DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Howard Solomon
Chief Executive Officer
Forest Laboratories, Inc.
909 Third Avenue
New York, NY10022

RE: NDA #21-742
Bystolic® (nebivolol) Tablets
MACMIS #16299

WARNING LETTER

Dear Mr. Solomon:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed an 8-Page Launch Journal Ad (44-1012123) (journal ad) for Bystolic® (nebivolol) Tablets (Bystolic) submitted by Forest Laboratories, Inc. (Forest) under cover of Form FDA-2253. The journal ad makes unsubstantiated superiority and mechanism of action claims, omits and minimizes risks associated with the use of Bystolic, and makes unsubstantiated efficacy claims for the drug. Thus, the journal ad misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n) and 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i); and (e)(6)(ii). These violations are concerning from a public health perspective because they suggest that Bystolic is safer and more effective than has been demonstrated by substantial evidence.

Background

According to its FDA-approved product labeling (PI), Bystolic is indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive agents.

The Clinical Pharmacology section of the PI states (in relevant part):

General

Nebivolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β_1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β_1 and β_2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant

concentrations. At clinically relevant doses, BYSTOLIC does not demonstrate α_1- adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β-blocking activity.

Pharmacodynamics

The mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Bystolic is associated with a number of serious risks. Bystolic is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh >B) and in patients who are hypersensitive to any component of the product. Bystolic therapy is also associated with warnings regarding abrupt cessation of therapy, cardiac failure, angina and acute myocardial infarction, bronchospastic diseases, anesthesia and major surgery, diabetes and hypoglycemia, thyrotoxicosis, peripheral vascular disease, non-dihydropyridine calcium channel blockers use, as well as precautions regarding use with CYP2D6 inhibitors, impaired renal and hepatic function, and anaphylactic reactions. Finally, Bystolic is associated with other risks as described in the Adverse Reactions section of its PI. For example, a number of treatment–emergent adverse events with an incidence ≥ 1% in bystolic-treated patients and at a higher frequency than placebo-treated patients were identified in clinical studies, including headache, fatigue, and dizziness.

Unsubstantiated Superiority and Mechanism of Action Claims

The journal ad is misleading because it implies that Bystolic is different from and superior to other β-adrenergic receptor blocking agents in the treatment of hypertension and that the antihypertensive mechanism of action of Bystolic has been established, when these implications have not been demonstrated by substantial evidence or substantial clinical experience. Specifically, the journal ad presents claims such as (emphasis added):

- "...a **novel** beta blocker" (page 1);
- "**Next generation** beta blocker" (pages 1, 3, 5, 7); and
- "**Unique** mechanism of action includes **cardioselective** beta blockade and **vasodilation**" (pages, 3, 4, and flow chart on page 4).

These and similar presentations are misleading because they imply that Bystolic's efficacy and mechanism of action make it superior as an antihypertensive to other β-adrenergic receptor blocking agents. FDA is not aware of any substantial evidence or substantial clinical experience that demonstrates that Bystolic represents a "novel" or "next generation" beta blocker for the treatment of hypertension. Indeed, we are not aware of any well-designed trials comparing Bystolic to other β-blockers. Furthermore, FDA is not aware of any data that would render Bystolic's mechanism of action "unique." Cardioselectivity and vasodilatory

effects are not unique qualities attributed only to Bystolic, but rather to multiple therapies within the drug's therapeutic class. The PI also states that the cardioselectivity of Bystolic is limited to extensive metabolizers and at doses of less than or equal to 10 mg, indicating that its cardioselectivity is modest.[1]

These claims are particularly concerning because, as stated in the PI, "[t]he mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established." FDA notes that the journal ad presents the following statement from the PI as a footnote at the bottom of pages three and four:

> In extensive metabolizers (most of the population) and at doses ≤10 mg, BYSTOLIC is preferentially β_1 selective. The mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

However, this footnote is insufficient to mitigate the misleading implications made by the claims.

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Although the journal ad does include important safety information on its second page, it omits and minimizes certain risks associated with Bystolic therapy, thereby implying that Bystolic is safer than other β-adrenergic receptor blocking agents. Specifically, although the PI for Bystolic includes a warning regarding use in patients with compensated congestive heart failure, this statement is omitted from the important safety information. The important safety information section on page 2 of the journal ad includes no mention at all of the precaution regarding the interaction with 2D6 inhibitors such as fluoxetine or paroxetine, two widely used drugs that can cause a nearly 10 fold increase in nebivolol blood levels, essentially eliminating its cardioselectivy if the dose is not reduced. Although you have attached the PI to the ad, it does not mitigate the misleading omission of risk information in the body of the ad.

In addition, the journal ad presents claims such as:

- "Favorable tolerability profile with a low incidence of beta blocker related side effects" (page 3); and
- ". . . favorable tolerability profile" (pages 2, 7).

The above claims misleadingly imply that the tolerability profile of Bystolic is better than the tolerability profile of other β-adrenergic receptor blocking agents when this has not been

[1] According to the Dosage and Administration section of the PI, the recommended starting dose of Bystolic is 5 mg once daily, with dose increases at 2-week intervals up to 40 mg per day, if needed.

demonstrated by substantial evidence or substantial clinical experience. FDA is not aware of any studies comparing Bystolic with other β-adrenergic blocking agents. Although the clinical trials section of the PI for Bystolic describes three placebo-controlled trials to support the efficacy of the product as an antihypertensive agent, no positive-controlled studies were included. Hence, differentiating from or comparing the incidence of beta blocker related side effects of Bystolic to other approved β-adrenergic receptor blocking agents cannot be substantiated by the PI. If you have data to substantiate these claims, please submit them to FDA for review. Furthermore, the claim, "favorable tolerability profile," misleadingly minimizes the risks associated with Bystolic. As described in the Background section above, the drug is associated with a number of serious risks.

Unsubstantiated Efficacy Claims

The journal ad presents the following statement in conjunction with a graph entitled, "Reductions From Baseline in Mean Sitting DBP and SBP at Trough at 3 Months" (bold emphasis original, underline emphasis added):

> **"<u>Efficacy demonstrated</u> across a broad range of patients**
> - Studies included the following hypertensive patient populations: 42% obese (BMI ≥ 30 kg/m^2), 6% poor metabolizers, ... and 7% diabetic" (page 5).

Because the subgroups listed in the bullet are presented in conjunction with the bolded header, it appears to suggest that Bystolic has demonstrated efficacy within each subgroup (obese, poor metabolizers, and diabetic). However, none of the efficacy trials were specifically designed to evaluate patients who were obese, poor metabolizers, or diabetic. FDA is only aware that effectiveness was established in black hypertensive patients and that effectiveness was similar in subgroups analyzed by age and sex.[2,3,4] FDA is not aware of any studies with Bystolic demonstrating efficacy in the above referenced subgroups (obese, poor metabolizers, and diabetic). Therefore, it is misleading to imply that efficacy was demonstrated in these subgroups when this has not been supported by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the journal ad misbrands Bystolic in violation of the Act, 21 U.S.C. 352(n) and 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i); and (e)(6)(ii).

DDMAC requests that Forest immediately cease the dissemination of violative promotional materials for Bystolic such as those described above. Please submit a written response to this letter on or before September 12, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Bystolic such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of

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[2] Effectiveness was established in Blacks, but as monotherapy, the magnitude of effect was somewhat less than in Caucasians.
[3] BYSTOLIC [package insert].
[4] Data on file, Forest Laboratories, Inc.

action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at (301) 847-8444. Please refer to MACMIS ID # 16299 and NDA # 21-742 in all future correspondence relating to this matter. DDMAC reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Bystolic comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams
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