DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC - 4 1997

TRANSMITTED VIA FACSIMILE

Gerald L. Limp
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
Zeneca Pharmaceuticals
1800 Concord Pike, P.O. Box 15437
Wilmington, DE 19850-5437

RE: NDA # 50-706
Merrem I.V. (Meropenem for injection)
MACMIS ID # 6001

Dear Mr. Limp:

The Division of Drug Marketing, Advertising and Communications (DDMAC), as part of its routine monitoring and surveillance program, has reviewed materials that promote Zeneca Pharmaceuticals'(Zeneca) product, Merrem I.V. These materials include brochure MR 1060 and brochure MR 1061 submitted on FDA Form 2253. DDMAC finds these promotional pieces to be in violation of the Federal Food, Drug, and Cosmetic Act and the applicable regulations.

Specifically, DDMAC objects to the following:

Misleading Cure Rate Presentation

Brochure # MR 10-60 and #MR 1061 contain a chart comparing the cure rates for Merrem vs Imipenem that is misleading because it fails to reveal material facts in light of the efficacy representation. Additionally, the chart implies a greater efficacy for meropenem in treating complicated appendicitis and peritonitis, than documented by substantial clinical evidence. Specifically, the chart fails to mention the efficacy rates Merrem and the comparator products demonstrated in the clinical studies used as the basis of approval. In these studies, Merrem was compared to imipenem, cefotaxime/metronidazole and clindamycin/tobramycin. The clinical cure rates, demonstrated in the clinical studies were 69%, 65%, 85% and 76%, respectively. Merrem I.V. was equivalent to imipenem and clindamycin/tobramycin and inferior to cefotaxime/metronidazole. Thus,

failure to include the efficacy rates demonstrated in the clinical studies used as the basis of approval, makes this presentation misleading.

Further, the reference cited in support of this efficacy claim, Kanellakopoulou et al,[1] is not adequate to support the higher efficacy rates than demonstrated for the approval of the product. The data referenced are from a single study of 16 patients conducted at one hospital in Greece. The study contains vague information as to the inclusion criteria and the basis for the diagnosis of the patients in the study. Thus, based on the information provided in this reference, the study does not provide substantial evidence to support the efficacy presentation.

- **"Better in vitro activity against enterobacteriaceae than imipenem/cilastatin"**

Brochure # MR 1060 and # MR 1061 also contain the above statement and an accompanying chart that compares the *in vitro* activity of meropenem and three other anti-infectives. The presentation of comparative *in vitro* data is misleading because it implies a superiority for Merrem IV over other anti-infective products without adequate clinical evidence for support. Further, in the clinical studies used as the basis of approval, Merrem IV was compared to imipenem, cefotaxime/metronidazole and clindamycin/tobramycin and shown to be equivalent to imipenem and inferior to cefotaxime/metronidazole. In addition, the reference cited in support of the *in vitro* presentation, Edwards JR,[2] is an overview of the microbiological activity of meropenem and is not considered substantial evidence to support the above claim. Although Zeneca provides the disclaimer that *"In vitro* activity does not necessarily correlate with *in vivo* effectiveness," this disclaimer is not sufficient to correct the misleading presentation.

The chart is also misleading because it does not clearly disclose the pathogens that Merrem IV is not indicated to treat clinically. For example, Merrem IV is not indicated to treat *Citrobacter diversus, C freundi, Enterobacter cloacae, Proteus mirabilis*, etc. In a letter dated August 16, 1997, DDMAC provided comments on this issue and recommended that Zeneca describe the data for Zeneca's product only and clearly indicate/separate the organisms that Merrem IV is indicated for from those that Merrem IV is not indicated to treat.

In order to address these objections, DDMAC recommends that Zeneca take the following actions:

1. Immediately discontinue the use of the above promotional material, and any other promotional materials for Merrem I.V. that contain the same or similar claims.

2. Provide a written response to DDMAC of your intent to comply with the above request and a list of promotional materials, containing the misleading presentations, that will be discontinued.

Zeneca's response should be received no later than December 18, 1997. If Zeneca has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

DDMAC reminds Zeneca that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 6001 in addition to the NDA number.

Sincerely,

Joy Ann Spearmon, Pharm.D., M.P.A.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications