



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20401/S-036

SUPPLEMENT APPROVAL

Biovail
Attention: Robert Ashworth, Ph.D.
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Dr. Ashworth:

Please refer to your Supplemental New Drug Application (sNDA) dated March 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tiazac (diltiazem hydrochloride) 120, 180, 240, 300, 360 and 420 mg Extended Release Capsules.

We acknowledge receipt of your amendments dated September 1 and November 11, 2010.

This "Prior Approval" labeling supplemental new drug application provides for the following revisions to the **DESCRIPTION**, **PRECAUTIONS**, **ADVERSE REACTIONS** and **OVERDOSAGE** sections of the package insert:

1. Under **DESCRIPTION**, the word, "cellular" was added in the sentence, "Cardizem (diltiazem hydrochloride) is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist)."
2. Under **DESCRIPTION**, the third paragraph was revised from:

Tiazac also contains: Microcrystalline Cellulose NF, Sucrose Stearate, Eudragit, Povidone USP, Talc USP, Magnesium Stearate NF, Hypromellose USP, Titanium Dioxide USP, Polysorbate NF, Simethicone USP, Gelatin NF, FD&C Blue #1, FD&C Red #40, D&C Red #28, FD&C Green #3, Black Iron Oxide USP, and other solids.

To read as follows:

Tiazac also contains: black iron oxide, D&C Red No. 28, ethyl acrylate and methyl methacrylate copolymer dispersion, FD&C Blue No. 1, FD&C Green No. 3, FD&C Red No. 40, gelatin, hypromellose, magnesium stearate, microcrystalline cellulose, polysorbate, povidone, simethicone, sucrose stearate, talc, and titanium dioxide

3. Under **PRECAUTIONS, Drug Interactions**, as requested in our September 21, 2009 letter, a new section was added. It reads:

Clonidine

Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concurrently with diltiazem. Monitor heart rate in patients receiving concomitant diltiazem and clonidine.

4. Under **PRECAUTIONS, Drug Interactions**, the section entitled, “Lovastatin” which read:

Lovastatin

In a ten-subject study, coadministration of diltiazem (120 mg bid, diltiazem SR) with lovastatin resulted in 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Was revised to read as follows:

Statins: Diltiazem is an inhibitor of CYP3A4 and has been shown to increase significantly the AUC of some statins. The risk of myopathy and rhabdomyolysis with statins metabolized by CYP3A4 may be increased with concomitant use of diltiazem. When possible, use a non-CYP3A4-metabolized statin together with diltiazem; otherwise, dose adjustments for both diltiazem and the statin should be considered along with close monitoring for signs and symptoms of any statin related adverse events.

In a healthy volunteer cross-over study (N=10), co-administration of a single 20 mg dose of simvastatin at the end of a 14 day regimen with 120 mg BID diltiazem SR resulted in a 5-fold increase in mean simvastatin AUC versus simvastatin alone. Subjects with increased average steady-state exposures of diltiazem showed a greater fold increase in simvastatin exposure. Computer-based simulations showed that at a daily dose of 480 mg of diltiazem, an 8-to 9-fold mean increase in simvastatin AUC can be expected. If co-administration of simvastatin with diltiazem is required, limit the daily doses of simvastatin to 10 mg and diltiazem to 240 mg.

In a ten-subject randomized, open label, 4-way cross-over study, co-administration of diltiazem (120 mg BID diltiazem SR for 2 weeks) with a single 20 mg dose of lovastatin resulted in 3- to 4-fold increase in mean lovastatin AUC and C_{max} versus lovastatin alone. In the same study, there was no significant change in 20 mg single dose pravastatin AUC and C_{max} during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

5. Under **ADVERSE REACTIONS, Other**, the phrase, “acute generalized exanthematous pustulosis” was added.
6. Under **ADVERSE REACTIONS, Other**, the phrase, “photosensitivity (including lichenoid keratosis and hyperpigmentation at sun-exposed skin areas)” was added.
7. Under **OVERDOSAGE, Hypotension**, the words, “levarterenol bitartrate” were replaced with “norepinephrine.”

We have completed our review of this supplemental application, as amended. 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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text for the package insert and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements and any 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(l)(1)(i)] in MS Word format that includes the changes approved in this

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to 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, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

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

/s/

MARGARET E PEASE FYE
11/22/2010

MARY R SOUTHWORTH
11/22/2010