DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 27 1997

TRANSMITTED BY FACSIMILE

Olivia Pinkett, Ph.D.
Director
U.S. Regulatory Affairs
SmithKline Beecham
1250 S. Collegeville Rd.
UP 4425
Collegeville, PA 19426

Re: **NDA 20-305**
Kytril (granisetron hydrochloride) Tablets
MACMIS ID #4921

Dear Dr. Pinkett:

This letter is in reference to SmithKline Beecham's (SB) submission dated August 23, 1996, of promotional materials under cover of FDA Form 2253 for Kytril (granisetron HCl). This submission included two reprints, one concerning the pharmacologic profile of granisetron and one concerning the efficacy and safety of granisetron.[1] The Division of Drug Marketing, Advertising, and Communications (DDMAC) regards these reprints to be false and/or misleading under the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

The reprint article by Blower implies that granisetron is superior to ondansetron. Blower states that granisetron blocks the enterochromaffin 5-HT_3 receptors and that ondansetron does not. A previous sentence states that exposure to chemotherapy or radiation releases 5-HT from the enterochromaffin cells in the small intestine. According to Blower, following exposure to chemotherapy or radiation, 5-HT is released from enterochromaffin cells and that both granisetron and ondansetron block vagal afferent 5-HT_3 receptors, but the enterochromaffin 5-

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[1] Peter Blower, "A Pharmacologic Profile of Oral Granisetron (Kytril Tablets)," Seminars in Oncology 1995;Supp.10:3-5.

Navari et al. "Efficacy and Safety of Granisetron, a Selective 5-Hydroxytryptamine-3 Receptor Antagonist, in the Prevention of Nausea and Vomiting Induced by High-Dose Cisplatin," Journal of Clinical Oncology 1994;12:2204-2210.

HT_3 receptors were blocked by granisetron and not by ondansetron. (See page 3 "Mechanism of Action of 5-HT_3 Receptor Antagonists"). These statements suggest that granisetron is superior to ondansetron following exposure to either chemotherapy or radiation therapy. Such implications are not supported by substantial evidence and therefore, considered to be false and/or misleading.

Moreover, the Blower article discusses the release of 5-HT from the enterochromaffin cells from exposure to radiation and anti-cancer cytostatic agents, implying that granisetron is safe and effective in treating radiation-induced therapy. The implication that granisetron is safe and effective in the treatment of radiation-induced nausea and vomiting results in the promotion of granisetron for unapproved uses. Therefore, SB should discontinue use of the Blower reprint in promotion immediately.

The article by Navari et al. discusses the use of unapproved doses. DDMAC notes that the article was based upon a pivotal study for granisetron. According to the Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data published in the October 8, 1996, edition of the Federal Register, if SB wishes to use the reprint of the article in promotion, it must disclose the differences between the article and the approved product labeling on the face of the reprint in a permanent manner. Without the prominent presentation of the differences in the study and the approved product labeling on the face of the reprint, use of this article is promoting unapproved doses and therefore, is false, lacking in fair balance, or otherwise misleading.

SB should immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter. We ask that SB provide a written response to DDMAC on or before March 14, 1997, describing the steps taken to ensure that the use of these materials have been discontinued.

SB's reply should be directed to the undersigned at the Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, Maryland 20857, or by facsimile at (301) 594-6771. DDMAC reminds SB that only written communications are considered official.

In all future correspondence regarding this matter, please refer to both the NDA number and the MACMIS File ID #4921.

Sincerely,

Stephen W. Sherman

Stephen Sherman, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising & Communications

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draft: SSherman	11/27/96
comment: JHankin	12/2/96
comment: TAbrams	12/10/96
revised: SSherman	1/24/97
comment: TAbrams	2/25/97
revised: SSherman	2/26/97
concur: TAbrams	2/27/96

cc:

HFD-40/NDA 20-305
HFD-40/chron/abrams/sherman
HFD-180/Fredd

MACMIS type code: LETT
MACMIS: VIOL

MACMIS ID #4921

Due Date: March 14, 1997
Close-out: NO

FOI Status: **RELEASEABLE**