



NDA 17-001/S-028

Valeant Pharmaceuticals International
Attention: Mr. Nils Hauptmann
Corporate Regulatory Affairs
One Enterprise
Aliso Viejo, CA 92656

Dear Mr. Hauptmann:

Please refer to your supplemental new drug application dated November 7, 2008, received November 10, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ancoban[®] (flucytosine) Capsules, 250 mg and 500 mg.

We acknowledge receipt of your submission dated February 4, 2009.

This supplemental new drug application (sNDA) provides for revisions to the Ancoban[®] labeling in response to the Agency's April 9, 2008 supplement request letter. These revisions reflect the new format of the **MICROBIOLOGY** section implemented for all antifungal product labeling, including interpretive criteria and breakpoints. In addition, this sNDA provides for revisions to the **ADVERSE REACTIONS** section and to the **PRECAUTIONS/Pregnancy: Teratogenic Effects. Pregnancy Category C** subsection that had been inadvertently left out from the labeling approved in S-027.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. This application provides for the following revisions to the content of labeling for the package insert (additions are noted with underline and deletions are noted with ~~strikethrough~~):

1. Under **MICROBIOLOGY/Mechanism of Action/Activity In Vitro**:

~~Flucytosine exhibited activity against *Candida* species and *Cryptococcus neoformans*. In vitro activity of flucytosine is affected by the test conditions. It is essential to follow the approved standard method guidelines.~~

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

Candida albicans

Cryptococcus neoformans

The following *in vitro* data are available, **but their clinical significance is unknown.**

Flucytosine exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 4 µg/mL, or less against most (>90%) strains of the following microorganisms, however, the safety and effectiveness of flucytosine in treating clinical infections due to these microorganisms have not been established in adequate and well control trials.

Candida dubliniensis

Candida glabrata

Candida guilliermondii

Candida lusitaniae

Candida parapsilosis

Candida tropicalis

Candida krusei should be considered to be resistant to flucytosine.

In vitro activity of flucytosine is affected by the test conditions. It is essential to follow the approved standard method guidelines.¹

Susceptibility Testing Methods

Cryptococcus neoformans:

No interpretive criteria have been established for *Cryptococcus neoformans*.

Candida species:

Broth Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *yeasts Candida spp.* to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth)¹ with standardized inoculum concentrations and standardized concentrations of flucytosine powder. The MIC values should be interpreted according to the following criteria: in Table 1.

| | |
|-------------|------------------|
| MIC (µg/mL) | Interpretation |
| ≤ 4 | Susceptible (S) |
| 8-16 | Intermediate (I) |
| ≥ 32 | Resistant (R) |

Table 1. Susceptibility Interpretive Criteria for Flucytosine.

| <u>Antifungal Agent</u> | <u>Broth Dilution at 48 hours</u> <u>(MIC in µg/mL)</u> | | |
|-------------------------|--|-------------------------|----------------------|
| | <u>Susceptible (S)</u> | <u>Intermediate (I)</u> | <u>Resistant (R)</u> |
| <u>Flucytosine</u> | <u>≤4.0</u> | <u>8.0-16</u> | <u>>32</u> |

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully

susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected. Because of other significant host factors, *in vitro* susceptibility may not correlate with clinical outcomes.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard flucytosine powder should provide the following MIC values: range of MIC values noted in Table 2. 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 Flucytosine to be Used in Validation of Susceptibility Test Results.

| <u>QC Strain</u> | <u>Macrodilution (MIC in µg/mL) @ 48 hours</u> | <u>Microdilution (MIC in µg/mL) @ 48 hours</u> |
|---|--|--|
| <u><i>Candida parapsilosis</i> ATCC 22019</u> | <u>0.12-0.5</u> | <u>0.12-0.5</u> |
| <u><i>Candida krusei</i> ATCC 6258</u> | <u>4.0-16</u> | <u>8.0-32</u> |

Acceptable ranges of MICs (µg/mL) for control strains for 48 hours reference broth macrodilution testing:

| <u>Microorganism</u> | <u>MIC (µg/mL)</u> | <u>[% of data included]</u> |
|---|--------------------|-----------------------------|
| <u><i>Candida parapsilosis</i> ATCC 22019</u> | <u>0.12-0.5</u> | <u>[98.6%]</u> |
| <u><i>Candida krusei</i> ATCC 6258</u> | <u>4.0-16</u> | <u>[96.8%]</u> |

Acceptable ranges of MICs (µg/mL) for control strains for 24 hour and 48 hour reference broth microdilution testing:

| <u>Microorganism</u> | <u>MIC (µg/mL) ranges for microdilution testing</u> | | | | | |
|---|---|-------------|---------------------------|-----------------|-------------|---------------------------|
| | <u>24 hour</u> | | | <u>48 hour</u> | | |
| | <u>Range</u> | <u>Mode</u> | <u>% of data included</u> | <u>Range</u> | <u>Mode</u> | <u>% of data included</u> |
| <u><i>Candida parapsilosis</i> ATCC 22019</u> | <u>0.06-0.25</u> | <u>0.12</u> | <u>99%</u> | <u>0.12-0.5</u> | <u>0.25</u> | <u>98%</u> |
| <u><i>Candida krusei</i> ATCC 6258</u> | <u>4.0-16</u> | <u>8.0</u> | <u>98%</u> | <u>8.0-32</u> | <u>16</u> | <u>99%</u> |

Drug Resistance

Flucytosine resistance may arise from a mutation of an enzyme necessary for the cellular uptake or metabolism of flucytosine or from an increased synthesis of pyrimidines, which compete with the active metabolites of flucytosine (fluorinated antimetabolites). Resistance to flucytosine has been shown to develop during monotherapy after prolonged exposure to the drug.

Candida krusei should be considered to be resistant to flucytosine.

2. Under PRECAUTIONS:

Pregnancy: Teratogenic Effects. Pregnancy Category C

Flucytosine was shown to be teratogenic (vertebral fusions) in the rat at doses of 40 mg/kg/day (298 mg/M²/day or 0.051 times the human dose) administered on days 7 to 13 of gestation. At higher doses (700 mg/kg/day; 5208 mg/M²/day or 0.89 times the human dose administered on days 9 to 12 of gestation), cleft lip and palate and micrognathia were reported. Flucytosine was not teratogenic in rabbits up to a dose of 100 mg/kg/day (1423 mg/M²/day or 0.243 times the human dose) administered on days 6 to 18 of gestation. In mice, 400 mg/kg/day of flucytosine (1380 mg/M²/day or 0.236 times the human dose) administered on days 7 to 13 of gestation was associated with a low incidence of cleft palate that was not statistically significant. Studies in pregnant rats have shown that flucytosine injected intraperitoneally crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. Ancobon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

3. Under ADVERSE REACTIONS:

- a. *Gastrointestinal:* Nausea, emesis, abdominal pain, diarrhea, anorexia, dry mouth, duodenal ulcer, gastrointestinal hemorrhage, acute hepatic injury including hepatic necrosis with possible fatal outcome in debilitated patients, hepatic dysfunction, jaundice, ulcerative colitis, enterocolitis, bilirubin elevation, increased hepatic enzymes.
- b. *Hematologic:* Anemia, agranulocytosis, aplastic anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia, and fatal cases of bone marrow aplasia.

4. Following REFERENCES at the end of the label, the following revisions were made:



Valeant Pharmaceuticals International North America
2300 Hyland Avenue One Enterprise
Costa Mesa Aliso Viejo, California 92626656
949-461-6000 949-461-6000

3355497EX067

Rev. ~~September~~ November 2006~~8~~

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the national Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, "SPL for approved NDA 17-001/S-028."

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in SPL format to include the changes approved in these applications. Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

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

REPORTING REQUIREMENTS

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 Ms. Diana Willard, Chief, Project Management Staff, 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

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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