DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Springs, MD 20993-0002

TRANSMITTED BY FACSIMILE

Jeffrey Buchalter
Chairman and CEO
Enzon Pharmaceuticals, Inc.
685 Route 202/206
Bridgewater, NJ 08807

RE: NDA # 50-724
Abelcet® (Amphotericin B Lipid Complex Injection)
MACMIS ID # 15020

WARNING LETTER

Dear Mr. Buchalter:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a flash card (ABL 100-059-0806) for Abelcet (Amphotericin B Lipid Complex Injection) submitted by Enzon Pharmaceuticals, Inc. (Enzon) under cover of Form FDA-2253. The flash card is misleading because it presents unsubstantiated superiority claims and overstates the efficacy of Abelcet. Thus, the flash card misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §352(a), and FDA implementing regulations. *Cf.* 21 CFR 202.1(e)(6)(i), (ii), (vii), (x), (xviii); (e)(7)(i). These violations are concerning from a public health perspective because they suggest that Abelcet is more effective than has been demonstrated and encourage its use before other therapeutic options when it is a second line agent.

Background

According to the approved product labeling (PI):

> ABELCET® is indicated for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy. This is based on open-label treatment of patients judged by their physicians to be intolerant to or failing conventional amphotericin B therapy (See DESCRIPTION OF CLINICAL STUDIES).

The Clinical Studies section of the PI states (in pertinent part, emphasis added):

> Data from 473 patients were pooled from three open-label studies in which ABELCET® was provided for the treatment of patients with invasive fungal infections who were judged by their physicians to be refractory to or intolerant of conventional amphotericin B, or who had

> preexisting nephrotoxicity. **Results of these studies demonstrated effectiveness of ABELCET® in the treatment of invasive fungal infections as a second line therapy**.
>
> Patients were defined by their individual physician as being refractory to or failing conventional amphotericin B therapy based on overall clinical judgement after receiving a minimum total dose of 500 mg of amphotericin B. Nephrotoxicity was defined as a serum creatinine that had increased to >2.5 mg/dL in adults and >1.5 mg/dL in pediatric patients, or a creatinine clearance of <25 mL/min while receiving conventional amphotericin B therapy.
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> …
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> For each type of fungal infection listed above there were some patients successfully treated. However, in the absence of controlled studies it is unknown how response would have compared to either continuing conventional amphotericin B therapy or the use of alternative antifungal agents.

Unsubstantiated Superiority/Overstatement of Efficacy Claims

The flash card is misleading because it suggests that Abelcet is superior to AmBisome[1] in the treatment of invasive fungal infections when this has not been demonstrated by substantial evidence or substantial clinical experience. It does this by emphasizing the benefits of early treatment, then contrasting Abelcet's more rapid release rate to AmBisome's and implying a clinical advantage when in fact no comparison trials show such an advantage.

First, the flash card states:

- "In the treatment of invasive fungal infections**…Big Threat. Delaying Appropriate Treatment Beyond 48 hours Increases Mortality 3-Fold**" (emphasis original)
- "Mortality rate was 3 times higher when antifungal therapy began > 48 hours compared to < 12 hours after first positive blood sample was taken"[2] along with a bar graph depicting this increase entitled "Treatment Delay…Increases Mortality Among Patients with Invasive Candidiasis…."
- "Fungal growth is dramatic over a 72-hour period" accompanied by an illustration entitled "Mold Showed Minimal Change In Vitro After 3 Hours and Considerable Growth After 72 Hours" containing pictures of three petri dishes depicting growth of *Aspergillus fumigatus* at three different time points (baseline, baseline plus three hours, and baseline plus 72 hours)

While the claims above don't mention Abelcet, these claims, in conjunction with claims on the other side of the flash card that describe a pharmacokinetic difference between Abelcet and AmBisome, create a claimed advantage, indeed a survival advantage, for Abelcet when no such advantage has ever been shown. Specifically, the other side of the flash card states:

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[1] AmBisome has four indications, one of which is the treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate.

[2] Morrell M, Fraser VJ, Kollef MH. Delaying the Empiric Treatment of *Candida* Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality. *Antimicrob Agents Chemother*. Sept. 2005;49(9):3640-3645.

- "In the treatment of invasive fungal infections…**Rapid Activity. 3-Hour Drug Mobilization with ABELCET®**" (emphasis original)
- "Amphotericin B is released from the lipid more rapidly after administration of ABELCET® than with AmBisome®…." above the following two graphs:
    - Bar graph entitled "ABELCET® vs AmBisome® After 3 Hours"[3] along with the claim "60% to 75% of the amphotericin B in ABELCET® was released within 3 hours, as compared to ≈0% of the amphotericin B in AmBisome® in one in vitro study"[3,4]
    - Graph entitled "Percentage of AmBisome® Released Over Time"[5] along with the claim "Only ≈25% of amphotericin B was released from the AmBisome® lipid after 72 hours in another single-dose study"
- "ABELCET®: faster delivery to the site of infection than AmBisome®",[2,6,7]
    - "More rapid uptake by macrophages"
    - "More rapid concentration in tissues at common sites of infection"

In total, the flash card is misleading for several reasons. First, the flash card is misleading because it suggests that because Abelcet has demonstrated certain *in vitro* activity (manifested in faster release of amphotericin B from the lipid complex, faster macrophage uptake, and more rapid concentration in tissues), it is clinically superior to AmBisome in reducing mortality from invasive fungal infections when this has not been demonstrated. None of the references cited[3,4,5,6,7] present a head-to-head clinical comparison of Abelcet to AmBisome in patients with an invasive fungal infection. The references cited[3,4] for the bar graph are a Letter to the Editor in the Journal of Liposome Research discussing pharmacokinetic differences demonstrated in various *in vitro* and animal studies among different amphotericin B formulations[2] and an *in vitro* study that examined the release of amphotericin B from four different amphotericin B lipid preparations and how the lipid composition (due to the lipid composition's effect on amphotericin B release) influenced anti-*Candida albicans* activity.[3] While the study's results are accurately presented in the bar graph, *in vitro* data do not constitute substantial evidence to support a claim or implication of superior clinical effectiveness. While we acknowledge the footnote below the bar graph, which states "Results from in vitro data do not necessarily predict clinical efficacy", this footnote does not mitigate the overwhelmingly misleading impression created by the piece in its entirety that Abelcet is superior to AmBisome.

The remaining references cited[5,6,7] in the piece primarily discuss *in vitro, in vivo* and pharmacokinetic findings and none of the references present a head-to-head clinical comparison of Abelcet to AmBisome in patients with invasive fungal infections to evaluate the reduction of hospital mortality, or any other potentially clinically meaningful outcome measure. One reference in the piece (Bekersky et al.) is a single-dose, pharmacokinetic study in healthy volunteers. This study compared the plasma protein binding and subsequent pharmacokinetic differences of AmBisome versus conventional

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[3] Taraschi TF, Beggs JM [Letter]. *J Liposome Res*. 2000;10:96-98.
[4] Legrand P Chéron M, Leroy L, Bolard J. Release of Amphotericin B from Delivery Systems and its Action against Fungal and Mammalian cells. *J Drug Target*. 1997;4(5):311-319.
[5] Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Plasma Protein Binding of Amphotericin B and Pharmacokinetics of Bound versus Unbound Amphotericin B after Administration of Intravenous Liposomal Amphotericin B (AmBisome) and Amphotericin B deoxycholate. *Antimicrob Agents Chemother*. 2002;46(3):834-840.
[6] van Burik J-AH, Bowden RA. Standard antifungal treatment, including role of alternative modalities to administer amphotericin B. *Baillière's Clin Infect Dis*. 1995;2:89-109.
[7] Hiemenz JW, Walsh TJ. Lipid formulations of Amphotericin B: Recent Progress and Future Directions. *Clin Infect Dis*. 1996;22(suppl 2):S133-S144.

amphotericin B. Another (van Burik et al.) is a chapter from a book, which provides a general overview of amphotericin B. The chapter presents no clinical efficacy data directly comparing Abelcet to AmBisome. Finally, the last reference (Hiemenz et al.) is a review of various amphotericin B lipid formulations. This review also presents no clinical efficacy data directly comparing Abelcet to AmBisome.

Misleading use of *in vitro* data is further exemplified by the petri dish graphics along with the claim that "Fungal growth is dramatic over a 72-hour period" and the presentation of a set of petri dishes entitled "Mold showed Minimal Change In Vitro **After 3 Hours** and **Considerable Growth After 72 Hours**" (emphasis added), again implying that there is a clinical benefit to Abelcet's "3-hour drug mobilization" when in fact no clinical advantage has been demonstrated. We note that no reference(s) were cited to support the petri dish presentation.

Apart from the inappropriate linkage of the value of early treatment to a claimed advantage of Abelcet over AmBisome, the Morrell et al., study does not establish the value of early treatment even though early initiation of treatment with an effective drug for a life-threatening illness may indeed be prudent. Morrell et al., is a retrospective cohort analysis of 157 patients with *Candida* bloodstream infections over a 4-year period (January 2001 through December 2004) at a single hospital center. One hundred thirty-four patients had empiric antifungal treatment begun after the results of fungal cultures were known. From the time that the first blood sample for culture that was positive was drawn, nine of the 134 patients treated received unidentified antifungal treatment(s) within 12 hours. The study found that patients who received antifungal treatment within 12 hours of having a positive blood culture drawn had a lower risk of hospital mortality than patients initiated on antifungal therapy after 12 hours (11.1% vs 33.1%), but the difference was not statistically significant (p=0.169). As concluded in the study itself, one of the important limitations to this study is that only nine patients (5.7%) received appropriate antifungal treatment within 12 hours of having a positive blood sample for culture drawn "which limits the generalization of…[the] results."[8] While the study's results are accurately depicted in the bar graph entitled, "Treatment Delay Increases Mortality Among Patients With Invasive Candidiasis", neither the text nor the graph communicate these important limitations to the findings presented. This omission further contributes to the misleading impression created by the piece as a whole that Abelcet is more effective than demonstrated.

To summarize, the references cited do not provide substantial evidence or substantial clinical experience to support any claims that Abelcet is superior to AmBisome in any regard or that early initiation of Abelcet reduces hospital mortality. The FDA is unaware of any adequate and well-controlled clinical trials comparing Abelcet to AmBisome in the treatment of invasive fungal infections or data to support that Abelcet reduces the incidence of hospital mortality. If you have data to support such claims, please submit the data to FDA for review.

Finally, the flash card contains the tagline that Abelcet is the "Right Choice. Right Now." These claims are misleading for the following two reasons. First, the claim "Right Choice" alone and in conjunction with the entire flash card presentation suggests a comparison and misleadingly implies that Abelcet is the antifungal of choice offering clinical benefits over any other treatment option, in the absence of any evidence, as discussed above. Second, the totality of the flash card presentation, and the complete claim "Right Choice. Right Now.", misleadingly imply that Abelcet is a first line

[8] Morrell et al, at 3644.

therapy. However, Abelcet is only approved for patients who did not respond to conventional amphotericin B therapy or are intolerant to it. In addition, the Clinical Study section of the PI states "Results of these studies demonstrated effectiveness of ABELCET® in the treatment of invasive fungal infections as a second line therapy" (see Background section). While we note that Abelcet's indication is stated in small type on the bottom half of one side of the flashcard, the inclusion of this information does not mitigate the misleading impression created by the prominent and repeated claims in the piece suggesting that Abelcet is first line therapy and should be used accordingly.

Conclusion and Requested Action

For the reasons discussed above, the flash card presents unsubstantiated superiority claims and overstates the efficacy of Abelcet. Accordingly, the flash card misbrands Abelcet in violation of the Act, 21 U.S.C. §352(a), and FDA implementing regulations. *Cf.* 21 CFR 202.1(e)(6)(i), (ii), (vii), (x), (xviii); (e)(7)(i).

DDMAC requests that Enzon immediately cease the dissemination of violative promotional materials for Abelcet such as those described above. Please submit a written response to this letter on or before June 5, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Abelcet, such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301.796.9877. In all future correspondence regarding this matter, please refer to MACMIS ID #15020 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Abelcet comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams

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