DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21742/S-007 **SUPPLEMENT APPROVAL**

Forest Laboratories, Inc.
Attention: Kathleen Waldron
Assistant Director, Regulatory Affairs
Harborside Financial Center
Plaza V
Suite 1900
Jersey City, NJ 07311

Dear Ms. Waldron:

Please refer to your supplemental new drug application dated May 1, 2009, received May 1, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Bystolic (nebivolol) 2.5 mg, 5 mg, 10 mg, and 20 mg Tablets.

We acknowledge receipt of your submissions dated May 27, June 8 and 16, July 9, 20, 22 and 31, August 6, 19, and 24, September 3, 16, and 22, October 6, 14, 23, and 26, November 2, 3, 6, 13, and 16, December 7, 9, 15, 17, and 18 2009 and January 5, February 1, 2, 12 and 18, 2010.

(b) (4)

This supplemental new drug application provides for conversion to the Physician Labeling Rule Format (PLR) and changes to the **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE EVENTS, USE IN SPECIFIC POPULATIONS, OVERDOSAGE, CLINICAL PHARMACOLOGY,** and the **PATIENT COUNSELING INFORMATION** sections of the label.

The following changes were made:

1. In **DOSAGE AND ADMINISTRATION/Hypertension**, the passive voice was converted to active voice in the first sentence of the first paragraph. The paragraph now reads:

The dose of BYSTOLIC must be individualized to the needs of the patient.

2. In **DOSAGE AND ADMINISTRATION/Renal Impairment**, the passive voice was converted to active voice in the first sentence of the first paragraph. The sentence now reads:

   In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed.

3. In **DOSAGE AND ADMINISTRATION/Hepatic Impairment**, the passive voice was converted to active voice in the first sentence of the first paragraph. The sentence now reads:

   In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed.

4. In **WARNINGS AND PRECAUTIONS/Abrupt Cessation of Therapy**, the passive voice was converted to active voice in the first paragraph. The paragraph now reads:

   Do not abruptly discontinue Bystolic therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of BYSTOLIC is planned, carefully observe and advise patients to minimize physical activity. Taper BYSTOLIC over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, re-start BYSTOLIC promptly, at least temporarily.

5. In **WARNINGS AND PRECAUTIONS/Anesthesia and Major Surgery**, the following text has been added as the first sentence of the first paragraph:

   Because beta-blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on beta-blockers should generally continue treatment throughout the perioperative period**.**

6. In **WARNINGS AND PRECAUTIONS/Diabetes and Hypoglycemia**, the passive voice was converted to active voice in the third sentence of the first paragraph. The sentence now reads:

   Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities.

7. In **WARNINGS AND PRECAUTIONS/Peripheral Vascular Disease**, the following text was deleted from the first paragraph:

Caution should be exercised in these patients.

8. In **WARNINGS AND PRECAUTIONS/Non-dihydropyridine Calcium Channel Blockers**, the first paragraph was changed from:

   Because of significant negative inotropic and chronotropic effects in patients treated with β- blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

   To:

   Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure in patients treated concomitantly with these agents.

9. In **WARNINGS AND PRECAUTIONS/Impaired Renal Function**, the first paragraph was changed from:

   BYSTOLIC should be used with caution in patients with severe renal impairment because of decreased renal clearance. BYSTOLIC has not been studied in patients receiving dialysis. *[see Pharmacokinetics in Special Populations (12.4) and DOSAGE AND ADMINISTRATION (2.1.1*

   To:

   Renal clearance of nebivolol is decreased in patients with severe renal impairment. BYSTOLIC has not been studied in patients receiving dialysis *[see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)]*.

10. In **WARNINGS AND PRECAUTIONS/Impaired Hepatic Function**, the first paragraph was changed from:

    BYSTOLIC should be used with caution in patients with moderate hepatic impairment because of decreased metabolism. Since BYSTOLIC has not been studied in patients with severe hepatic impairment, BYSTOLIC is contraindicated in this population *[see Pharmacokinetics in Special Populations (12.4) and DOSAGE AND ADMINISTRATION (2.1.2)]*.

    To:

    Metabolism of nebivolol is impaired in patients with moderate hepatic impairment. BYSTOLIC has not been studied in patients with severe hepatic

impairment *[see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)]*.

11. In **WARNINGS AND PRECAUTIONS/Risk of Anaphylactic Reactions**, the first paragraph was changed from:

    While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

    To:

    While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

12. In **WARNINGS AND PRECAUTIONS**, a separate heading has been added for the information regarding Pheochromocytoma. The section now reads:

    **Pheochromocytoma**

    In patients with known or suspected pheochromocytoma, initiate an α-blocker prior to the use of any β-blocker.

13. In **DRUG INTERACTIONS/Hypotensive Agents**, the passive voice was converted to active voice throughout the first paragraph. The paragraph now reads:

    Do not use BYSTOLIC with other β-blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added β-blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity. In patients who are receiving BYSTOLIC and clonidine, discontinue BYSTOLIC for several days before the gradual tapering of clonidine.

14. In **DRUG INTERACTIONS/Calcium Channel Blockers**, the first paragraph was changed from:

    BYSTOLIC should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), of antiarrhythmic agents, such and disopyramide, are used concurrently.

    To:

BYSTOLIC can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide.

15. In **USE IN SPECIFIC POPULATIONS/Labor and Delivery**, the passive voice was converted to active voice in the second sentence of the second paragraph. The sentence now reads:

    Use BYSTOLIC during pregnancy only if the potential benefit justifies the potential risk to the fetus.

16. In **USE IN SPECIFIC POPULATIONS/Heart Failure**, the first paragraph was changed from:

    In a placebo-controlled trial, 1067 patients receiving BYSTOLIC were 70 years of age and older with chronic heart failure. *[see Clinical Studies (14.2)]*

    To:

    In a placebo-controlled trial of 1067 patients over 70 years of age with chronic heart failure receiving a maximum dose of 10 mg per day for a median of 20 months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens, consider discontinuation of BYSTOLIC.

17. In **OVERDOSAGE**, the words “because of” replace the words “due to”. The first sentence of the third paragraph now reads:

    Because of extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

18. In **OVERDOSAGE**, the fourth paragraph was changed from:

    If overdose occurs, BYSTOLIC should be stopped and general supportive and specific symptomatic treatment should be provided. Based on expected pharmacologic actions and recommendations for other β-blockers, the following general measures should be considered when clinically warranted:

    To:

    If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other β-blockers, consider the following general measures when clinically warranted:

19. In **OVERDOSAGE**/*Heart Block (second or third degree)*, the passive voice was converted to active voice in the first sentence of the first paragraph. The sentence now reads:

    Monitor and treat with isoproterenol infusion.

20. In **OVERDOSAGE**/*Hypoglycemia*, the second paragraph was changed from:

    In the event of intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period consistent with the 12-19 hour effective half-life of BYSTOLIC. Supportive measures should continue until clinical stability is achieved.

    To:

    Supportive measures should continue until clinical stability is achieved. The half-life of low doses of nebivolol is 12-19 hours.

21. In **CLINICALPHARMACOLOGY/Renal Disease**, the first paragraph was changed from:

    The apparent clearance of nebivolol was unchanged following a single 5 mg dose of BYSTOLIC in patients with mild renal impairment (ClCr 50 to 80 mL/min, n=7), and it was reduced negligibly in patients with moderate (ClCr 30 to 50 mL/min, n=9), but by 53% in patients with severe renal impairment (ClCr <30 mL/min, n=5). The dose of BYSTOLIC should be adjusted in patients with severe renal impairment. BYSTOLIC should be used with caution in patients receiving dialysis, since no formal studies have been conducted in this population *[see DOSAGE ANDADMINISTRATION (2)]*.

    To:

    The apparent clearance of nebivolol was unchanged following a single 5 mg dose of BYSTOLIC in patients with mild renal impairment (ClCr 50 to 80 mL/min, n=7), and it was reduced negligibly in patients with moderate (ClCr 30 to 50 mL/min, n=9), but clearance was reduced by 53% in patients with severe renal impairment (ClCr <30 mL/min, n=5). No studies have been conducted in patients on dialysis *[see Dosage and Administration (2)]*.

22. In **CLINICALPHARMACOLOGY/Drug-Drug Interactions**, the passive voice was converted to active voice in the first sentence of the first paragraph. The sentence now reads:

    Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When BYSTOLIC is co-administered with an inhibitor or an inducer of

this enzyme, monitor patients closely and adjust the nebivolol dose according to blood pressure response.

23. In **PATIENT ADVICE**, the passive voice was converted to active voice in this section. The section now reads:

    Advise patients to take BYSTOLIC regularly and continuously, as directed. BYSTOLIC can be taken with or without food. If a dose is missed, take the next scheduled dose only (without doubling it). Do not interrupt or discontinue BYSTOLIC without consulting the physician.

    Patients should know how they react to this medicine before they operate automobiles, use machinery, or engage in other tasks requiring alertness.

    Advise patients to consult a physician if any difficulty in breathing occurs, or if they develop signs or symptoms of worsening congestive heart failure such as weight gain or increasing shortness of breath, or excessive bradycardia.

    Caution patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, that β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.

24. In **FDA Approved Patient Labeling/PATIENT INFORMATION/WHAT IS BYSTOLIC**, the words "less than" replace the word "under" in the first sentence of the third paragraph.

25. The revision date and version number have been updated.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed agreed-upon labeling (text for the package insert, and text for the patient package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 021742/S-007".

## LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Agreed-upon labeling text
Agreed-upon text for the patient package insert

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-21742 | SUPPL-7 | FOREST LABORATORIES INC | NEBIVOLOL TABLETS 1.25/2.5/5/10/20MG |

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

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/s/

NORMAN L STOCKBRIDGE
02/19/2010