DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

Sharon W. Shapowal, R.Ph.
Associate Director
U.S. Regulatory Affairs
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101

MAR 18 1998

RE: NDA 50-590; s-030
Timentin (ticarcillin disodium/clavulanate potassium)
MACMIS ID # 6419

Dear Ms. Shapowal:

Reference is made to SmithKline Beecham Pharmaceuticals' (SKB) brochure identified as "T15550 Feb. 1998" for Timentin. This brochure was submitted to the Division of Drug Marketing, Advertising, and Communications' (DDMAC) by SKB in draft form on February 17, 1998, with a request for comments. DDMAC provided extensive comments on the content of the brochure in a letter to SKB dated March 11, 1998, indicating that certain claims and representations in the brochure would be false or misleading, and were not substantiated. Although SKB had requested comments, on February 27, 1998, SKB submitted the brochure pursuant to the post-marketing reporting requirements and acknowledged that it had disseminated the brochure.

DDMAC reviewed the final brochure and finds that it contains claims and representations that are false or misleading in violation of the Federal Food, Drug, and Cosmetic Act and the applicable regulations for the following reasons.

Indication

The brochure is misleading because the statements regarding the indication for Timentin are incomplete. SKB fails to prominently present the "Note" information that is part of the "Indications and Usage" Section of the approved product labeling for Timentin. The "Note" is a bolded statement that presents a significant

limitation to the pediatric uses that is the focus of the brochure. The "Note" states that there are insufficient data to support the use of Timentin in pediatric patients under three months of age and in all pediatric patients for the treatment of septicemia and/or infections where the suspected or proven pathogen is *Haemophilus influenzae* type B. Nonetheless, SKB fails to disclose the "Note" in its entirety, and only discloses its concepts on the bottom of page 17 of the brochure as an unrelated statement following three tables that present data on *in vitro* susceptibility. However, the "Note" is an integral part of the clinical indication for appropriate use of Timentin and must be expressed as part of the indication.

Presentation of Safety Information

Brochure T15550 is misleading because it fails to include adequate risk information associated with the use of Timentin. Promotional materials must present information relating to contraindications, warnings, precautions, and adverse effects with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness. The above brochure contains effectiveness claims but fails to include an adequate presentation of risk information associated with the use of Timentin. For example, this promotional brochure fails to include the information that "Timentin is contraindicated in patients with a history of allergic reactions to any of the penicillins," in the presentation of risk information.

Efficacy Presentations

The presentation of specific clinical/bacteriologic efficacy rates for the following infections: lower respiratory tract (LRI), intra-abdominal, bone and joint, skin and skin structure, urinary tract infections (UTI), and endomyometritis, are misleading because the rates are not based upon data derived from adequate and well controlled clinical studies, using appropriate endpoints, in a pediatric population. The Agency determined that Timentin is safe and effective, for the above conditions, in pediatric patients pursuant to the Pediatric Rule. This rule provides for the granting of pediatric indications based on pharmacokinetic, pharmacodynamic, and safety profile data. However, claims of specific clinical/bacteriologic efficacy rates must be based on adequate and well controlled clinical trials in the targeted population.

Thus, claims stating specific clinical/bacteriologic efficacy rates in the pediatric population, for

the indicated conditions are misleading.

Additionally, the clinical scenario, that appears on page 14, of a 3-year-old child with a temperature of 104°F and diffuse myalgias, is misleading because it fails to state a specific indication. This clinical scenario, as described, is consistent with a viral illness where an antipyretic medication would likely be the drug of choice, not Timentin.

In Vitro Presentation

The presentation of *in vitro* data is misleading because it is presented in a way that suggests clinical relevance. Specifically, the statement "Its time to take action," when juxtaposed with the accompanying *in vitro* presentation, imply that Timentin is indicated to treat infections caused by each of the pathogens in the presentation. Additionally, the *in vitro* presentation combines selected pathogens for which Timentin is indicated and pathogens for which Timentin is not indicated. For example, Timentin is not indicated to treat conditions caused by coagulase-negative *Staphylococcus* (methicillin-susceptible), *Enterococcus faecalis, Streptococcus* Group B, etc., but these pathogens are included in the presentation.

Although SKB provides a disclaimer that states that "In vitro susceptibility does not necessarily imply *in vivo* efficacy," the presence of this statement does not correct the misleading impression created by the two page *in vitro* presentation. Moreover, this statement is presented as a footnote and is not presented with a prominence and readability reasonably comparable to the presentation of the information that claims or suggests effectiveness.

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

1. Immediately discontinue the use of all brochures and any other promotional materials for Timentin that contain the same or similar violations.

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.

SKB's response should be received no later than 10 business days from the issue date of this letter. If SKB 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 SKB that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 6419 in addition to the NDA number.

Sincerely,

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