DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-506/S-009

Astellas Pharma US, Inc.
Attention: Mr. Robert M. Reed
Director, Regulatory Affairs
Three Parkway North
Deerfield, Illinois 60015-2548

Dear Mr. Reed:

Please refer to your supplemental New Drug Application dated February 5, 2007, received February 6, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MYCAMINE® (micafungin sodium) for Injection, 50mg/vial and 100 mg/vial.

We acknowledge receipt of your submission dated August 1, 2007.

This supplemental new drug application provides for the following changes to the package insert (~~strikethrough~~ indicates deletion, underline indicates addition):

1. The **PRECAUTIONS/Carcinogenesis, Mutagenesis and Impairment of Fertility** subsection is revised as follows:

   ~~No life time studies in animals were performed to evaluate the carcinogenicity potential of MYCAMINE. Micafungin sodium was not mutagenic or clastogenic when evaluated in a standard battery of *in-vitro* and *in-vivo* tests (i.e., bacterial reversion - *S. typhimurium*, *E. coli*; chromosomal aberration; intravenous mouse micronucleus).~~

   Hepatic carcinomas and adenomas were observed in a 6-month intravenous toxicology study with an 18-month recovery period of micafungin sodium in rats designed to assess the reversibility of hepatocellular lesions.-

   Rats administered micafungin sodium for 3 months at 32 mg/kg/day (corresponding to 8 times the highest recommended human dose [150 mg/day], based on AUC comparisons), exhibited colored patches/zones, multinucleated hepatocytes and altered hepatocellular foci after 1 or 3 month recovery periods, and adenomas were observed after a 21-month recovery period. Rats administered micafungin sodium at the same dose for 6 months exhibited adenomas after a 12-month recovery period; after an 18-month recovery period, an increased incidence of adenomas was observed, and additionally, carcinomas were detected. A lower dose of micafungin sodium (equivalent to 5 times the human AUC) in the 6-month rat study resulted in a lower incidence of adenomas and carcinomas following 18 months recovery. The duration of micafungin dosing in these rat studies (3 or 6 months) exceeds the usual duration of MYCAMINE dosing in patients, which is typically less than 1 month for treatment of esophageal candidiasis, but dosing may exceed 1 month for *Candida* prophylaxis.

Although the increase in carcinomas in the 6-month rat study did not reach statistical significance, the persistence of altered hepatocellular foci subsequent to micafungin dosing, and the presence of adenomas and carcinomas in the recovery periods suggest a causal relationship between micafungin sodium, altered hepatocellular foci, and hepatic neoplasms. Whole-life carcinogenicity studies of MYCAMINE in animals have not been conducted, and it is not known whether the hepatic neoplasms observed in treated rats also occur in other species, or if there is a dose threshold for this effect.

Micafungin sodium was not mutagenic or clastogenic when evaluated in a standard battery of *in-vitro* and *in-vivo* tests (i.e., bacterial reversion - *S. typhimurium*, *E. coli*; chromosomal aberration; intravenous mouse micronucleus).

Male rats treated intravenously with micafungin sodium for 9 weeks showed vacuolation of the epididymal ductal epithelial cells at or above 10 mg/kg (about 0.6 times the recommended clinical dose for esophageal candidiasis, based on body surface area comparisons). Higher doses (about twice the recommended clinical dose, based on body surface area comparisons) resulted in higher epididymis weights and reduced numbers of sperm cells. In a 39-week intravenous study in dogs, seminiferous tubular atrophy and decreased sperm in the epididymis were observed at 10 and 32 mg/kg, doses equal to about 2 and 7 times the recommended clinical dose, based on body surface area comparisons. There was no impairment of fertility in animal studies with micafungin sodium.

2. The **ANIMAL TOXICOLOGY** section is revised as follows:

~~High doses of mycafungin sodium have been associated with irreversible changes to the liver when administered for prolonged periods. In a 13-week intravenous rat study (dosed to 5-times clinical exposure, based on body surface area comparisons), with four- or 13-week recovery periods, colored patches/zones, multinucleated hepatocytes and altered cell foci remained at the end of the recovery period. In a similar 13-week intravenous dog study with 40week recovery (doses to 10 times clinical exposure), liver discoloration, cellular infiltration and hypertrophy remained visible at the end of the 13-week recovery period.~~

High doses of micafungin sodium (5 to 8 times the highest recommended human dose, based on AUC comparisons) have been associated with irreversible changes to the liver when administered for 3 or 6 months, and these changes may be indicative of pre-malignant processes (See **PRECAUTIONS-Carcinogenesis, Mutagenesis and Impairment of Fertility**).

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 submitted on August 1, 2007, and with the minor editorial revision ("See **PRECAUTIONS - Carcinogenesis, Mutagenesis and Impairment of Fertility"**) as listed at the end of the **ANIMAL TOXICOLOGY** section of the package insert.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. 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
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Christina H. Chi, PH.D., Regulatory Health Project Manager, at (301) 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.

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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