DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

M 22 L3n

January 21, 1999

Transmitted via Facsimile

Wayne Yetter
President and CEO
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936

Re: Lescol (fluvastatin sodium) Capsules
NDA 20-261
MACMIS ID # 7505

WARNING LETTER

Dear Mr. Yetter:

This Warning Letter addresses Novartis Pharmaceuticals Corporation's ("Novartis") dissemination of a television broadcast advertisement for Lescol (fluvastatin sodium) Capsules. This advertisement was broadcast during August September, and October 1998, in various regions and areas of the United States. The Division of Drug Marketing, Advertising, and Communications, ("DDMAC") has just become aware of this advertisement. Based on our review, we conclude that Novartis' television broadcast advertisement is false or misleading, and lacking in fair balance in violation of the Federal Food, Drug, and Cosmetic Act ("Act"), 21 U.S.C. §§ 331(a),(b) and 352(n), and applicable regulations. By its dissemination or publication of this advertisement, Novartis is misbranding Lescol.

This matter raises significant concern because Novartis failed to submit copies of this television broadcast advertisement at the time of initial dissemination or publication as required by the post-marketing reporting regulations, 21 CFR 314.81(b)(3)(i). Novartis' failure to submit the required information prevented the agency from acting promptly to stop the dissemination of a false or misleading advertisement and resulted in violative messages being disseminated to a far larger consumer audience than might have otherwise occurred.

Background

Lescol (fluvastatin sodium) Capsules is a cholesterol lowering agent that acts through the inhibition of an enzyme referred to as HMG-CoA. It is a member of the "statin" class of pharmacological agents. There are presently six products in this class on the market in the United States. All of these agents have demonstrated the ability to lower cholesterol levels as an adjunct to an appropriate diet, however, they are not necessarily comparable in effectiveness. Although Novartis has demonstrated that Lescol is safe and effective "as an adjunct to diet in the treatment of elevated total cholesterol and LDL-C ...," it has not demonstrated that Lescol provides comparable effectiveness to these other products. Moreover, some of these other statin products have demonstrated important and significant effectiveness in reducing the risk of primary or secondary myocardial infarction and cardiovascular mortality as well as other uses. Lescol has not been shown to have all of these effects.

Violations

A. Misleading Effectiveness Claims

Lescol is indicated "as an adjunct to diet to reduce elevated total cholesterol (Total-C) and LDL-C levels ..." and "to slow the progression of coronary atherosclerosis...." In this television advertisement, Novartis misleadingly suggests that Lescol is similar in effectiveness to other cholesterol lowering agents including Pravachol, Mevacor, and Zocor, and that the only difference between these agents is cost. Novartis names these three cholesterol agents and states that "Lescol works like most commonly prescribed cholesterol drugs." However, in adequate and well-controlled clinical trials, some of these "other cholesterol agents" have demonstrated additional benefits in the treatment of cardiovascular morbidity and mortality, including reducing the risk of stroke and transient ischemic attack. Novartis has not demonstrated that Lescol provides any of these benefits nor that Lescol is comparable in effectiveness to these other agents for its' indicated uses.

B. Inadequate Risk Information

The advertisement is misleading because it minimizes risks associated with the use of Lescol. First, the "Warnings" section of the approved product labeling describes liver function abnormalities that have been associated with Lescol and recommends (in bold type) that liver function tests be performed before the initiation of therapy, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically thereafter, such as semiannually. Novartis minimizes the significance of this important risk information by failing to state why such tests

are recommended, i.e., because Lescol can cause liver problems (abnormalities of liver function).

Second, the statement "Tell your doctor about any medications you are taking, or any muscle pain or weakness you have on Lescol" is an inadequate disclosure of this important warning and thus, is misleading. Muscle weakness is a sign of potentially serious side effects, namely myopathy and rhabdomyolysis with potential complications of renal dysfunction. Accordingly, such information should be presented so that patients know why it is important to tell their health care professional about these symptoms.

C. Insufficient Adequate Provision

Broadcast advertisements must contain a brief summary of all necessary information related to side effects and contraindications unless adequate provision is made for the dissemination of the approved product labeling, 21 CFR 202.1(e)(1). The focus of this regulation is on the dissemination of risk information, not coupons or discount certificates. However, in this ad, reference to the 800 number only specifically addresses the availability of a rebate coupon, and the references to the World Wide Web site and the concurrently running print ad are of insufficient prominence and duration to be read and processed by viewers. Additionally, the statement "Ask your doctor if Lescol is right for you" is insufficient to communicate that the physician or health care professional is a source of additional information about Lescol.

D. Misleading Comparative Claims

The advertisement is misleading and unsupported with respect to the claim that Lescol costs less. First, Novartis alleges that consumers may save up to 60% based solely on a price comparison between reported retail prices. The disclosure "Based on retail pricing of the most commonly prescribed doses" does not effectively communicate to consumers the various limitations of the price claim that are not related to individual retail outlet differences. For example, without context, patients already taking another cholesterol-lowering medication are not likely to understand that they may need a different dose of Lescol in order to obtain the same effect, and that this difference may reduce any potential savings. In addition, there may be additional costs incurred for laboratory tests and office visits because of the need to titrate the dose of Lescol. Furthermore, any valid comparison of cost should be based on the cost of therapy to obtain equivalent lipid lowering effects. Thus, a patient on a commonly prescribed dose of another cholesterol lowering agent may need a much higher, more costly dose of Lescol to obtain equivalent cholesterol lowering effects or may not be able to obtain equivalent effects within the recommended dose range. In fact, because of dosing differences, Lescol may cost more than the other agents. In

addition, we note that consumers switched to Lescol based on potential savings may not obtain the proven additional benefits demonstrated by some of the other agents.

Second, the disclosure itself is displayed neither prominently nor long enough to allow consumers to read and process its meaning.

The relative costs of Lescol to other cholesterol lowering agents is the focus of this television advertisement. This focus, coupled with the misleading suggestions that these products provide comparable clinical benefit, suggests that Lescol is the preferred cholesterol lowering treatment. However, the advertisement fails to adequately communicate that the overall relative clinical benefit to risk profile of Lescol, as well as cost, are important parts of the decision patients would make with their physician.

E. Failure to Submit Post-marketing Reports

Although this advertisement was initially disseminated last August, Novartis failed to submit copies of the advertisement to FDA until FDA requested copies of the advertisement. Such submissions are required at the time of first use. The failure to submit this advertisement as required resulted in a significantly larger consumer audience receiving false or misleading information about the safety and effectiveness of Lescol.

Conclusions and Recommendations

It is our understanding that the dissemination of this advertisement has ceased. However, Novartis' dissemination of this violative ad over a period of a few months has resulted in the dissemination of false, misleading, unbalanced and incomplete information to consumers. Accordingly, Novartis should assure FDA that this advertisement and similar advertisements, broadcast or print, and labeling pieces, are not being disseminated anywhere in the United States.

In addition, Novartis should provide a complete list of the television stations that ran this advertisement and the number of times it was broadcast. Finally, Novartis should propose an action plan to disseminate accurate and complete information to the audience that received the misleading message. This action plan should provide for the dissemination of accurate and complete information in a manner comparable to the dissemination of the violative messages. Novartis' action plan should include, but cannot be limited to, a consumer print ad, and should be submitted to DDMAC for approval. The plan should be implemented as soon as possible after such approval.

In addition, because of its failure to meet its responsibilities under 21 CFR 314.81 (b)(3)(i), Novartis should review its promotional materials for all of its products and assure FDA that it, in fact, has submitted all of its other promotional materials pursuant to the post-marketing reporting requirements. Any materials not previously submitted should be submitted as soon as discovered. Novartis should inform DDMAC of when it expects to complete this review.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of Novartis' promotional campaign for Lescol and we may determine that additional remedial measures may be necessary to fully correct the misleading messages resulting from Novartis' violative conduct. Novartis' response should be received no later than February 5, 1999.

If Novartis has any questions or comments, please contact Jayne Peterson, R.Ph., J.D., Chin Koerner, M.S., M.Ed., or Norman A. Drezin, Esq. 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 Novartis that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID # 7505.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

/S/

Minnie Baylor-Henry
Director
Division of Drug Marketing,
Advertising, and Communications