DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JAN 19 1999

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs
Pharmaceutical Division
Novartis Pharmaceuticals Corporation
556 Morris Avenue
Summit, NJ 07901-1398

RE: **NDA# 20-364**
Lotrel (amlodipine besylate/benazepril HCl) Capsules
MACMIS ID# 7315

Dear Mr. Schlotfeldt:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Lotrel (amlodipine besylate/benazepril HCl) capsules, disseminated by Novartis Pharmaceuticals Corporation (Novartis) that violate the Federal Food, Drug and Cosmetic Act and its implementing regulations. Reference is made to selected promotional materials for Lotrel, including brochure (LTR-1015), journal ad (C-LTR-1007), hospital display panels (LTR-9164, LTR-9164A, LTR-9164B), and reprint carrier (LTR-8015), submitted under cover of Form FDA 2253. DDMAC has reviewed these materials and has determined that they contain promotional claims that are false or misleading, and lacking in fair balance.

Misrepresentation of dosing and administration

In these materials, Novartis presents the following claim:

> When your patients on Norvasc (amlodipine) 5 mg need greater BP control...instead of titrating to Norvasc 10 mg...Go to Lotrel to boost control and guard against edema

This claim implies that it is both preferable and appropriate to switch patients to Lotrel if they demonstrate an inadequate antihypertensive response to Norvasc 5 mg[1]

1. Norvasc (amlodipine besylate) is a product of Pfizer Inc.

monotherapy. However, the approved product labeling (PI) for Lotrel states "[t]o minimize dose-independent hazards, it is usually appropriate to begin therapy with Lotrel only after a patient has either (a) failed to achieve the desired antihypertensive effect with one or the other monotherapy, or (b) demonstrated inability to achieve adequate antihypertensive effect with amlodipine therapy without developing edema." Therefore, because Lotrel is associated with dose-independent risks for both amlodipine and benazepril, monotherapy with Norvasc 10 mg should be evaluated prior to switching to Lotrel, unless the patient is experiencing amlodipine-induced edema at the 5 mg dose. Thus, DDMAC considers these claims to be misleading because they promote a dosing regimen that is inconsistent with the PI for Lotrel.

Misleading use of a clinical study to imply clinical benefit

In the reprint carrier and brochure, Novartis presents claims and quotations from a reprint of the "HOT" study, summarized by Hansson et al.,[2] including the following:

- The most successful therapy to achieve lower BP goals was combination therapy
- For major cardiovascular events the lowest point of risk was at a mean achieved diastolic blood pressure of 82.6 mm Hg...

Novartis also presents numerous claims for the clinical benefit of Lotrel with these claims. For example, in the brochure, immediately following the above claim concerning reducing the risk of major cardiovascular events, Novartis presents a claim and a graph depicting that, in a separate clinical trial, "...only Lotrel maintained BP below 90 mm Hg...." These claims and representations imply that Lotrel has demonstrated a clinical benefit in reducing cardiovascular morbidity and mortality. However, Lotrel was not evaluated in the HOT study, so this implied benefit for Lotrel on cardiovascular morbidity and mortality has not been demonstrated in the HOT study, or in other clinical trials. Therefore, Novartis' appropriating the results of the HOT study to imply the same or similar clinical benefit in patients receiving Lotrel is misleading because they are not based on substantial evidence derived from adequate and well-controlled clinical trials in which Lotrel was the drug studied. DDMAC notes that Novartis presents a disclaimer that "Lotrel was not included in the HOT study and has not been demonstrated to reduce CV morbidity and mortality" with these presentations. However, the misleading promotional messages are not corrected by inclusion of this disclaimer.

---

2. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *The Lancet*. 1998, 351:1755-1762.

Misrepresentation of Indication and Usage

In the brochure, Novartis presents the claim that the "JNC VI recommends low-dose combination therapy," followed by this quotation from the JNC VI[3] report:

> ...combinations of low doses of 2 agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose-dependent adverse effects.

This claim and quotation suggest that Lotrel is indicated for use as initial therapy for the treatment of hypertension because of its additive effect on reducing blood pressure and its minimizing effect on adverse events. However, the Indications and Usage section the PI for Lotrel states that "this fixed combination is not indicated for the initial therapy of hypertension." Therefore, Novartis' presentation of claims or quotations from the JNC VI report that imply that Lotrel is recommended for use as initial therapy is misleading because it implies greater use for Lotrel than has been demonstrated by substantial evidence, and is inconsistent with the PI. DDMAC notes that Novartis presents a small disclaimer at the bottom of the page that "Lotrel is not indicated for the initial treatment of hypertension." However, this disclaimer does not correct the misleading promotional messages made by presentation of these claims, nor does it adequately or prominently convey the limitations to the indications and usage of Lotrel.

Misrepresentations of safety and tolerability

In the brochure and hospital display panels, Novartis presents claims and representations of Lotrel's superiority over Norvasc with respect to incidence of edema. Novartis presents the results from a clinical trial[4] in a graph, depicting the incidence of edema for the treatment groups as follows: Lotrel 5/20 mg (3.6%), Lotrel 5/10 mg (2.2%), Norvasc 10 mg (25%) and Norvasc 5 mg (6.9%). However, this trial does not provide substantial evidence for comparisons of individual adverse event rates. Furthermore, the results for edema that are presented are substantially different than those observed in the much larger patient population described in the clinical trials for amlodipine. Therefore, results regarding edema incidence rates for this study may not accurately reflect actual incidence rates, and as presented, are misleading because they

---

3. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Archives of Internal Medicine*. 1997, 157:2413-2446.

4. Data on file, Novartis.

misrepresent the safety profile associated with the use of Norvasc. A sponsor misbrands its own drug product by making false or misleading representations about another product.

Lack of fair balance

Promotional materials must present information about the risks associated with the use of the drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. Techniques likely to achieve emphasis include, but are not limited to typography, layout, contrast, headlines, paragraphing, and white space. In these promotional pieces, efficacy claims are presented in bolded, bulleted, and colorful type. However, all risk information is presented in small sized type at the bottom of the pieces. Presentation of risk information in this manner is not sufficient to provide prominence and readability comparable with the presentation of information relating to effectiveness of the drug. Therefore, these promotional materials are lacking in fair balance.

Novartis should immediately cease distribution of these and other similar promotional materials for Lotrel that contain the same or similar claims or presentations. Novartis should submit a written response to DDMAC on or before February 2, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Novartis should include the date on which these and other similarly violative materials were discontinued.

Novartis 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 Novartis that only written communications are considered official.

In all future correspondence regarding this particular matter please refer to MACMIS ID #7315 in addition to the NDA number.

Sincerely,

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