incidence of clinical adverse experiences was high (67/69 or 93%) majority of which were considered serious (75.9%), although the incidence of drug-related clinical adverse experiences was 13.8%. While the incidence of serious clinical adverse experiences was high (75.9%), the investigators attributed only one adverse event to the drug. 41% of patients discontinued therapy due to an adverse event,

most of these adverse events relate to the underlying disease, or worsening of invasive aspergillosis. While 37/69 (53%) of the patients died, none of these deaths were attributed directly to Cancidas®. Adverse events in this patient population include death (55.6%), edema/swelling (19.5%), fever (22.2%), hypertension (19.4%), rash (16.7%), nausea (13.9%), and headache (15.3%). Serious adverse events are summarized in the table in the following page.

Drug related adverse events developed in 10 patients. These included headaches (1), nausea (2), fever (2), flushing (2), rash (1), hypotension (1), vasovagal event (1), pulmonary infiltrates (1), hypokalemia (1) and renal insufficiency (1). Flushing was a distinctive drug related adverse event in two patients. One patient was a 45 year-old female who experienced flushing ("sensation of warmth") accompanied by a rash, stomatitis and peri-buccal exanthema starting on Day 3 through 6 of Cancidas® therapy. These symptoms resolved on continued Cancidas® therapy with no associated eosinophilia, or increased liver function tests.

Rashes were seen in 12 additional patients without any other feature compatible with a histamine reaction. Only one serious clinical adverse event was drug related, that of a 38 year old patient post allogeneic bone marrow transplant for multiple myeloma who developed pulmonary infiltrates, for which the investigator discontinued therapy. None of the other serious adverse events, including deaths, edema/swelling, or hypotension were drug related.

Laboratory Adverse Events in Invasive Aspergillosis:

Twenty-six of sixty-eight patients (38.2%) in Study 019 experienced a laboratory adverse event. Of these 26, 11 (42%) were considered drug related. Nevertheless, the overall incidence of drug related adverse events in this population of severely ill patients on multiple medications is 16% (11/68). Only one of these adverse events was considered a serious drug-related adverse event. This was the patient (Patient 0056) who developed renal insufficiency and hypercalcemia described subsequently (see Other safety issues section). The most common laboratory adverse event was an increase in alkaline phosphatase (21.1%), increased AST (14.8%) and ALT (14%). Only one of these hepatic adverse events was considered drug-related (Patient 316), whereas the rest of the cases were confounded by other factors and were judged by the investigators to be unrelated to the study drug. The other drug related adverse events include elevated eosinophils in 2 patients (14% 17% of WBC for patients 0059 and 0251, both resolved), isolated proteinuria in 3 patients, increased tacrolimus levels in 2 patients and one report each of elevated serum LDH, hypokalemia, neutropenia, thrombocytopenia, elevated PTT and hematuria. Other than the patient with hypercalcemia, none of these drug-related adverse events was considered serious.

Summary of Safety in Invasive Aspergillosis:

The dose employed in the invasive aspergillosis study was similar to that utilized in the mucosal Candida studies. However, given the severe underlying diseases predisposing to aspergillosis and the longer duration of treatment for this infection, the adverse event rates from this study are higher than those reported for the patients with mucosal Candidiasis. Nevertheless, while clinical adverse events were frequent (93.1%) and often serious (75.9%) in the 69 patients with invasive aspergillosis, the incidence of drug-related clinical adverse experiences was 13.8% compared to the 48% rate in the Candida comparative trials. No deaths were directly attributable to the drug, and only one serious drug related adverse event was felt to be drug-related. This database had the potential of demonstrating adverse event rates from longer treatment exposures but the confounding factors in the severely ill patient makes it difficult to obtain an accurate picture of the events attributable to the drug alone.

Applicant's Adverse Events by Body System in Invasive Aspergillosis Infections (019)

Adverse Event	N	(%)	Drug Related
Body as a whole	57	(79.2)	5
Aspergillosis	11	(15.3)	
Death	40	(55.6)	
Fever	16	(22.2)	2
Edema/swelling	14	(18.5)	
Vasovagal reaction	1	(1.4)	1
Warm sensation	1	(1.4)	1
Cardiovascular	33	(45.8)	3
Arrhythmia	5	(6.9)	
Heart failure	3	(4.2)	
Hypertension	7	(9.8)	1
Hypotension	14	(19.4)	
Infused-vein complication	6	(8.6)	2
Respiratory	50	(69.4)	1
Aspergillosis, pulmonary	4	(5.6)	
Asphyxiation	1	(1.4)	
Dyspnea	7	(10.1)	1
Respiratory distress	5	(6.9)	
Respiratory distress syndrome	4	(5.6)	
Respiratory failure	11	(15.3)	
Respiratory insufficiency	5	(6.9)	
Rales	7	(10.1)	
Bronchitis	2	(2.8)	
Congestion, nasal	7	(10.1)	
Pneumonia (1 proven viral, 1 proven bacterial, 4 no etiology	7	(10.1)	
Hemoptysis	4	(5.6)	
Hemorrhage, pulmonary	3	(4.2)	
Wheezing	1	(1.4)	
Digestive	35	(48.6)	4
Nausea	10	(13.9)	2
Vomiting	8	(11.1)	2
Diarrhea	11	(15.3)	1
Hepatomegaly	3	(4.2)	
Oral candidiasis	3	(4.2)	
Skin and skin appendage	27	(37.5)	2
Flushing	2	(2.8)	2
Erythema	5	(6.9)	
Rash	12	(16.7)	1
Pruritus	2	(2.8)	
Metabolic	16	(22.2)	2
Acidosis	3	(4.2)	1
Anaphylaxis	1	(1.4)	
Hypokalemia	1	(1.4)	1
Fluid overload	2	(2.8)	
Nervous system	27	(37.5)	1
Headache	11	(15.3)	1
Agitation	4	(5.6)	
Cerebral cyst	2	(2.8)	
Delirium	2	(2.8)	
Tremor	2	(2.8)	
Urogenital System	14	(19.4)	1
Renal insufficiency	4	(5.6)	
Renal insufficiency, acute	2	(2.8)	
End stage renal disease	1	(1.4)	
Renal dysfunction	1	(1.4)	1
Infection	3	(4.2)	

Safety Update:

In a communication dated 11/28/00, the applicant provided a safety update that covered adverse events reported between the study cut-off dates through July 31, 2000. The medical officer has reviewed the adverse event reports from this study and has arrived at the same conclusions as the original submission.

Other safety issues:

Transaminase elevations: (see report by Dr. Leonard Sacks in appendix)

An elevation of transaminases, > 3 times the ULN and associated with elevations in bilirubin, was seen in about 2% of patients who received the proposed 50-mg dose. This was similar in frequency to fluconazole, developed in the third week of treatment and resolved in three weeks. None of these elevations were considered serious and did not result in drug discontinuations. There were too few subjects who received the 70-mg dose to exclude a dose relationship.

In the clinical pharmacology studies, transaminase elevations were associated with cyclosporine. Even when the drug was given alone, there appeared to be a trend to greater frequency of transaminase elevations, but the number of exposures were too few to define this relationship.

Elevations in serum calcium / creatinine:

One patient developed hypercalcemia (to 12 mg/dL) and renal insufficiency that could not be attributed to concomitant medication, underlying disease of invasive aspergillosis. The hypercalcemia and renal insufficiency resolved with drug discontinuation. One other patent with HIV developed modest hypercalcemia (10 mg/dL) that resolved spontaneously without drug discontinuation.

Pulmonary infiltrates and Respiratory Adverse Events:

A summary of respiratory adverse events in the clinical trials is shown in the following table.

Study	AE	Drug D/C	DRAE	Serious AE	Serious DRAE	Deaths	Deaths DRAE	Hospitalized	Bronchitis	Infiltrates
19	38	15	1	20	1	17	0	9	1	7
003	10	1	0	4	0	3	0+	0	2	4
004	32	1	1	7	0	0	0	6	7	9
007	5	1	0	1	0	1	0	1	1	1
Total	85(25)	18	2	32	1	20	0	16	11	21

+one patient had tachypnea with initial IV infusion, but died of Pseudomonas pneumonia

Bronchitis symptoms, including "allergy", cough, or "wheeze" was reported frequently in the mucosal candidiasis studies. In addition, pulmonary infiltrates, considered to be possibly PCP were also noted in the predominantly HIV population. Some of these adverse events were serious, resulting in hospitalization or death in three patients. However, since PCP is a frequent pathogen in this group of patients, this is a significant confounder for these adverse events.

Similarly, respiratory adverse events were frequent in the invasive aspergillosis study, 38/58 patients (66%) had an adverse event, of which 20 (52.6%) were considered serious and 19 of which resulted in drug discontinuations, even if only one event was considered drug related. Cough was the most frequent adverse event. Others include dyspnea, rales, shortness of breath, etc. Respiratory symptoms in Study 019 could not be differentiated from the underlying disease in many instances, with 17 deaths from a respiratory adverse event, none considered drug related. Serious adverse events included progression of new infiltrates or progression of infiltrates, ARDS, pulmonary edema, lung hemorrhage. These adverse events are not unexpected in a population of patients with severe underlying disease and a highly mortal pulmonary infection.

One case of pulmonary infiltrates was attributed to the drug. One patient (186) had resolving invasive aspergillosis and was symptomatically improved when he developed pulmonary infiltrates, cough and dyspnea during IV treatment. These symptoms were mild to moderate in intensity and required hospitalization. A plausible reason could not be found for the infiltrates and the investigator considered this event possibly drug related.

One other patient, who was enrolled into the invasive aspergillosis protocol after the cut off date, developed a fatal respiratory adverse event. This patient had received a bone marrow transplant and was stable regarding his underlying disease when he developed a limited lobar infection that on resection turned out to be due to aspergillus and the mucorales. He had received a dose of caspofungin before surgery and could not be extubated post-operatively. He went into frank ARDS and died. He received a total of three doses of Cancidas® Autopsy revealed diffuse alveolar damage with ARDS considered being the cause of death. The etiology of ARDS could not be determined. No pathogen was identified to explain the pulmonary infiltrates.

> MO comment: It could be argued that the nature of these respiratory adverse events do not pose an undue risk over that of untreated aspergillosis. On the other hand, in a patient with limited pulmonary reserve, capillary leak from histamine release could be a detrimental event, and this risk should not be imposed if other alternatives do exist.

Histamine release:

Histamine release appeared to be related to rapidity of dose infusion in animals. When Cancidas® was administered to patients, symptoms compatible with histamine release were also noted. Eosinophilia rarely accompanied these symptoms.

Definite histamine release:

32-year-old female enrolled in Compassionate Use Protocol 024 on 1/4/01for invasive aspergillosis with biphenotypic leukemia, and diabetes. Ten minutes into the first infusion of Cancidas® she developed dyspnea, stridor, wheezing and accentuation of a pre-existing macular skin rash. Treatment was stopped and patient received hydrocortisone, 100 mg IV and diphenhydramine, 50 mg IV, with symptom resolution.

Probable histamine release (rash or respiratory symptoms developing concurrently)

Study	Subject	Symptoms
001	0016	pruritus, nasal congestion, lip swelling, wheezing
002	0043	neck erythema, pruritus, near syncope
003	0118	fever, bronchitis and bronchospasm, tachypnea, tachycardia
003	0683	fever, rash, wheeze, interstitial pulmonary infiltrates
004	1338	facial pruritus and rash, tachypnea, tachycardia
004	2311	facial edema, dyspnea
021	0924	rash, tachycardia, pruritus, "hypertrophy" of the pharynxPossible histamine mediated reactions (distinctive symptom/s that occurred independently)
003	0686	fever, rash, neutropenia
003	0868	erythema, hypotension, headache
003	0661	rash, dermatitis, fever, pancytopenia, antral gastritis
003	0777	fever, hepatitis, rash, gastritis, cough
003	0826	fever, dermatitis, eosinophilia
004	1311	facial swelling
004	2302	allergic rash leading to drug discontinuation
004	2304	bronchospasm, cough , wheeze
004	1049	rash and bronchitis
004	1338	rash and dyspnea
004	2351	rash, pruritus, bronchitis
004	2353	rash and cough
004	2354	rash, cough, dyspnea, pneumonia
002	0203	rash and pruritus, occurring daily, proximate to the IV site , lasting a few minutes
019	0412	flushing, rash, mouth rash, vagal reaction, itchy eyes
019	0411	flushing, fever, rash, dyspnea, tachycardia
007	0659	fever, hypotension, erythema, nasal congestion
019	0016	dyspnea, crepitations, expiratory wheezing, paratracheal adenopathy, facial swelling all during the phase of IV treatment, "not requiring drug discontinuation",
019	0017	tachycardia, facial edema, hypotension, neck redness, fever

019	0057	respiratory distress, erythema, rash
019	0187	dyspnea, fever, rash, pulmonary infiltrates

MO comment: The extent of histamine mediated responses may have been modulated by the frequent co-administration of corticosteroids in the invasive aspergillosis study and the co-administration of anti-histamines in the comparative blinded candidiasis studies. Since it is uncertain whether the drug itself, a metabolite, or the production of a protein-complexed hapten that induces these reactions, the timing of the symptoms beyond the first infusion do not necessarily exclude histamine release as a mechanism for the symptom complex described here.

Glucocorticoids:

On 2/10/99 Dr. David Stevens, Professor of Medicine of Stanford University and at the Santa Clara Valley Health and Hospital System alerted the Division regarding mortality findings in mice that received another echinocandin under development by [redacted] and glucocorticoids together. In his mouse model, Dr. Stevens explored the interaction between the echinocandin [redacted] with glucocorticoids in mice, after earlier observations in his laboratory that DBA/2 mice pretreated with cortisone acetate followed by intraperitoneal treatment with the investigational drug resulted in deleterious outcomes. Deaths were noted as early as Day 3 of concurrent treatment with [redacted] 25 mg/kg IP, QD and hydrocortisone, whereas neither those that received [redacted] alone nor those concomitantly treated with dexamethasone had this outcome. Histological observations revealed acute infarcts in the kidney, intravascular calcific material and embolic materials in arterioles in lung, and myocardium. Most of the deaths occurred while treatment was being received, although some of the deaths occurred after the 10-day course of treatment and were not accompanied by similar histopathological findings.

Dr. Stevens found that these adverse events were not gender specific, as they were described in male and female mice, although they seemed to be species-specific, since no deaths occurred in CD1 mice, and only in the complement deficient, DBA/2 mice

The pre-clinical information submitted to Cancidas® shows no similar data to suggest such an interaction. Pre-clinical toxicology studies in mice were restricted to initial acute toxicity studies, with more extensive studies in rats and monkeys. In the NDA submitted, pre-clinical toxicology information in mice consisted of 2 studies with 33 ICR mice that received Cancidas®,sdministered intravenously and another study of Cancidas® administered orally 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, the information suggests no signal for early deaths 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).

Because the histopathological features of the deaths in the mice suggested embolic or infarctive processes, we looked at these events in the clinical studies. Adverse events suggesting embolic or vaso-occlusive events is summarized in the following table:

ADVERSE EVENTS SUGGESTING A VASCULAR /EMBOLIC NATURE in PK and Candida Studies :

STUDY	Identifier	Adverse event	Onset/DRUG	Steroid
PK - 017	727, 42/M	leg pain, DVT	10 days post 50 mg Cancidas®	none
Candida-04	2355, 29/M	central quadrantanopia	13 days post 10days 50mg Cancidas®	none (prednisone 1 month pre trx)
Candida-20	5641, 56/M	MI, fatal, no post	5 days post 10days 50 mg Cancidas®	none
Candida-20	5577, 42/F	cerebral infarct	follow-up period FLUCONAZOLE	none
Candida-20	5361, 43/F	TIA	IV therapy period FLUCONAZOLE	none
Candida-20	5597, 19/F	cerebral ischemia	follow-up period FLUCONAZOLE	none

ADVERSE EVENTS SUGGESTING A VASCULAR /EMBOLIC NATURE in the aspergillus study :				
STUDY	Identifier	Adverse event	Onset/DRUG	Steroid
019	057	femoral artery thrombosis	IV therapy, Cancidas® 50 mg	none
019	217	DVT	IV therapy, Cancidas® 50 mg	medroxyprogesterone
019	417	Superior vena caval syndrome	4 days post Cancidas® 50 mg	dexamethasone

These adverse events developed in patients who were not receiving corticosteroids concurrently. In the invasive aspergillosis study, 61 of the 69 treated patients (88.4%) were on corticosteroids. Furthermore, both the underlying disease (malignancy) and invasive aspergillosis are associated with these events as well.

Lastly 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 and the rate of vascular events (excluding phlebitis) appears to be similar between Cancidas® and fluconazole. The sponsor also submitted an analysis of deaths in patients in the candidiasis and invasive aspergillosis studies and found no correlation between deaths and glucocorticoid exposure.

Adverse events suggesting embolic / vaso-occlusive events:

STUDY	Cancidas®		Comparator	
	Steroids	No Steroids	Steroids	No steroids
003	0/8	0/66	0/33	0/21
004	0/19	1/86*	0/21	0/68
020	0/10	1/74	0/13	3/80
TOTAL	0/37	2/226(0.89%)	0/67	3/169(1.8%)
1 patient on prednisolone as pretreatment				
019	4/61	0/2	—	----

In summary, the preclinical study that suggests an increased mortality in DBA mice that receive hydrocortisone but not dexamethasone together with an echinocandin has not been replicated in patients receiving Cancidas® Moreover, other animal models using different species of mice that received immunomodulating corticosteroid doses have not shown an increased mortality. Furthermore, the clinical studies presented thus far do not show an increase in vascular or embolic events in the patients that received steroids and Cancidas®.

Safety Conclusions

Cancidas® is frequently associated with systemic symptoms such as fever, myalgias, flu-like symptoms, nausea and vomiting. Local infusional toxicities are also frequent, including phlebitis, pain, erythema and rash. Cancidas® is rarely associated with renal toxicity and electrolyte abnormalities are less frequent than those seen with amphotericin B. Transaminase elevations occurred at a frequency and magnitude similar to that seen with fluconazole. Its safety profile against drugs currently approved for this indication is not known.

There are important gaps in the safety information that could limit the drug's use for this indication. These include the lack of information on the safe use of the drug with cyclosporine, the lack of efficacy information on higher doses, the lack of safety information for longer treatment courses, and the lack of information on CNS distribution. The size of the database makes it difficult to understand the dose relatedness of the most frequently observed laboratory adverse event. For example, for the 70-mg dose, the database allows one to detect clinically significant hepatotoxicity if the incidence in the population were at least 5%. While it is true that this may not tip the balance against the benefit afforded by the drug for this indication, because the drug is likely to find off label use at higher doses, this information would allow a more informed decision to pursue such a treatment strategy. This issue becomes even more important were the drug to be used off label when other treatment alternatives exist, or when it should find use for less severe indications.

The antifungal agents used for patients refractory to or intolerant of amphotericin B include itraconazole and the three lipid formulations. Itraconazole, like Cancidas® is less fungicidal and like Cancidas® is indicated for use in patients who are intolerant or failing treatment with the polyenes. Since fluconazole, which is of the same class of drugs, is associated with less infusional toxicites and a similar hepatotoxic profile, it is anticipated that itraconazole may have a similar favorable profile compared to Cancidas® with the advantage of transitioning to an oral formulation on discharge. The lipid amphotericin B products are all associated with dose limiting toxicities when the dose is maximized. We do not know how Cancidas® compares in efficacy to these agents against aspergillus and whether dose limiting toxicities occur with Cancidas®, as they do with the lipid formulations of amphotericin B. Further, these agents are known to vary in their renal toxicity potential, as well as their pharmacokinetics. The small unilamellar formulation has been shown to have a safety advantage over the other lipid formulations, and in addition, is known to distribute differently than the others, achieving better blood levels, and in animals, to achieve therapeutically relevant lung levels. In the itraconazole intolerant or refractory patient, or the patient with baseline renal insufficiency, this agent offers a therapeutic option with the advantage of the known efficacy of the parent compound against aspergillus. The benefit afforded by an additional treatment alternative such as Cancidas® should be accompanied by sufficient characterization of its activity and safety limitations, to allow an individuation of treatment for the broad class of patients susceptible to this infection.

Risk Benefit Analysis:

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 but its predictable toxicity limits its use. The lipid amphotericin agents result in less toxicity, and in many instances are considered to have supplanted amphotericin B as initial therapy (22), but when given in sufficiently high doses, similarly result in some nephrotoxicity. Itraconazole, available as intravenous and oral formulations 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. Antifungal agents with a favorable safety profile compared to amphotericin B and less pharmacokinetic interactions than itraconazole will provide an important alternative for invasive aspergillosis. The echinocandins have the potential of filling the need for efficacious therapy when standard drugs have failed, or when toxicity limits their use. The indication sought in this NDA targets this select group of patients.

The aggregate of information supporting the efficacy of Cancidas® in invasive aspergillosis includes the efficacy demonstrated in the open label study, Study 019, the activity of the drug demonstrated *in vitro*, the demonstrated efficacy in clinically analogous animal models, the reported antifungal activity in supportive studies and a comparison of this information to the known efficacy of other antifungals from the clinical reviews of NDAs submitted to the Agency as well as the reported antifungal efficacy 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 with the expert panel having 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 are 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. The overall risk of drug-related adverse events for this patient population is outweighed by the benefit of treatment with Cancidas®. 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. While these outcomes may be on the low end of the scale, in the truly refractory patient at greatest risk, invasive aspergillosis is highly fatal. 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. 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 with limited therapeutic options.

Financial Disclosures:

The following investigators hold financial interests requiring disclosure. None of these investigators participated in the invasive aspergillosis trials. The measures designed to minimize bias in the candidiasis trials, in which they participated, appear to be sufficient to maintain trial integrity.

Investigators and Sub-investigators Who Hold Financial Interests Requiring Disclosure

Protocol/Site	Investigator	Financial Interest	Steps Taken to Minimize Bias
004-022	Smith, Perry		bias minimized through trial design i.e., randomized, double-blind, multi-center
020-061	Rafael E. Campo		bias minimized through trial design i.e., randomized, double-blind, multi-center
004-007 020-007	Richard Graybill		bias minimized through trial design i.e., randomized, double-blind, multi-center
020-041	Craig McClain		bias minimized through trial design, i.e. randomized, double-blind, multi-center

Labeling issues:

The Adverse Reactions section of the label lists the frequency of adverse events observed in the Cancidas® - treated patients from the clinical trials.

The following are recommendations for the drug label:

1) The agents utilized as initial therapy in Study 019 should be listed in the Indications section,

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 in patients without evidence of a clinical response has not been demonstrated. The safety of long term (>14 days) exposures has not been studied adequately."

4) A serious adverse event section should be added, listing histamine release and pulmonary infiltrates as adverse events.

Dosing and administration issues:

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 (35mg) 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.

Use in 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. Becasue the pharmacokinetic parameter of 20% increase in AUC is not felt to be a clinically significant increase, no dose adjustment is recommended on the basis of gender. There were, however, only 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, is felt to be of no clinical significance 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 the 70 - mg loading dose, in moderate hepatic insufficiency patients. Ongoing studies are designed to address whether dose reductions are warranted for patients with severe hepatic insufficiency.

Conclusions and Recommendations:

There is substantial evidence that Cancidas®is safe and effective for invasive aspergillosis for invasive aspergillosis in patients refractory to or intolerant of other therapies.

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:

1. The agents utilized as initial therapy in Study 019 should be listed in the Indications section.
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 in patients without evidence of a clinical response has not been demonstrated. The safety of long term (>14 days) drug exposure has not been studied adequately."*
4. A serious adverse event section should be added, listing histamine release and pulmonary infiltrates as adverse events.

c. The following Phase IV commitments should be carried out by the applicant:

1. Evaluation of efficacy and safety of the 70-mg dose alone or in addition to standard therapy in patients with invasive aspergillosis refractory to standard therapy
2. Collection of long term safety data (>21 days)
3. Evaluation of safety with cyclosporine and tacrolimus
4. Further characterization of pharmacokinetics of caspofungin with metabolic inducers

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Appendix:

A. Reconciliation of Efficacy Populations:

1. Patient reconciliation of evaluability and outcome assessments by the Applicant, Expert Panel and Medical Officer

(Expert panel outcome based on individual case summaries, not on electronic database)

#	Patient ID	Applicant E(MITT/CE)	O	Expert Panel E (MITT/CE)	O	Medical Officer E(MITT/CE)	O
1	001	yes	St	yes	St	yes	F
2	002	yes/no	F	yes/no	F	yes/no	F
3	016	yes	CR	yes	PR	yes	S
4	017	yes	St	yes	F	yes	F
5	018	yes	F	yes	F	yes	F
6	019	yes	CR	yes	PR+	yes	S
7	056	yes	F	yes	St	yes	F
8	057	yes	F	yes	F	yes	F
9	058	yes	PR	yes	PR	yes	S
10	059	yes	F	yes	F	yes	F
11	060	yes	F	yes	F	yes	F
12	061	yes	CR	yes	PR	yes	S
13	062	yes	PR	yes	PR	yes	S
14	063	yes	St	yes	PR	yes	S
15	064	yes/no	F	yes/no	F	yes/yes	F
16	101	yes/no	F	yes/no	F	yes/yes	F
17	186	yes	F	yes	F	yes	F
18	187	yes	F	yes	F	yes	F
19	216	yes/no	CR+	yes/no	F	yes/no	F
20	217	yes	PR	yes	F	yes	F
21	218	yes	St	yes	St	yes	F
22	219	yes	CR	yes	CR	yes	S
23	246	yes	F	yes	F	yes	F
24	247	no/no	Not IA	no/no	not IA	yes/no	F
25	248	yes	CR	yes	PR	yes	S
26	251	yes	PR	yes	PR	yes	S
27	252	yes/no	F	yes/no	F	yes/yes	F
28	256	yes	PR	yes	PR	yes	S
29	296	yes	F	yes	F	yes	F
30	297	yes	PR	yes	F	yes	F
31	301	yes/no	F	yes/no	F	yes/no	F
32	316	yes	CR	yes	PR	yes	S
33	317	yes	PR	yes	PR	yes	S
34	326	yes	PR	yes	PR	yes	S++
35	327	yes	PR	yes	PR	yes	S
36	328	yes	CR	yes	PR	yes	S
37	329	yes/no	F	yes/no	F	yes/no	F
38	330	yes	CR	yes	CR	yes	S
39	366	yes	CR	yes	CR	yes	S
40	371	yes	PR	yes	PR	yes	S
41	411	yes	PR	yes	PR	yes	S
42	412	yes	F	yes	F	yes	F
43	417	yes	PR	yes	PR	yes	S
44	426	yes	F	yes	F	yes	F
45	427	yes	F	yes	F	yes	F
46	446	yes	F	yes	St	yes	F
47	471	yes	PR	no/no	U	no/no	U

48	476	no/no	not IA	no/no	not IA	no/no	notIA
49	486	yes	St	yes	F	yes	F
50	501	yes	F	yes	F	yes	F
51	502	yes/no	PR	no/no	U	no/no	U
52	503	yes	F	yes	F	yes	F
53	504	no/no	not IA	yes	F	yes	F
54	505	yes	PR	yes	PR	yes	S
55	506	yes/no	F	yes/no	F	yes/yes	F
56	507	yes	F	yes	F	yes	F
57	508	yes/no	F	yes/no	F	yes/no	F
58	509	yes	CR	yes	PR	yes	S
59	065	yes	CR	yes	CR	no/no	E
60	102	yes/ yes	PR	yes	PR	yes/yes	S
61	191	yes/no	F	yes/no	F	yes/no	F
62	291	yes	PR	yes	PR	yes	S
63	318	yes	F	yes	F	yes	S
64	386	yes	F	yes	F	yes	F
65	472	yes	F	yes	F	yes	F
66	510	no/no	not IA	no	not IA	yes/no	F
67	511	no/no	not IA	no	not IA	yes/no	F
68	512	yes/no	F	yes/no	F	yes/yes	F
69	536	yes	F	yes	F	yes/yes	F
Success(%)		29/64(45.3)		25/63(39.7)		25/65(38.5)	
CR		12		4			
PR		17		21(-1)			
ST		5		4			
F		30		34		33	
Exclusions,							
Unevaluables		5		6(+1)		4	

*prophylaxis, not treatment

MITT EFFICACY	24/55 (44)	22/54 (41)	22/55(40)
CE EFFICACY	22/45 (49)	21/45 (47)	21/49 (43)

U=unevaluable
S=success
F=failure
not IA =not invasive aspergillosis

The Applicant excluded the following patients from evaluation:
Patient 247 [redacted] was excluded by the applicant for failing to meet diagnostic criteria at entry. The basis for this was because a pre-study blood culture positive for fungus, which was initially considered to have been Aspergillus, and which would have made the patient refractory to Ambisome, turned out to be *Trichoderma ssp.* Trichoderma resembles aspergillosis in tissue and may have been responsible for the lung lesions demonstrated on pathology. However, prior respiratory cultures were positive for Aspergillus (BAL performed 11/12/98 with 2 colonies of *Aspergillus fumigatus* (with yeast), and an earlier sputum 10/31/98 also revealed *Aspergillus fumigatus.*)
Open lung biopsy on 11/7/98 showed organizing pneumonia with fungal elements (initially read as candida) revised on 1/12/00 as "consistent with invasive aspergillosis". A chest CT on 11/06/98 showed nodules, as did another CT on 11/14/98. Blood cultures drawn 11/20/98 grew *Trichoderma spp.* Cancidas® therapy was started 11/18/98=11/23/8, evaluation was stable disease.

MO disposition: This patient fulfilled the criteria for definite IA based on a positive pathology and a BAL culture. The patient was refractory based on chest x-rays done a week apart while on Ambisome, that showed neither resolution nor improvement of the pulmonary nodules. The *Trichoderma spp.* grown from the blood culture cannot have been the reason for a decision to consider this patient as refractory to Ambisome because Cancidas® was initiated 2 days before identification of a blood isolate, which is an infection that developed while on drug therapy. This patient is valid for inclusion into the

ITT analysis, with an outcome of failure at end-of therapy. This patient is invalid for inclusion in the CE population, which requires seven days of therapy with the study drug.

Patient 476 [redacted] was entered into the trial based on only 1 positive Galactomannan with a suspicious chest x-ray. Several BAL cultures obtained on 11/10,18/10, 22/10 and 25/10 were negative for *Aspergillus spp.*

MO disposition: Medical Officer agrees with this exclusion.

Patient 504 [redacted] fulfilled the criteria for probable IA based on 2 positive cultures and supportive chest x-rays. This patient was excluded by the Applicant from analysis because no Aspergillus was found on autopsy and an alternative cause of death was identified. While this patient was receiving Itraconazole 400-mg daily (15/03/98 to 22/03/98), BAL cultures performed on 17/03/99 and 25/03/99 grew *Aspergillus fumigatus* and progressive chest radiographs were consistent with Aspergillosis. After receiving 12 days of treatment with Cancidas® (from 02/04/99 to 13/04/99) she was evaluated as a clinical failure. While on Cancidas®, she developed breakthrough fungemia due to *C. albicans*, with multiple positive blood cultures from 01/04/99 to 05/04/99. A new femoral catheter was inserted on 05/04/99, removed on 09/04/99, and salvage therapy with amphotericin B was started. She died from recurrence of underlying disease, and an autopsy performed on 15/04/99 showed no evidence of pulmonary Aspergillosis although cultures grew *Rhodotorula species*.

MO disposition: This patient fulfilled baseline criteria for inclusion into the studies as a case of probable aspergillosis. The clinical deterioration on Cancidas® and the development of breakthrough fungemia are the basis for an outcome of failure at end of therapy. The investigator attributed the death to the underlying disease. The lack of histopathological evidence of aspergillosis at death could be interpreted to mean as successful treatment with salvage Amphotericin B and should not invalidate inclusion at baseline set on predetermined criteria.

B. Fungal Infections reported as adverse events on treatment with Cancidas®:

1) Non-comparative invasive aspergillosis studies:

Protocol 07:

Site/Case#	AE	Study phase	Outcome	Study Day
004/1644	Oral thrush	Follow-up	Recovered	30
004/1647	Oral thrush	Follow-up	Recovered	35
007/006	Oral thrush	Follow-up	Recovered	22

Protocol 019:

Site/Case#	AE	Study phase	Outcome	Study Day
004/001	Oral thrush	IV treatment	Not recovered	9
004/016	Candidiasis,oral	IV treatment	Recovered (itra)	133
008/060	Aspergillosis, pulmonary	Follow-up?	Not recovered	20
008/064	Aspergillosis, pulmonary	Follow-up	Not recovered	16
021/187	Aspergillosis, pulmonary	IV treatment	Not recovered	6
022/191	Aspergillosis, pulmonary	IV treatment	Not recovered	1
030/340	Aspergillosis	Follow-up	Not recovered	24
041/301	Aspergillosis	IV treatment	Not recovered	2
046/329	Aspergillosis	IV treatment	Not recovered	4
04/503	Aspergillosis	IV treatment	Not recovered	29
046/504	Candidemia	IV treatment	Not recovered	7
046/506	Aspergillosis	IV treatment	Not recovered	73
046/507	Aspergillosis	IV treatment	Not recovered	61
046/511	Aspergillosis	Follow-up	Recovered	10
046/512	Aspergillosis	IV treatment	Not recovered	4
075/471	Aspergillosis	IV treatment	Not recovered	3
075/471	Aspergillosis	IV treatment	Not recovered	13
075/472	Aspergillosis	IV treatment	Not recovered	13
---/247	Trichoderma fungemia	IV treatment	Recovered	3

2) Comparative Candidiasis studies:

Protocol 003:				
005/840	Histoplasmosis	Follow-up	Not recovered	20
007/690	Oral thrush	Follow-up	Not recovered	69
Protocol 004				
001/1301	Oral/Esophageal candidiasis	Post -study	Not recovered	36
005/1334	Oral candidiasis	IV treatment	Recovered	11
005/1338	Oral candidiasis	Follow-up	Not recovered	7
005/1339	Oral candidiasis	Follow-up	Recovered	13
015/1381	Oral candidiasis	Follow-up	Not recovered	15
023/1137	Oral candidiasis	Follow-up	Not recovered	37
035/2403	Cryptococcal meningitis	Follow-up	Not recovered	12
037//2091	Cryptococcal meningitis	Follow-up	Not recovered	27
038/2028	Oral candidiasis	Follow-up	Recovered	21
038/2029	Oral candidiasis	Follow-up	Recovered	21
038/2030	Oral candidiasis	Follow-up	Not recovered	21
038/2325	Esophageal candidiasis	Follow-up	Not recovered	24
038/2350	Oral candidiasis	Follow-up	Not recovered	13
038/2353	Oral candidiasis	Follow-up	Not recovered	24
040/1493	Cryptococcal meningitis	IV treatment	Not recovered	1
040/1499	Oral candidiasis	IV treatment	Recovered	5
Protocol 020:				
047/5531	Cryptococcal meningitis	Follow-up	Not recovered	29
047/5533	Oral candidiasis	Follow-up	Recovered	19
051/5593	Esophageal candidiasis	Follow-up	Recovered	36
051/5639	Esophageal candidiasis	Follow-up	Recovered	40
051/5640	Oral candidiasis	Follow-up	Recovered	31
051/5643	Esophageal candidiasis	Follow-up	Recovered	32
051/5646	Oral candidiasis	Follow-up	Recovered	28
	Esophageal candidiasis	Follow-up	Recovered	36
054/5478	Cryptococcal meningitis	Follow-up	Recovered	17
055/5463	Oral candidiasis	Follow-up	Recovered	27
055/5470	Cryptococcal meningitis	Follow-up	Recovered	22
	Oral candidiasis	Follow-up	Recovered	22
	Esophageal candidiasis	Follow-up	Not recovered	29

3. Timing of onset of fungal infections reported as adverse events:

Infections that developed on treatment (days after start of Cancidas®):

Site/Case#	AE	Day
040/1493	Cryptococcal meningitis	1
040/1499	Oral candidiasis	5
005/1334	Oral candidiasis	11
004/001	Oral thrush	9
004/016	Candidiasis, oral	133
021/187	Aspergillosis, pulmonary	6
022/191	Aspergillosis, pulmonary	1
041/301	Aspergillosis	2
046/329	Aspergillosis	4
04/503	Aspergillosis	29
046/504	Fungemia	7
046/506	Aspergillosis	7
046/507	Aspergillosis	61
046/512	Aspergillosis	4
075/471	Aspergillosis	3

075/471	Aspergillosis	13
075/472	Aspergillosis	13
---/247	Trichoderma fungemia	3

Infections that developed post treatment (days after end of Cancidas®):

Site/Case#	AE	Day
004/1644	Oral thrush	30
004/1647	Oral thrush	35
007/006	Oral thrush	22
008/060	Aspergillosis, pulmonary	20
008/064	Aspergillosis, pulmonary	16
030/340	Aspergillosis	24
046/511	Aspergillosis	10
005/840	Histoplasmosis	20
007/690	Oral thrush	69
001/1301	Oral/Esophageal	36
005/1338	Oral candidiasis	7
005/1339	Oral candidiasis	13
015/1381	Oral candidiasis	15
023/1137	Oral candidiasis	37
035/2403	Cryptococcal meningitis	12
037//2091	Cryptococcal meningitis	27
038/2028	Oral candidiasis	21
038/2029	Oral candidiasis	21
038/2030	Oral candidiasis	21
038/2325	Esophageal candidiasis	24
038/2350	Oral candidiasis	13
038/2353	Oral candidiasis	24
047/5531	Cryptococcal meningitis	29
047/5533	Oral candidiasis	19
051/5593	Esophageal candidiasis	36
051/5639	Esophageal candidiasis	40
051/5640	Oral candidiasis	31
051/5643	Esophageal candidiasis	32
051/5646	Oral candidiasis	28
	Esophageal candidiasis	36
054/5478	Cryptococcal meningitis	17
055/5463	Oral candidiasis	27
055/5470	Cryptococcal meningitis	22
	Oral candidiasis	22
	Esophageal candidiasis	29

C. Effects of caspofungin on the liver:

Medical Officer Review by Dr. Leonard Sacks

The effect of caspofungin on liver function tests was evaluated in 3 data sets; phase 1 studies, phase II and III comparative studies, and phase III non-comparative studies:

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Comparative phase II and III studies (protocols 020, 003 and 004)

All comparative clinical studies were examined to determine whether an excess frequency of liver function abnormalities was seen in patients treated with caspofungin.

Table 4: Mean Alanine transaminase levels and proportion of patients with elevations >ULN (by treatment arm and study phase)
(Reviewer's analysis)

Mean alanine transaminase levels and % of patients >ULN									
	Caspo 70mg		**Caspo 50mg**		**Caspo 35mg**	**Fluconazole**		**Ampho B**	
020 (172 patients)									
	-	-	Mean	>ULN	-	mean	>ULN	-	
Baseline	-	-	42	27/81 (33%)	-	46	24/91 (26%)	-	
On Rx	-	-	40	30/79 (38%)	-	43	43/91 (47%)	-	
Follow up	-	-	47	33/80 (41%)	-	48	36/88 (41%)	-	
003 (128 patients)									
	Mean	>ULN	mean	>ULN	-	-	-	mean	>ULN

Baseline	32	6/22 (27%)	29	10/36 (28%)	-		-	-	28	8/46 (17%)
On Rx	32	9/26 (35%)	28	14/42 (33%)	-		-	-	33	21/48 (44%)
Follow up	34	8/19 (42%)	45	10/34 (29%)	-		-	-	36	14/40 (35%)
				004 (139 patients)						
	Mean	>ULN	mean	>ULN	mean	>ULN	-	-	mean	>ULN
Baseline	40	9/37 (24%)	39	10/34 (29%)	49	15/34 (44%)	-	-	39	9/34 (26%)
On Rx	41	13/37 (35%)	44	15/34 (44%)	61	21/33 (64%)	-	-	51	14/33 (42%)
Follow up	40	15/35 (43%)	49	17/32 (53%)	64	21/32 (66%)	-	-	47	16/32 (50%)

MO comment: Increases in the mean levels of ALT on treatment were not consistently seen and were most evident in the subset of patients treated with the lowest dose of caspofungin.
Elevations of ALT from baseline occurred in all treatment groups. They were numerically no more frequent in patients treated with caspofungin than in those treated with comparators. Elevations of ALT were more frequent in all the arms of study 004 than in the two other comparative studies. Paradoxically, the arm receiving the lowest dose of caspofungin (35mg) was most affected. The numbers of patients in each arm are insufficient to allow a conclusion on the relation of this adverse event to the dose used.

The table below shows that frequency of treatment related elevations of transaminases was similar for caspofungin-treated and comparator-treated subjects. Bilirubin elevations were not observed in caspofungin-treated patients participating in the comparative studies.

Table 5: Treatment related elevations of ALT, AST or Bilirubin by treatment group
(Adapted for NDA submission, sponsor's table E-30)

	Caspo 35 (n=34)	Caspo 50 (n=164)	Caspo70 (n=65)	AmB(n=89)	Fluconazole (n=93)
ALT	8/33 (24%)	17/162 (10%)	7/65 (11%)	20/88 (23%)	11/92 (12%)
AST	9/33 (27%)	21/162 (13%)	7/65 (11%)	20/88 (23%)	12/92 (13%)
Bilirubin	0/33 (0%)	0/163 (0%)	0/65 (0%)	4/88 (5%)	3/92 (3%)

MO comment: Among caspofungin treated patients, elevations of transaminases were most commonly seen in the small number of patients treated with the 35mg dose. The frequency of these elevations was numerically similar to those seen among patients treated with amphotericin B

Mean bilirubin levels did not change significantly during these studies as shown below.
Table 6: Mean bilirubin levels by treatment arm and study phase (reviewer's analysis)

Mean bilirubin levels in umol/L					
	Caspo 70	Caspo 50	Caspo 35	Fluconazole	Ampho B
020 (172 patients)					
Baseline	9	-	-	9	-
On therapy	9	-	-	9	-
Follow up	9	-	-	10	-
003 (128 patients)					
Baseline	10	9	-	-	10
On therapy	9	9	-	-	10
Follow up	10	10	-	-	10
004 (139 patients)					
Baseline	8	10	9	-	10
On therapy	8	9	9	-	10
Follow up	9	10	9	-	11

Table 7: Proportion of patients with non-baseline alkaline phosphatase >3xULN (all comparative studies)

	Cancidas 70	Cancidas 50	Cancidas 35	Fluconazole	Ampho B
On therapy or follow-up	5/65 (7.7%)	7/164 (4.3%)	1/34 (2.9%)	5/93 (5.4%)	4/88 (4.5%)

MO comment: A trend to dose related elevations of alkaline phosphatase levels was observed. These elevations did not differ significantly from those seen among patients treated with comparator agents.

To characterize patients with a combination of LFT abnormalities consistent with a drug induce hepatitis, those individuals who developed concurrent elevations of transaminases and bilirubin were examined. The incidence of such abnormalities was calculated for each treatment group as shown below.

Table 8: Numbers of patients in controlled studies

Study	Caspo 35	Caspo50	Caspo70	Flucon200	AmphoB
020	-	84	-	93	-
003	-	46	28	-	54
004	34	34	37	-	35
Total	34	164	65	93	89

Total patients treated with any dose of Caspofungin = 263
Total patients treated with any comparator = 182

Table 9: Proportion of patients in each treatment group with ALT and AST and BR >ULN (reviewer's analysis)

Caspo 35	Caspo50	Caspo70	Flucon200	AmphoB
2/34 (6%)	7/164 (4%)	0/65 (0%)	3/93 (3%)	4/89 (4%)

The most extreme abnormalities of liver function were examined below by selecting treatment emergent elevations of transaminases greater than 3xULN and concurrent elevations of bilirubin >ULN.

Table 10: Patients on controlled studies with ALT or AST > 3 X ULN and total bilirubin >ULN (20mg/dl) (reviewer's analysis)

Study	Patient #	ALT (U/L)	AST (U/L)	B*	Rx	Rel day	Age	Sex	Race
020	5463	381	225	51	Caspo50	28		male	Mestizo
020	5537	355	1042	43	Flu200	22		male	mestizo
020	5573	148	121	22	Caspo50	26		male	Caucasian
020	5904	139	<3XULN	24	Caspo50	5		male	Hispanic
020	5958	<3XULN	199	28	Flu200	35		male	Hispanic
003	162	344	307	31	Caspo50	18	31	male	Hispanic
004	1517	124	<3XULN	22	Caspo35	4	53	male	Caucasian
004	1145	582	617	39	Caspo35	28	42	male	caucasian

*Bilirubin in umol/L.

Proportion of patients on controlled studies with ALT or AST > 3 X ULN and total bilirubin >20
Caspofungin 6/263 comparator 2/182 p=0.48

MO comment: Significant elevations of transaminases (>3XULN) and concurrent bilirubin elevations were seen rarely in patients treated with caspofungin and fluconazole who participated in controlled clinical studies. The frequency of these abnormalities did not differ significantly between caspofungin and comparator treated groups of patients. Among the patients treated with caspofungin there was no suggestion of a dose related effect on liver function. The findings suggest that caspofungin may cause a hepatitis like reaction most evident about 3 to 4 weeks after initiation of therapy, at a frequency similar to that seen for fluconazole.

Uncontrolled studies 007 and 019

The mean levels of ALT by treatment phase were examined in the uncontrolled clinical studies.

Protocol 007 examined 14 patients with HIV disease and candidiasis receiving either 70 mg or 50 mg of caspofungin daily.

Table 11: Mean ALT levels by study phase for protocol 007 (Reviewer's analysis)

Mean alanine transaminase levels		
Study 007		
	Caspo 70 (n=6)	Caspo 50 (n=8)
Baseline	23	20
On therapy	29	28
Follow up	28	168[1]

[1] the high values in this group were all contributed by the same patient who developed a hepatitis picture towards the end of therapy. Maximum ALT was 1480, on day 27, falling to 72 on day 42. (Patient #1677)

Two of the 8 patients in the 50mg arm and 2 of the 6 in the 70mg arm developed increases in ALT. Only those in the higher dose arm were considered by the investigator to be drug-related, where the levels peaked at 61U/L and 56 U/L respectively and resolved on follow-up.

Among the 58 patients with aspergillus infections who participated in protocol 019, 21.1% experienced elevations of alkaline phosphatase, 14% experienced elevations of ALT and 14.8% experienced elevations of AST. All these elevations were associated with the patients' underlying diseases and were not attributed to the drug by the investigators.

Among the participants in studies 007 and 019, only one subject had concurrent elevations of ALT, AST and Bilirubin above the upper limit of normal

Table 12: Patient with treatment related concurrent elevations of ALT, AST and Bilirubin >ULN in protocols 007 and 019 (reviewer's analysis)

Study	Patient #	ALT (U/L)	AST (U/L)	B*	Rx (mg/kg)	Rel day	Age	Sex	Race	Outcome	Comment
007	1677	1480	3939	77	Caspo50	27	43	m	black	Partial resolution by day 34	Baseline LFTs normal, HBCAb and HBSAg (+) at baseline HBSAb (-), Hep C antibody (+)

*Bilirubin in umol/L.

MO comment: Hepatitis serology suggests that this may represent reactivation of a chronic hepatitis B infection

MO Conclusions: *Caspofungin is associated with reversible elevations of AST, ALT and alkaline phosphatase. These were found to occur at frequencies similar to those seen in patients treated with comparator agents. Concurrent elevations of transaminases and bilirubin were rare and equally frequent in caspofungin-treated and comparator treated patients. Elevations of transaminases were most common in patients who received caspofungin together with cyclosporine A.*

D. Summary of Antiviral Drugs Advisory Committee Deliberations:

The Antiviral Drugs Advisory Committee held a meeting on January 10, 2001 at the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland. There were approximately 200 people in attendance. The meeting was chaired by Roy M. Gulick, M.D., M.P.H.

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