DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 26 1997

**TRANSMITTED VIA FACSIMILE**

Phyllis Lambridis
Director, Regulatory Affairs and Compliance
Barr Laboratories, Inc.
P.O. Box 2900
Pomona, NY 10970-0519

**Re: ANDA 40-145**
Warfarin Sodium Tablets, USP
MACMIS File ID #5681

Dear Ms. Lambridis:

This letter is in reference to Barr Laboratories, Inc.'s (Barr) promotional materials for its warfarin sodium tablets, USP. Based on materials the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed as part of its monitoring program[1], Barr is promoting warfarin for unapproved uses, unapproved doses, and is using false and/or misleading statements concerning its drug. Additionally, Barr's promotional materials are lacking in fair balance or otherwise misleading. These promotional materials are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and regulations promulgated thereunder. Our specific objections follow:

**Unapproved Uses**

On page 13 of the promotional brochure identified as WARMD.002, Barr presents the recommended therapeutic ranges (INR) for warfarin for various conditions. These conditions include peripheral artery disease, valvular lesions, and recurrent deep vein thrombosis. However, warfarin is not indicated for these conditions. Thus, Barr is recommending the use of warfarin for conditions in which the drug has been not demonstrated to be safe and effective.

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[1] These materials were simultaneously disseminated for promotional use and submitted to DDMAC for comment. DDMAC does not comment on promotional materials currently in use.

Additionally, Barr states in some of its promotional materials that warfarin can be used to treat "patients with heart disease"[2] and warfarin is a "cardiovascular treatment."[3] However, the approved indications for warfarin do not include broad indications of "heart disease" or "cardiovascular treatment."

**Unapproved Doses**

In the brochure WARMD.002 discussed above, Barr also recommends therapeutic ranges for warfarin in various conditions that have not been demonstrated to be safe and effective. For example, Barr recommends an International Normalized Ratio (INR) between 3.0 - 4.5 for prosthetic heart valves. However, the approved product labeling states that the recommended therapy for mechanical heart valves is warfarin necessary to achieve an INR of between 2.5 -3.5. For bioprosthetic heart valves, based on limited data, the labeling recommends warfarin therapy to an INR of 2.0 - 3.0. Moreover, there is a bolded warning in the approved product labeling that "an INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding." Thus, by recommending INR levels above 4.0, Barr is increasing the risk of patients developing bleeds.

Additionally, Barr states in a patient brochure (WARPAT.001, pages 4-5), that, at first, blood tests may be needed "every day or two" and then as therapy is continued, "you will probably only need blood tests every 4 to 6 weeks." However, the approved product labeling states that "[t]he PT should be determined daily after the administration of the initial dose until the PT/INR results stabilize in the therapeutic range.... Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined." Thus, Barr is promoting warfarin with monitoring recommendations that are beyond labeling and that could significantly increase risk.

**False and/or Misleading Statements**

Barr has also presented statements in some of its promotional materials that are false and/or misleading. For example, Barr states that it uses "industry-established dosage colors for safety and enhanced patient compliance." However, Barr has neither made reference to, nor described the industry-established standard for colors of warfarin tablets.

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[2] Press release issued by Barr Laboratories dated October 1, 1996, concerning the pending approval of warfarin sodium.

[3] Press release issued by Barr Laboratories dated July 28, 1997, concerning shipments of warfarin sodium.

**Fair Balance**

Barr's promotional materials also are lacking in fair balance or otherwise misleading. Barr should include in its presentation of recommended therapeutic ranges the bolded warning that an INR greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding. Barr should also include in its promotional materials that the most serious risks associated with anticoagulant therapy with warfarin sodium are hemorrhage in any tissue or organ, and less frequently, necrosis and /or gangrene of skin and other tissues. Numerous factors, alone or in combination, including travel, changes in drug therapies and diet, and environment may influence the response of the patient to anticoagulants.

**Other Violations**

Several of Barr's promotional pieces make reference to FDA's approval of its ANDA and generic warfarin product. Such statements are specifically prohibited by the Act (21 USC §301(l)).

Finally, these materials are labeling under the Act and its implementing regulations and therefore, should be accompanied by the approved product labeling, not the brief summary. Under the Act, the brief summary is used in conjunction with drug advertisements, not promotional materials deemed to be labeling.

**Requested Actions**

Barr should immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter.

In a letter to DDMAC dated August 4, 1997, Barr states or suggests that there was limited distribution of its materials and that such distribution has ceased. However, in a press release dated August 8, 1997, Barr stated that these materials "were never distributed." Barr's response to this letter should clarify these inconsistent statements and state whether these materials were distributed. If these materials were distributed, Barr should provide information about how many copies were distributed, to whom, and what corrective action has been taken. We note that, based on this information, the agency may request additional corrective action.

Barr should submit a written response to DDMAC on or before September 6, 1997, describing the steps that it has taken to ensure that these promotional activities and the use of these promotional materials have ceased.

Barr should address any correspondence or additional questions to the undersigned at the Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17 B-17, 5600

Fishers Lane, Rockville, Maryland 20857. DDMAC reminds Barr that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID #5681, in addition to the NDA number.

Sincerely,

Stephen W. Sherman

Stephen W. Sherman
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications