DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

Marie DeGayner Kuker
3M Pharmaceuticals
Regulatory Affairs
3M Center, Bldg 260-6A-22
St. Paul, MN 55144

NOV - 1 1999

RE: **NDA#** 18-830
Tambocor (flecainide acetate) Tablets
MACMIS ID# 8093

Dear Ms. DeGayner Kuker:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Tambocor (flecainide acetate) tablets, disseminated by 3M Pharmaceuticals (3M) that violate the Federal Food, Drug and Cosmetic Act and its implementing regulations. Reference is made to a reprint carrier (TM 0825), submitted under cover of Form FDA 2253. DDMAC has reviewed this promotional labeling piece for Tambocor and has determined that it contains promotional claims that are false or misleading, and lacking in fair balance.

Unsubstantiated superiority claims

In this reprint carrier, 3M presents claims and representations derived from two open-label, clinical trials comparing Tambocor and propafenone in patients with paroxysmal atrial fibrillation/flutter (PAF).[1,2] Your presentation states or implies that Tambocor is safer and more tolerable than propafenone. For example, you present the following quotation excerpted from the Aliot reprint:

> In paroxysmal AF [atrial fibrillation] and paroxysmal atrial flutter, flecainide and propafenone are equally effective. However, in this study the probability for a patient to

1. Aliot E, Denjoy I, et al. Comparison of the safety and efficacy of flecainide versus propafenone in hospital out-patients with symptomatic paroxysmal atrial fibrillation/flutter. *Am J Cardiol.* 1996;77:66A-71A.

2. Chimienti M, Cullen MT, et al. Safety of long-term flecainide and propafenone in the management of patients with symptomatic paroxysmal atrial fibrillation: Report from the flecainide and propafenone Italian study investigators. *Am J Cardiol.* 1996;77:60A-65A.

> stay on flecainide after 1 year had a tendency to be higher than the probability to stay on propafenone due to a greater proportion of secondary effects with propafenone.

Further, you present tables comparing incidence rates of adverse events from these clinical trials, most of which are higher for the propafenone treatment group. The quotation and tables imply that Tambocor is superior to propafenone with respect to its safety and tolerability profile. However, these open-label trials are inadequate in design to support any claim of superior efficacy, safety, or tolerability for Tambocor over propafenone. For example, the Aliot study used an unapproved dosing regimen (i.e., BID) and an unapproved dose (i.e., 1200 mg/day) for propafenone. Therefore, your stated or implied superiority claims are misleading because they are not based on substantial evidence.

Misrepresentations of efficacy

In addition, you have presented graphs and claims that imply that Tambocor is more efficacious than demonstrated by substantial evidence. For example, to summarize results of the Chimienti study, you present a bar graph that depicts a 77% "estimated success rate after 1 year," that is "based on the number of patients who completed the study and were not discontinued because of adverse experiences and/or inadequate response." Similarly, to summarize the results of the Aliot study, you present the "rates of successful therapy" as "the proportion of patients who remained on flecainide over the course of 1 year was 0.619." These presentations imply that patients achieving "successful therapy" were attack free. This implication is misleading because these "success rates" included patients who were not attack free. For example, the Aliot reprint states that "if the first month of therapy (dosage adjustment period) is excluded, approximately 30% of the patients in both groups completed the study without symptomatic attacks." In addition, the approved product labeling (PI) for Tambocor states that "in two randomized, crossover, placebo-controlled clinical trials of 16 weeks double-blind duration, 31% of patients with paroxysmal atrial fibrillation/flutter (PAF) receiving flecainide were attack free, whereas 8% receiving placebo remained attack free." Therefore, your presentations of these high "rates of successful therapy" for Tambocor are misleading because they imply greater efficacy than what was demonstrated in these clinical trials, and what has been demonstrated by substantial evidence. Further, as stated above, these trials are inadequate in design to evaluate efficacy rates.

Unsubstantiated patient compliance claim

In this reprint carrier, you present the claim "convenient BID dosing for patient compliance." However, Tambacor's twice-daily dosing regimen has not been adequately evaluated to support a claim for patient compliance. Patient compliance may be influenced by a number of factors, including patient variables (e.g., motivation, memory, etc.), economic variables, drug-related variables (e.g., complex dosing regimens, intolerable side effects), etc. Therefore, DDMAC considers this claim to be misleading because it has not been supported by adequate evidence.

Lacking in fair balance

Promotional materials are lacking in fair balance or otherwise misleading if they contain a representation or suggestion that a drug is safer, has fewer or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence. In this reprint carrier, you have presented selected risk information for Tambocor. DDMAC has reviewed the content of this information and has determined that it is insufficient to convey the serious risks associated with Tambocor therapy. Specifically, you have failed to disclose: a) the contraindications for use, b) information from the boxed warning of the PI, including results of the CAST trial, c) that Tambocor can cause new or worsened supraventricular or ventricular arrhythmias, and d) that there is no evidence from controlled trials that the use of Tambocor favorably affects survival or the incidence of sudden death. In addition, the risk information that is presented on the bottom of the page is minimized by the header that states that Tambocor "provides well-tolerated therapy." Therefore, your presentation lacks fair balance with respect to content of risk information.

3M should immediately cease distribution of this reprint carrier and other similar promotional materials for Tambocor that contain the same or similar claims or presentations. 3M should submit a written response to DDMAC on or before November 15, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, 3M should include a list of materials discontinued, and the date on which these materials were discontinued.

3M 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-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds 3M that only written communications are considered official.

In all future correspondence regarding this particular matter please refer to MACMIS ID #8093 in addition to the NDA number.

Sincerely,

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