



NDA 21-227/S-022

Merck Research Laboratories
Attention: Chitrananda Abeygunawardana, Ph.D.
Associate Director, Regulatory Affairs
PO Box 1000
UG2D-068
North Wales PA 19454

Dear Dr. Abeygunawardana:

Please refer to your supplemental new drug application dated and received July 3, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CANCIDAS[®] (caspofungin acetate) for Injection, 50mg/vial and 70mg/vial.

This "Prior Approval" supplemental new drug application, submitted in response to the Supplement Request letter dated June 20, 2008 provides for the following revisions to the package insert.

1. In the **CLINICAL PHARMACOLOGY/MICROBIOLOGY/Mechanism of Action** subsection of the package insert, the second paragraph is modified as follows:

~~Caspofungin exhibits *in vitro* activity against *Aspergillus* species (*Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus terreus*) and *Candida* species (*Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*). Susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) method M38-A (for *Aspergillus* species) and M27-A (for *Candida* species). Standardized susceptibility testing methods for echinocandins have not been established for yeasts and filamentous fungi, and results of susceptibility studies do not correlate with clinical outcome.~~

has been shown to be active both *in vitro* and in clinical infections against most strains of the following microorganisms:

Aspergillus fumigatus
Aspergillus flavus
Aspergillus terreus
Candida albicans
Candida glabrata
Candida guilliermondii
Candida krusei
Candida parapsilosis
Candida tropicalis

Susceptibility Testing Methods^{1,2}
Aspergillus species and other filamentous fungi

No interpretive criteria have been established for Aspergillus species.

Candida species

The interpretive standards for caspofungin against Candida species are applicable only to tests performed using Clinical Laboratory and Standards Institute (CLSI) microbroth dilution reference method M27A for MIC (partial inhibition endpoint) read at 24 hours.

Broth Microdilution Techniques: Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of Candida spp. To antifungal agents. MICs should be determined using a standardized procedure at 24 hours². Standardized procedures are based on a microdilution method (broth) with standardized inoculum concentrations and standardized concentrations of caspofungin powder. The MIC values should be interpreted according to the criteria provided in Table 1.

TABLE 1
Susceptibility Interpretive Criteria for Caspofungin

Pathogen	Broth Microdilution MIC* (µg/mL) at 24 hours		
	<u>S</u>	<u>I</u>	<u>R</u>
<u>Candida species</u>	<u><2</u>	<u>(+)</u>	<u>(+)</u>

* A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

† The current absence of data on caspofungin-resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding test results suggestive of a "Non-Susceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard caspofungin powder should provide the following range of values noted in Table 2.

¹ Clinical Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Approved Standard M38-A. Clinical Laboratory Standards Institute, Villanova, PA.

² Clinical Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved Standard M27-A3. Clinical Laboratory Standards Institute, Villanova, PA.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

TABLE 2

Acceptable Quality Control Ranges* for Caspofungin to be used in Validation of Susceptibility Test Results

<u>QC strain</u>	<u>Broth microdilution (MIC in µg/mL) at 24-hour</u>
<u><i>Candida parapsilosis</i> ATCC† 22019</u>	0.25 – 1.0
<u><i>Candida krusei</i> ATCC 6258</u>	0.12 – 1.0

* Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive interlaboratory variation during initial quality control studies.

† ATCC is a registered trademark of the American Type Culture Collection.

2. The **CLINICAL PHARMACOLOGY/MICROBIOLOGY/Drug Resistance** subsection of the package insert, is modified as follows:

Drug Resistance

~~Mutants of *Candida* with reduced susceptibility to caspofungin have been identified in some patients during treatment. Similar observations were made in a study in mice infected with *C. albicans* and treated with orally administered doses of caspofungin. MIC values for caspofungin should not be used to predict clinical outcome, since a correlation between MIC values and clinical outcome has not been established.~~

A caspofungin MIC of ≤ 2 µg/mL (Susceptible) indicates that the *Candida* isolate is likely to be inhibited if caspofungin therapeutic concentrations are achieved; there is insufficient treatment outcome information on isolates with reduced caspofungin susceptibility to define categories other than susceptible. Breakthrough infections with *Candida* isolates requiring caspofungin concentrations > 2 µg/ml for growth inhibition have developed in a mouse model of *C. albicans* infection and in some patients with *Candida* infections. Some of these isolates had mutations in the *FKS1* gene.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text submitted July 3, 2008. .

Submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA

(21 CFR 314.80 and 314.81).

If you have any questions, call Christina Chi, Regulatory Project Manager, at (301)796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Patient Package Insert

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/s/

Renata Albrecht
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