DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

NOV 20 1997

Ms. Catherine K. Clark
Director, US Regulatory Affairs
SmithKline Beecham Pharmaceuticals
1250 S. Collegeville Road, PO Box 5089
Collegeville, PA 19426-0989

RE: NDA# 20-297
Coreg (carvedilol) Tablets
MACMIS ID #5645

Dear Ms. Clark:

As part of the Division of Drug Marketing, Advertising and Communications' (DDMAC) routine monitoring of promotional activities, it has come to our attention that SmithKline Beecham (SmithKline) distributed promotional materials for Coreg (carvedilol) tablets which were in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, we refer to two brochures (CO6532 and CO 6527) distributed at the Annual Meeting of the American Heart Association in Orlando, Florida, November 10-12, 1997, and three brochures (CO6080, CO6043, and CO5857) submitted under cover of Form FDA 2253 on October 31, 1997. DDMAC has reviewed these brochures and determined that they promote Coreg in a manner that is considered false and/or misleading.

Reference is also made a sales/promotional aid (CO8686) in which SmithKline claimed that patients using Coreg demonstrated "improvement in well-being." This claim was derived from a study that subjectively elicited physicians' and patients' global assessments on a questionnaire. This questionnaire was comprised of two questions, one for the physician to subjectively rate his/her impression of the patient's improvement and one for the patient to subjectively rate his/her impression of improvement. DDMAC objected this claim in a letter dated July 31, 1997, because the questionnaire did not meet the substantiation requirements for health-related quality of life claims.

Subsequently, SmithKline, in letters dated August 27, 1997, and September 30, 1997, and a facsimile dated September 2, 1997, proposed revising this claim to "improvement in clinical status." In letters dated, September 11, 1997, and October 17, 1997, and a teleconference dated October 30, 1997, DDMAC objected to the proposed revision because DDMAC considers "clinical status" to be a broad clinical claim with broad implications that should be substantiated by instruments that have been validated to measure all the important contributors to the

condition, in the disease state and with the drug therapy in question. The results of the global assessment questionnaire did not meet these criteria.

Currently, in brochures CO6527, CO5857, and CO6043, SmithKline uses the term "clinical status" to describe results of the global assessment questionnaire. DDMAC reiterates that the results of the global assessment questionnaire are not validated objective clinical end-points and cannot be used to substantiate the broad clinical claim of clinical status. Therefore, DDMAC considers these materials to be false and/or misleading because the claim "improvement in clinical status" overstates the subjective global assessments obtained from this questionnaire.

In addition, in brochures CO6532 and CO6080, SmithKline has combined information relating to results of the subjective physicians' global assessment, entitled "patient status," with measurements of improvement in patients' left ventricular ejection fraction (LVEF). This consists of two sets of graphs, one for mild heart failure, and the other for moderate heart failure. DDMAC has reviewed this graphic representation and considers it to be false and/or misleading for the following reasons:

Patient status

DDMAC considers use of "patient status" to describe the results of the global assessment questionnaire to overstate the subjective measure of global assessment by physicians. Description of the results of this questionnaire should be consistent with language in the approved product labeling for Coreg (i.e., Subjective Measures: "...patients' and investigators' global assessments showed significant improvement in most studies").

As previously stated in DDMAC's October 17, 1997, letter, to provide fair balance, a statement summarizing the results of the other subjective measure of Coreg's efficacy should be added to SmithKline's claim to be consistent with the approved product labeling [e.g., "quality of life, as measured with a standard questionnaire (a primary end-point in one study), was unaffected by carvedilol"].

Graphic representations

Graphs should clearly, fairly, and accurately depict study results. In order to avoid misrepresentation of study results on a graph, text discussing the study results should be placed directly adjacent to the graph, and should expressly refer to the graph. The graphs in these brochures do not meet these criteria, and therefore, misrepresent study results. The y-axis labels appear above the graph, with a notation at the bottom of the page that these measures were "based on physician global assessments of patient status." This information does not accurately describe the data presented graphically (see above comments regarding "patient status"), and if the notation were accurate, it should be

displayed with more prominence and in closer proximity to the y-axis label. The x-axis is not labeled, so the timing of these measurements is not clear. In addition, text adjacent to the graph should include information about the design of the study (i.e., open-label, randomized, placebo-controlled, study population and duration).

Lastly, in brochures CO5857 and CO6527, SmithKline presents efficacy results for Coreg as "...reducing death and total hospitalizations by 25%, 39%, and 49%" (page 12). The approved product labeling for Coreg states that the US studies demonstrated a reduction in death and total hospitalizations by 19%, 39%, and 49%, and by 25% in the Australia-New Zealand study. DDMAC would consider "cherry-picking" and presenting the most favorable results to be false and/or misleading since they do not accurately represent the results of the clinical trials and are not consistent with the approved product labeling.

For the reasons cited above, DDMAC would consider these brochures to be false and/or misleading since they misrepresent the results of the subjective measure of patients' and investigators' global assessment, and/or misrepresent efficacy results, and are not consistent with the approved product labeling.

SmithKline should immediately cease distribution of these and any other similar promotional materials for Coreg that contain the same or similar claims or presentations. SmithKline should submit a written response to DDMAC on or before December 4, 1997, describing its intent and plans to comply with the above.

SmithKline should direct its response to 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 SmithKline that only written communications are considered official.

In all future correspondence regarding this particular issue, please refer to MACMIS ID #5645 in addition to the NDA number.

Sincerely,

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications