DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-001/S-027

Valeant Pharmaceuticals International
Attention: Mr. Arthur L. Rosenthal, R.A.C.
Director, Corporate Regulatory Affairs
3300 Hyland Avenue
Costa Mesa, CA 92626

Dear Mr. Rosenthal:

Please refer to your supplemental new drug application dated October 26, 2005, received October 27, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ancobon® (flucytosine) Capsules, 250 mg and 500 mg.

We acknowledge receipt of your submission dated April 27, 2006.

Your submission of May 11, 2006 constituted a complete response to our April 27, 2006 action letter.

This supplemental new drug application provides for the following (inserted text is double underlined and deleted text is ~~strikethrough~~):

1. Revise the first paragraph of the **CLINICAL PHARMACOLOGY** section as follows:

   Flucytosine is rapidly and virtually completely absorbed following oral administration. Ancobon is not metabolized significantly when given orally to man. Bioavailability estimated by comparing the area under the curve of serum concentrations after oral and intravenous administration showed 78% to 89% absorption of the oral dose. Peak ~~blood~~ serum concentrations of 30 to 40 µg/mL were reached within 2 hours of administration of a 2-~~gm~~ oral dose to normal subjects. ~~The mean blood concentrations were~~ Other studies revealed mean serum concentrations of approximately 70 to 80 µg/mL 1 to 2 hours after a dose in patients with normal renal function ~~who~~ receiv~~ed~~ing a 6-week regimen of flucytosine (150 mg/kg/day given in divided doses every 6 hours) in combination with amphotericin B. The half-life in the majority of ~~normal~~ healthy subjects ranged between 2.4 and 4.8 hours.

2. Revise the last paragraph of the **CLINICAL PHARMACOLOGY** section as follows:

   In vitro studies have shown that 2.9% to 4% of flucytosine is protein-bound over the range of therapeutic concentrations found in the blood. Flucytosine readily penetrates the blood-brain barrier, achieving clinically significant concentrations in cerebrospinal fluid. ~~Studies in pregnant rats have shown that flucytosine injected intraperitoneally crosses the placental barrier (see **PRECAUTIONS**).~~

3. Replace the entire **MICROBIOLOGY** section, including the **Mechanism of Action**, **Activity In Vitro**, **Drug Resistance** and **Drug Combination** subsections as follows:

Mechanism of Action

~~Flucytosine has *in vitro* and *in vivo* activity against *Candida* and *Cryptococcus*. Although the exact mode of action is unknown, it has been proposed that flucytosine acts on fungal organisms by by competitive inhibition of purine and pyrimidine uptake and indirectly by intracellular metabolism to 5-fluorouracil. Flucytosine enters the fungal cell via cytosine permease; thus, flucytosine is metabolized to 5-fluorouracil within fungal organisms. The 5-fluorouracil is extensively incorporated into fungal RNA and inhibits synthesis of both DNA and RNA. The result is unbalanced growth and death of the fungal organism. Antifungal synergism between Ancobon and polyene antibiotics, particularly amphotericin B, has been reported.~~

~~***Actions:*** Flucytosine has *in vitro* and *in vivo* activity against Candida and Cryptococcus. The exact mode of action against these fungi is not known. Ancobon is not metabolized significantly when given orally to man.~~

~~***Susceptibility:*** *Cryptococcus:* Most strains initially isolated from clinical material have shown flucytosine minimal inhibitory concentrations (MIC's) ranging from .46 to 7.8 µg/mL. Any isolate with an MIC greater than 12.5 µg/mL is considered resistant. *In vitro* resistance has developed in originally susceptible strains during therapy. It is recommended that clinical cultures for susceptibility testing be taken initially and at weekly intervals during therapy. The initial culture should be reserved as a reference in susceptibility testing of subsequent isolates.~~

~~*Candida:* As high as 40% to 50% of the pretreatment clinical isolates of Candida have been reported to be resistant to flucytosine. It is recommended that susceptibility studies be performed as early as possible and be repeated during therapy. An MIC value greater than 100 µg/mL is considered resistant.~~

~~Interference with *in vitro* activity of flucytosine occurs in complex or semisynthetic media. In order to rely upon the recommended *in vitro* interpretations of susceptibility, it is essential that the broth medium and the testing procedure used be that described by Shadomy.~~

Mechanism of Action

Flucytosine is taken up by fungal organisms via the enzyme cytosine permease. Inside the fungal cell, flucytosine is rapidly converted to fluorouracil by the enzyme cytosine deaminase. Fluorouracil exerts its antifungal activity through the subsequent conversion into several active metabolites, which inhibit protein synthesis by being falsely incorporated into fungal RNA or interfere with the biosynthesis of fungal DNA through the inhibition of the enzyme thymidylate synthetase.

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.[1]

Susceptibility Tests

Cryptococcus neoformans:

No interpretive criteria have been established for *Cryptococcus neoformans*[1].

Candida:

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

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

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:

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

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

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

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

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.

Drug Combination
Antifungal synergism between flucytosine and polyene antibiotics, particularly amphotericin B has been reported *in vitro*. Ancobon is usually administered in combination with amphotericin B due to lack of cross-resistance and reported synergistic activity of both drugs.

4. Revise the last paragraph of the **INDICATIONS AND USAGE** section as follows:

   ~~With the exception of urinary tract infection,~~ Ancobon should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of ~~rapid~~ the emergence of resistance to Ancobon ~~in *Candida* and *Cryptococcus* isolates in patients receiving Ancobon alone~~ (See **MICROBIOLOGY)**.

5. Revise the third sentence of the first paragraph of the **WARNINGS** section as follows:

   Ancobon ~~blood~~ serum concentrations should be monitored to determine the adequacy of renal excretion in such patients.

6. Add the following paragraph to the end of the **DOSAGE AND ADMINISTRATION** section:

   Ancobon should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to Ancobon (See **Microbiology).**

7. Revise the **REFERENCES** section as follows:

   1. ~~Shadomy S. *Appl Microbiol.* June 1969; 17: 871 - 877.~~
   1. Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard-Second Edition. NCCLS Document M27-A2, 2002 Volume 22, No 15, NCCLS, Wayne, PA, August 2002.

We 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.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 17-001/S-027**." Approval of this submission by FDA is not required before the labeling is used.

Submit revised 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
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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, please call Kristen Miller, Pharm.D., Regulatory Health 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

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