DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-001/S-019, S-020

ICN Pharmaceuticals, Inc.
Attn: Anil K. Hiteshi, R.A.C.
Manager, Corporate Regulatory Affairs
International Headquarters
ICN Plaza
3300 Hyland Avenue
Costa Mesa, California 92626

Dear Mr. Hiteshi:

Please refer to your supplemental new drug application (NDA 17-001/S-019), dated December 11, 1996, received December 12, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ANCOBON® (flucytosine) capsules.

We acknowledge receipt of your submissions dated December 24, 1997 and April 23, 2003.

This "Changes Being Effected" supplemental new drug application provides for revisions to **WARNINGS** and **ADVERSE REACTIONS** to strengthen the safety information. The package insert was revised as follows. Added text is double underlined and deleted text is in ~~strikethrough~~.

1. **WARNINGS**

The following sentence was added to the second paragraph.

Bone marrow toxicity can be irreversible and may lead to death in immunosuppressed patients.

2. **PRECAUTIONS**

Throughout this section, when referring to preclinical studies, the trade name Ancobon was changed to the generic name flucytosine.

3. **ADVERSE REACTIONS**

Cardiovascular: myocardial toxicity and ventricular dysfunction were added.

Gastrointestinal: acute hepatic injury with possible fatal outcome in debilitated patient was added.

Psychiatric: allergic reactions, and Lyell's syndrome were added.

Please also refer to your supplemental new drug application (NDA 17-001/S-020), dated December 12, 1996, received December 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ANCOBON® (flucytosine) capsules:

We acknowledge receipt of your submissions dated April 15, November 25, and December 24, 1997, and April 23, 2003.

This supplemental new drug application provides for the revision of the *Pediatric Use* subsection of the labeling as required by the Final Rule for Specific Requirements on Content and Format of Labeling for Human Prescription Drugs - **Pediatric Use** published in the Federal Register on December 13, 1994, 201.57(f)(9)(iv). The package insert was revised as follows. Added text is double underlined and deleted text is in ~~strikethrough~~.

4. The Roche emblem was removed above the ANCOBON name and ~~brand of~~ was removed beneath it.

5. **CLINICAL PHARMACOLOGY**

- The double underlined sentence was added, and *in vitro* was italicized. Throughout the label ~~mcg/mL~~ was changed to µg/mL:

> Flucytosine is rapidly and virtually completely absorbed following oral administration. 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 concentrations of 30 to 40 µg/mL ~~mcg/mL~~ were reached within 2 hours of administration of a 2-gm oral dose to normal subjects. The mean blood concentrations were approximately 70 to 80 µg/mL ~~mcg/mL~~ 1 to 2 hours after a dose in patients with normal renal function who received 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 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 *-fluoro-*-ureido-propionic acid metabolite. A small portion of the dose is excreted in the feces.

- This section was added:

> ***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 µg/mL, 27.7 µg/mL, and 83.9 µg/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 µg/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). M~~m~~edian serum flucytosine concentrations at steady state were calculated to be 57 ± 10 µg/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 µg/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.

6. ***Microbiology***

In vitro and *in vivo* were italicized in this section.

7. **INDICATIONS AND USAGE**

The following paragraph was added to the end of this section:

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 emergence of resistance to Ancobon in Candida and Cryptococcus isolates in patients receiving Ancobon alone.

8. **PRECAUTIONS**

This section was revised as follows:

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.~~Antifungal synergism between Ancobon and polyene antibiotics, particularly amphotericin B, has been reported.~~

Drug/Laboratory Test Interactions: Measurement of serum creatinine levels should be determined by the Jaffé reaction,~~method,~~ 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. ~~as it does when the dry-slide enzymatic method with the Kodak Ektachem analyzer is used.~~

Carcinogenesis, Mutagenesis, Impairment of Fertility: in 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 animals on the effects of flucytosine on fertility or reproductive performance. The fertility and reproductive performance of the offspring

(F_1 generation) of mice treated with 100 mg/kg/day (345 mg/M^2/day or 0.059 times the human dose), 200 mg/kg/day (690 mg/M^2/day or 0.118 times the human dose) or 400 mg/kg/day (1380 mg/M^2/day or 0.236 times the human dose)~~100, 200 or 400 mg/kg/day~~ 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.~~ Although standard segment II studies have not been done, f~~Flucytosine was shown to be teratogenic (vertebral fusions) in the rat at doses of 40 mg/kg/day (298 mg/M^2/day or 0.051 times the human dose) administered on days 7 to 13 of gestation. ~~(0.27 times the maximum human dose, based on nominal dose).~~ At higher doses (700 mg/kg/day; 5208 mg/M^2/day or 0.89 times the human dose administered on days 9 to 12 of gestation),~~4.7 times the maximum human dose, based on nominal dose),~~ 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/M^2/day or 0.243 times the human dose) administered on days 6 to 18 of gestation.(0.68 times the maximum human dose, based on nominal dose).~~ In mice, 400 mg/kg/day of flucytosine (1380 mg/M^2/day or 0.236 times the human dose) administered on days 7 to 13 of gestation ~~(2.7 times the maximum human dose, based on nominal dose)~~ was associated with a low incidence of cleft palate that was not statistically significant. 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.

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.

9. **ADVERSE REACTIONS**

This paragraph was revised as follows:

Gastrointestinal: Nausea, emesis, abdominal pain, diarrhea, anorexia, dry mouth, duodenal ulcer, gastrointestinal hemorrhage, acute hepatic injury with possible fatal outcome in debilitated patients, hepatic dysfunction, jaundice, ulcerative colitis, bilirubin elevation, increased hepatic enzymes.

We completed our review of these applications, as amended. These applications are 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 submitted April 23, 2003).

Please submit the FPL electronically 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, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 17-001/S-019, S-020." In addition, please submit a clean copy MS Word version of the label on diskette to the electronic document room, and as a desk copy. Approval of these submissions by FDA is not required before the labeling is used.

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, HF-2
FDA
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 Christine Lincoln, RN, MS, MBA, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

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

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/s/

Renata Albrecht

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