



NDA 021742/S-013

**SUPPLEMENT APPROVAL**

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

Dear Ms. Waldron:

Please refer to your Supplemental New Drug Application (sNDA) dated June 29, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bystolic (nebivolol) 2.5 mg, 5 mg, 10 mg and 20 mg tablets.

This Prior Approval supplemental new drug application provides for the following labeling revisions consistent with the March 2011 Guidance for Industry “Hypertension *Indication: Drug Labeling for Cardiovascular Outcome Claims*” in addition to other changes.

In **HIGHLIGHTS OF PRESCRIBING INFORMATION** the following has been added or ~~deleted~~;

The dosage form and route of administration description in the Product Title Line has been changed from, “tablets” to “tablets, for oral use.”

Under **HIGHLIGHTS, INDICATIONS AND USAGE**

BYSTOLIC is a beta-adrenergic blocking agent indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1.1)

In **FULL PRESCRIBING INFORMATION**, the following has been added or ~~deleted~~;

Under **INDICATIONS AND USAGE**,

BYSTOLIC is indicated for the treatment of hypertension, to lower blood pressure [see *Clinical Studies (14.1)*]. BYSTOLIC may be used alone or in combination with other antihypertensive agents [see *Drug Interactions (7)*].

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including the class to which this drug principally belongs. There are no controlled trials demonstrating risk reduction with Bystolic.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Under **USE IN SPECIFIC POPULATIONS**,

In Section 8.1 Pregnancy, "Teratogenic Effects: Category C" has been moved from the title line of Section 8.1 to a separate line.

Under **CLINICAL STUDIES**,

There are no trials of BYSTOLIC demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

Under **PATIENT INFORMATION**,

**What is high blood pressure (hypertension)?**

Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too great.

High blood pressure makes the heart work harder to pump blood through the body and causes damage to the blood vessels. BYSTOLIC tablets can help your blood vessels relax so your blood pressure is lower.

Medicines that lower your blood pressure lower your chance of having a stroke or heart attack.

Throughout the label, BYSTOLIC has been capitalized.

We have completed our review of this supplemental application. 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, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(1)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To

facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

**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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, PharmD  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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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/  
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MARY R SOUTHWORTH  
12/14/2011