DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

MAY 28 1998

Mark Robbins, Ph.D., J.D.
Vice President, Scientific Affairs
Upsher-Smith Laboratories, Inc.
14905 23rd Avenue North
Minneapolis, MN 55447-4709

RE: **ANDA 75-135**
Pacerone (Amiodarone HCl) Tablets, 200 mg
MACMIS ID # 6652

Dear Dr. Robbins:

Reference is made to Upsher-Smith Laboratories, Inc.'s (Upsher) submission of proposed promotional materials for Pacerone (Amiodarone HCl) Tablets, 200 mg, dated May 1, 1998, to the Division of Drug Marketing, Advertising, and Communications (DDMAC). Prior to responding to Upsher's request for comments, DDMAC became aware that several promotional materials for Pacerone had been disseminated. DDMAC reviewed these promotional materials and determined that they are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Reference is made to DDMAC's letter, dated May 14, 1998, requesting information concerning the extent to which promotion of Pacerone with these materials has occurred.

In a letter, dated May 19, 1998, Upsher responded that these, or similar pieces,† were disseminated

On May 20, 1998, DDMAC and Upsher held a teleconference for the purpose of identifying all other promotional materials that have been disseminated. In a letter, dated May 21, 1998, Upsher identified the following materials that are currently in use for the promotion of Pacerone:

- (PC10A 398)
- (PC01A)
- (PC08A 0398)
- (PC15A 0498)
- (PC16A 0498)
- (PC04A 0398)
- (PC05A 0398)

† Similar pieces identified as New Product Information (PC08A 0398) and (PC16A 0498).

- (PC09A)
- (PC02A 0398)
- (PC03A 0398)
- (PC01 0498)
- (PC02 0598)
- (PC13A 0598)
- (PC14A 0498)
- (HSGCADD 0498)

Many of the above promotional pieces and other proposed pieces, contain the same, or similar claims. For this reason, DDMAC selectively reviewed the following promotional materials disseminated by Upsher: (PC15A 0498), (PC05A 0398), and (PC04A 0398) and has determined that they contain promotional claims that are false or misleading, and lacking in fair balance. DDMAC's comments on one piece are applicable all other pieces in which the same, or similar claims or representations are made.

- Lacking in fair balance

Upsher makes claims concerning Pacerone's indication for use in the first paragraph of the letter. However, Upsher does not present any risk information associated with the use of this drug. Promotional materials must present information about the risks associated with the use of the drug in a manner that is reasonably comparable to that of claims concerning the drug's efficacy. Pacerone is associated with significant risks, as listed in the Contraindications, Warnings, Precautions, and Adverse Reactions sections of the approved product labeling. This risk information should be prominently presented in the text of the letter. The footnote directing the reader to the full product labeling is not adequate in content or prominence to correct Upsher's presentation. Therefore, DDMAC considers this piece to be lacking in fair balance because it fails to present risk information associated with Pacerone's use.

In the piece, Upsher presents Pacerone as the "first AB-rated generic to Cordarone."* However, this claim for Pacerone is not accompanied by any risk information. As stated above, risk information associated with the use of the drug should be presented in a manner that is reasonably comparable to that of claims concerning the drug's efficacy. Therefore, DDMAC considers this piece to be lacking

* Cordarone (amiodarone HCl) Tablets is a product of Wyeth-Ayerst Laboratories.

in fair balance because it fails to present risk information associated with the use of Pacerone, or a prominent reference to the location of such risk information. DDMAC suggests that Upsher present either the boxed warning from the approved product labeling, or a prominent statement that directs the reader to the boxed warning in the approved product labeling accompanying this piece.

- Misrepresentation of indications and usage

In the first paragraph of the letter, Upsher states that "Pacerone Tablets are an AB-rated, economical brand of Amiodarone HCl indicated for the treatment of documented life threatening recurrent ventricular arrhythmias." This claim overstates the indications and usage of Pacerone. The approved product labeling states that "[b]ecause of the life-threatening side effects and the substantial management difficulties associated with amiodarone use...Pacerone (Amiodarone HCl) is indicated **only** for the treatment of the following documented, life-threatening recurrent ventricular arrhythmias **when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated**" [emphasis added]. Upsher's statement suggests that Pacerone could be used as a first-line agent, which is inconsistent with the approved product labeling. Therefore, DDMAC considers this piece to be false or misleading because it misrepresents the indications and usage of Pacerone.

- Misrepresentations of efficacy

Upsher presents the claim "electrical impact," to describe Pacerone's efficacy. This claim suggests a high efficacy rate for Pacerone. However, the approved product labeling for Pacerone describes that predicting the efficacy of an antiarrhythmic agent is difficult and controversial, and that overall arrhythmia-recurrence rates (fatal and nonfatal) were highly variable. The Monitoring Effectiveness section of the approved product labeling states "[i]n most cases, considering only patients who seemed to respond well enough to be placed on long-term treatment, recurrence rates have ranged from 20 to 40% in a series with a mean follow-up of a year or more." In addition, there is no evidence from controlled trials that Pacerone favorably affects survival. Therefore, DDMAC considers Upsher's description of Pacerone's efficacy to be misleading because it implies a higher efficacy rate than that demonstrated by substantial evidence.

In addition, in this promotional piece, Upsher presents the statement that Pacerone is "a new force in antiarrhythmic therapy." This statement implies that Pacerone represents a new, previously unavailable, treatment option for patients with arrhythmias. However, Pacerone is

an AB-rated, bioequivalent to Cordarone. Therefore, DDMAC considers this statement to be misleading because it misrepresents the fact that Pacerone is a generic drug.

- Misrepresentation of indications and usage

  Upsher presents the claim "[i]n life-threatening VT/VF," to describe Pacerone's indications and usage. In addition, Upsher presents information concerning Pacerone's indications under separate headers titled "impact" and "response." DDMAC considers these presentations to misrepresent the indications and usage for Pacerone as stated in the approved product labeling. The claim "in life-threatening VT/VF" lacks context to adequately convey the population indicated for Pacerone's use (see above paragraph concerning this issue). In addition, under the header "response," Upsher presents claims for Pacerone's efficacy in patients who have failed to respond, or are intolerant, to other therapies. Although these are the limitations to Pacerone therapy, Upsher's presentation misleadingly implies drug efficacy and patient benefit. DDMAC considers these presentations to be misleading because they overstate the indications and usage of Pacerone, and are inconsistent with the approved product labeling.

- Lacking in fair balance

  Upsher presents risk information associated with Pacerone's use in the "Caution" section of this promotional piece. As the first statement of this section, Upsher presents the following claim: "Pacerone is a powerful agent that carries the potential for serious adverse reactions." DDMAC considers that use of the term "powerful" to describe Pacerone's efficacy in this section minimizes the importance and seriousness of the risks associated with Pacerone's use. The purpose of the "Caution" section is to alert the practitioner of the serious adverse events associated with the use of Pacerone, not to make claims for Pacerone's efficacy. In addition, Upsher fails to present information related to the difficulties associated with dosage adjustment or discontinuation as described in the boxed warning of the approved product labeling. Therefore, DDMAC considers this promotional piece to be lacking in fair balance because it fails to provide sufficient emphasis on the significant risk information associated with Pacerone's use.

- Misrepresentation of economic benefit

  Upsher presents the statments that pharmacists should "[n]otify patients of an economical alternative" and "[a]sk them if they are interested in saving money." Upsher also presents prices based on AWP and WAC. DDMAC considers these claims to be misleading without the addition of context to clarify that the prices presented may not reflect actual prices paid by consumers or pharmacies.

- Misleading use of a headline

  Upsher presents important safety information concerning appropriate initiation and monitoring of Pacerone under the headline "[e]xpertise." This headline and subsequent presentation of monitoring information describes the necessary "expertise" of the physician administering Pacerone, not a quality or characteristic of Pacerone. DDMAC considers this presentation to be misleading because it minimizes the importance of the monitoring information associated with Pacerone's use.

Failure to submit pursuant to post-marketing reporting requirements

None of the above pieces were submitted on Form FDA 2253 at the time of initial dissemination, pursuant to the post-marketing reporting requirements for promotional labeling and advertising, 21 CFR 314.81(b)(3)(i). Therefore, promotion of Pacerone has occurred in violation of the post-marketing reporting requirements of the Act.

Upsher should immediately cease distribution of these and all other promotional materials for Pacerone that contain the same or similar claims or presentations. Upsher should submit a written response to DDMAC, on or before June 11, 1998, describing its intent and plans to comply with the above.

Upsher 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, Maryland 20857. DDMAC reminds Upsher that only written communications are considered official. In all correspondence regarding this particular matter, please refer to MACMIS ID #6652, in addition to the ANDA number.

Sincerely,

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