

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do **NOT** send this page with the letter.

Application: NDA 17-001/S-028

Document Type: NDA Letters
Document Group: NDA Supplement Approval Letters
Document Name: Approval, effective on date of letter, based on enclosed labeling text or submitted draft labeling (with or without **minor editorial** revisions included in the letter).
Shortcut ID Code: SNDA-I1

COMIS Decision Code: AP

Drafted by: DWillard: 4/23/09
Revised by:
Initialed by:
Finalized:
Filename:

DFS Key Words:

Notes:

Version: 11/18/05

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 lusitanae

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>

NDA 17-001/S-028

Page 4

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®

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 20068

NDA 17-001/S-028
Page 5

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

ANCOBON[®]

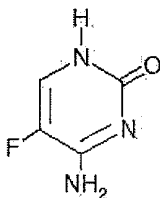
(flucytosine)
CAPSULES

WARNING

Use with extreme caution in patients with impaired renal function. Close monitoring of hematologic, renal and hepatic status of all patients is essential. These instructions should be thoroughly reviewed before administration of Ancobon.

DESCRIPTION

Ancobon (flucytosine), an antifungal agent, is available as 250 mg and 500 mg capsules for oral administration. Each capsule also contains corn starch, lactose and talc. Gelatin capsule shells contain parabens (butyl, methyl, propyl) and sodium propionate, with the following dye systems: 250 mg capsules — black iron oxide, FD&C Blue No. 1, FD&C Yellow No. 6, D&C Yellow No. 10 and titanium dioxide; 500 mg capsules — black iron oxide and titanium dioxide. Chemically, flucytosine is 5-fluorocytosine, a fluorinated pyrimidine which is related to fluorouracil and floxuridine. It is a white to off-white crystalline powder with a molecular weight of 129.09 and the following structural formula:



CLINICAL PHARMACOLOGY

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 serum concentrations of 30 to 40 µg/mL were reached within 2 hours of administration of a 2 g oral dose to normal subjects. 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 receiving 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 healthy subjects ranged between 2.4 and 4.8 hours. Flucytosine is excreted via the kidneys by means of glomerular filtration without significant tubular reabsorption. More than 90% of the total radioactivity after oral administration was recovered in the urine as intact drug. Flucytosine is deaminated (probably by gut bacteria) to 5-fluorouracil. The area under the curve (AUC) ratio of 5-fluorouracil to flucytosine is 4%. Approximately

1% of the dose is present in the urine as the α -fluoro- β -ureido-propionic acid metabolite. A small portion of the dose is excreted in the feces.

The half-life of flucytosine is prolonged in patients with renal insufficiency; the average half-life in nephrectomized or anuric patients was 85 hours (range: 29.9 to 250 hours). A linear correlation was found between the elimination rate constant of flucytosine and creatinine clearance.

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.

Pharmacokinetics in Pediatric Patients

Limited data are available regarding the pharmacokinetics of Ancobon administered to neonatal patients being treated for systemic candidiasis. After five days of continuous therapy, median peak levels in infants were 19.6 $\mu\text{g/mL}$, 27.7 $\mu\text{g/mL}$, and 83.9 $\mu\text{g/mL}$ at doses of 25 mg/kg (N=3), 50 mg/kg (N=4), and 100 mg/kg (N=3), respectively. Mean time to peak serum levels was of 2.5 ± 1.3 hours, similar to that observed in adult patients. A good deal of interindividual variability was noted, which did not correlate with gestational age. Some patients had serum levels $> 100 \mu\text{g/mL}$, suggesting a need for drug level monitoring during therapy. In another study, serum concentrations were determined during flucytosine therapy in two patients (total assays performed =10). Median serum flucytosine concentrations at steady state were calculated to be $57 \pm 10 \mu\text{g/mL}$ (doses of 50 to 125 mg/kg/day, normalized to 25 mg/kg per dose for comparison). In three infants receiving flucytosine 25 mg/kg/day (four divided doses), a median flucytosine half-life of 7.4 hours was observed, approximately double that seen in adult patients. The concentration of flucytosine in the cerebrospinal fluid of one infant was 43 $\mu\text{g/mL}$ 3 hours after a 25 mg oral dose, and ranged from 20 to 67 mg/L in another neonate receiving oral doses of 120 to 150 mg/kg/day.

MICROBIOLOGY

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 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 *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 criteria in Table 1.

Table 1. Susceptibility Interpretive Criteria for Flucytosine.

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

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 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.

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

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.

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.

INDICATIONS AND USAGE

Ancobon is indicated only in the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*.

Candida: Septicemia, endocarditis and urinary system infections have been effectively treated with flucytosine. Limited trials in pulmonary infections justify the use of flucytosine.

Cryptococcus: Meningitis and pulmonary infections have been treated effectively. Studies in septicemias and urinary tract infections are limited, but good responses have been reported.

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**).

CONTRAINDICATIONS

Ancobon should not be used in patients with a known hypersensitivity to the drug.

WARNINGS

Ancobon must be given with extreme caution to patients with impaired renal function. Since Ancobon is excreted primarily by the kidneys, renal impairment may lead to accumulation of the drug. Ancobon serum concentrations should be monitored to determine the adequacy of renal excretion in such patients. Dosage adjustments should be made in patients with renal insufficiency to prevent progressive accumulation of active drug.

Ancobon must be given with extreme caution to patients with bone marrow depression. Patients may be more prone to depression of bone marrow function if they: 1) have a hematologic disease, 2) are being treated with radiation or drugs which depress bone marrow, or 3) have a history of treatment with such drugs or radiation. Bone marrow toxicity can be irreversible and may lead to death in immunosuppressed patients. Frequent monitoring of hepatic function and of the hematopoietic system is indicated during therapy.

PRECAUTIONS

General

Before therapy with Ancobon is instituted, electrolytes (because of hypokalemia) and the

hematologic and renal status of the patient should be determined (see **WARNINGS**). Close monitoring of the patient during therapy is essential.

Laboratory Tests

Since renal impairment can cause progressive accumulation of the drug, blood concentrations and kidney function should be monitored during therapy. Hematologic status (leucocyte and thrombocyte count) and liver function (alkaline phosphatase, SGOT and SGPT) should be determined at frequent intervals during treatment as indicated.

Drug Interactions

Cytosine arabinoside, a cytostatic agent, has been reported to inactivate the antifungal activity of Ancobon by competitive inhibition. Drugs which impair glomerular filtration may prolong the biological half-life of flucytosine.

Drug/Laboratory Test Interactions

Measurement of serum creatinine levels should be determined by the Jaffé reaction, since Ancobon does not interfere with the determination of creatinine values by this method. Most automated equipment for measurement of creatinine makes use of the Jaffé reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Flucytosine has not undergone adequate animal testing to evaluate carcinogenic potential. The mutagenic potential of flucytosine was evaluated in Ames-type studies with five different mutants of *S. typhimurium* and no mutagenicity was detected in the presence or absence of activating enzymes. Flucytosine was nonmutagenic in three different repair assay systems (i.e., rec, uvr and pol).

There have been no adequate trials in animals on the effects of flucytosine on fertility or reproductive performance. The fertility and reproductive performance of the offspring (F₁ generation) of mice treated with 100 mg/kg/day (345 mg/M²/day or 0.059 times the human dose), 200 mg/kg/day (690 mg/M²/day or 0.118 times the human dose) or 400 mg/kg/day (1380 mg/M²/day or 0.236 times the human dose) of flucytosine on days 7 to 13 of gestation was studied; the *in utero* treatment had no adverse effect on the fertility or reproductive performance of the offspring.

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.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ancobon, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The efficacy and safety of Ancobon have not been systematically studied in pediatric patients. A small number of neonates have been treated with 25 to 200 mg/kg/day of flucytosine, with and without the addition of amphotericin B, for systemic candidiasis. No unexpected adverse reactions were reported in these patients. It should be noted, however, that hypokalemia and acidemia were reported in one patient who received flucytosine in combination with amphotericin B, and anemia was observed in a second patient who received flucytosine alone. Transient thrombocytopenia was noted in two additional patients, one of whom also received amphotericin B.

ADVERSE REACTIONS

The adverse reactions which have occurred during treatment with Ancobon are grouped according to organ system affected.

Cardiovascular: Cardiac arrest, myocardial toxicity, ventricular dysfunction.

Respiratory: Respiratory arrest, chest pain, dyspnea.

Dermatologic: Rash, pruritus, urticaria, photosensitivity.

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.

Genitourinary: Azotemia, creatinine and BUN elevation, crystalluria, renal failure.

Hematologic: Anemia, agranulocytosis, aplastic anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia, and fatal cases of bone marrow aplasia.

Neurologic: Ataxia, hearing loss, headache, paresthesia, parkinsonism, peripheral neuropathy, pyrexia, vertigo, sedation, convulsions.

Psychiatric: Confusion, hallucinations, psychosis.

Miscellaneous: Fatigue, hypoglycemia, hypokalemia, weakness, allergic reactions, Lyell's syndrome.

OVERDOSAGE

There is no experience with intentional overdosage. It is reasonable to expect that overdosage may produce pronounced manifestations of the known clinical adverse reactions. Prolonged serum concentrations in excess of 100 µg/mL may be associated with an increased incidence of toxicity, especially gastrointestinal (diarrhea, nausea, vomiting), hematologic (leukopenia, thrombocytopenia) and hepatic (hepatitis).

In the management of overdosage, prompt gastric lavage or the use of an emetic is recommended. Adequate fluid intake should be maintained, by the intravenous route if necessary, since Ancobon is excreted unchanged via the renal tract. The hematologic parameters should be monitored frequently; liver and kidney function should be carefully monitored. Should any abnormalities appear in any of these parameters, appropriate therapeutic measures should be instituted.

Since hemodialysis has been shown to rapidly reduce serum concentrations in anuric patients, this method may be considered in the management of overdosage.

DOSAGE AND ADMINISTRATION

The usual dosage of Ancobon is 50 to 150 mg/kg/day administered in divided doses at 6-hour intervals. Nausea or vomiting may be reduced or avoided if the capsules are given a few at a time over a 15-minute period. If the BUN or the serum creatinine is elevated, or if there are other signs of renal impairment, the initial dose should be at the lower level (see **WARNINGS**).

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**).

HOW SUPPLIED

Capsules, 250 mg (gray and green), imprinted ANCOBON[®] 250 ICN, bottles of 100 (NDC 0187-3554-10). *Capsules*, 500 mg (gray and white), imprinted ANCOBON[®] 500 ICN, bottles of 100 (NDC 0187-3555-10).

Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).

REFERENCES

- 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.



Valeant Pharmaceuticals North America
One Enterprise
Aliso Viejo, California 92656
949-461-6000

3355497EX07

Rev. November 2008

**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
5/4/2009 03:21:50 PM