



NDA 50740/S-021

SUPPLEMENT APPROVAL

Astellas Pharma U.S., Inc.
Attention: Robert M. Reed
Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Mr. Reed:

Please refer to your Supplemental New Drug Application (sNDA) dated April 22, 2011, received April 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AmBisome (amphotericin B) liposome for Injection.

We acknowledge receipt of your amendment dated December 19, 2011.

This "Changes Being Effected" supplemental new drug application provides for the following changes to the package insert, as well as various editorial changes (additions are noted by underline and deletions are noted by ~~strikethrough~~):

1. Under **DESCRIPTION** the section was revised to use amphotericin B molecules instead of amphotericin molecules in the Cross Section View of Liposome diagram.
2. Under **MICROBIOLOGY**, the section was revised as follows:

Mechanism of Action

Amphotericin B, the active ingredient of AmBisome, acts by binding to the sterol component, ergosterol, of a the cell membrane of susceptible fungi. It forms transmembrane channels leading to alterations in cell permeability through which monovalent ions (NA⁺, K⁺, H⁺, and Cl⁻) leak out of the cell resulting and in cell death. While amphotericin B has a higher affinity for the ergosterol component of the fungal cell membrane, it can also bind to the cholesterol component of the mammalian cell leading to cytotoxicity. AmBisome, the liposomal preparation of amphotericin B, has been shown to penetrate the cell wall of both extracellular and intracellular forms of susceptible fungi.

Activity In Vitro and In Vivo

AmBisome has shown *in vitro* activity comparable to amphotericin B against the following organisms: *Aspergillus* ~~species~~ (*A. fumigatus*, *Aspergillus* ~~flavus~~), *Candida*

~~species (*C. albicans*, *Candida*-*krusei*, *Candida*-*lusitaniae*, *Candida*-*parapsilosis*, *Candida*-*tropicalis*), *Cryptococcus neoformans*, and *Blastomyces dermatitidis*. However, standardized techniques for susceptibility testing of antifungal agents have not been established and results of such studies do not necessarily correlate with clinical outcome.~~

~~AmBisome is active in animal models against *Aspergillus fumigatus*, *Candida albicans*, *Candida krusei*, *Candida lusitaniae*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Leishmania donovani*, and *Leishmania infantum*. The administration of AmBisome in these animal models demonstrated prolonged survival of infected animals, reduction of microorganisms from target organs, or a decrease in lung weight.~~

Drug Resistance

Mutants with decreased susceptibility to amphotericin B have been isolated from several fungal species after serial passage in culture media containing the drug, and from some patients receiving prolonged therapy. Drug combination studies *in vitro* and *in vivo* suggest that imidazoles may induce resistance to amphotericin B. However, the clinical relevance of drug resistance has not been established.

Susceptibility Testing

Standardized methods of *in vitro* antifungal susceptibility testing have been developed for testing yeasts (1,2,3) and filamentous fungi (4,5). The clinical relevance of the test results is not always clear.

3. Under **PRECAUTIONS**, following the **Laboratory Tests** subsection, a **Drug-Laboratory Interactions: Serum phosphate false elevation** subsection was added follows:

Laboratory Tests

Patient management should include laboratory evaluation of renal, hepatic and hematopoietic function, and serum electrolytes (particularly magnesium and potassium).

Drug-Laboratory Interactions: Serum phosphate false elevation

False elevations of serum phosphate may occur when samples from patients receiving AmBisome are analyzed using the PHOSm assay (e.g. used in Beckman Coulter analyzers including the Synchron LX20). This assay is intended for the quantitative determination of inorganic phosphorus in human serum, plasma or urine samples.

4. Under **ADVERSE REACTIONS** following the **Urogenital System** subsection a **Post-marketing Experience** subsection was added as follows:

Urogenital System

Abnormal renal function, acute kidney failure, acute renal failure, dysuria, kidney failure, toxic nephropathy, urinary incontinence, and vaginal hemorrhage.

Post-marketing Experience

The following infrequent adverse experiences have been reported in post-marketing surveillance, in addition to those mentioned above: angioedema, erythema, urticaria, bronchospasm, cyanosis/hypoventilation, pulmonary edema, agranulocytosis, hemorrhagic cystitis, and rhabdomyolysis.

5. Following the **HOW SUPPLIED** section a **References** subsection was added as follows:

HOW SUPPLIED

AmBisome for Injection is available as single cartons (equivalent to 50mg amphotericin B) and in packs of ten individual vial cartons (NDC 0469-3051-30).

Each carton contains one pre-packaged, disposable sterile 5 micron filter.

References

1. Clinical and Laboratory Standards Institute (CLSI). Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard - 3rd edition. CLSI document M27- A3. CLSI, 940 West Valley Rd. Suite 1400, Wayne, PA 19087-1898, 2008.
2. CLSI. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeast; 3rd Informational Supplement. CLSI document M27-S3, 2008.
3. CLSI. Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts; Approved Guideline- 2nd edition. CLSI document M44-A2, 2009.
4. CLSI Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi; Approved Standard – 2nd edition. CLSI document M38-A2, 2008.
5. CLSI. Method for Antifungal Disk Diffusion Susceptibility Testing of Nondermatophyte Filamentous Fungi; Approved Guideline. CLSI document M51-A, 2010.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content

of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number and annual report date.

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 Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Deputy Director for Safety
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

SUMATHI NAMBIAR
03/08/2012