



NDA 020198/S-023

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals
Attention: Darshan Patel, Pharm.D.
Global Regulatory Affairs
PO Box 1000
Montville, NJ 07045-1000

Dear Dr. Patel:

Please refer to your Supplemental New Drug Application (sNDA) dated August 31, 2010, received August 31, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adalat CC (nifedipine) 30 mg, 60 mg, and 90 mg Extended Release Tablets.

This “Prior Approval” supplemental new drug application provides for changes to the **DESCRIPTION, CONTRAINDICATIONS, PRECAUTIONS, ADVERSE EXPERIENCES, and OVERDOSAGE** sections of the package insert.

The following changes were made:

1. Under **DESCRIPTION**, the third paragraph was revised from:

Inert ingredients in the formulation are: hydroxypropylcellulose, lactose, corn starch, crospovidone, microcrystalline cellulose, silicon dioxide, and magnesium stearate. The inert ingredients in the film coating are: hypromellose, polyethylene glycol, ferric oxide, and titanium dioxide.

To:

Inert ingredients in the formulation are: hydroxypropylcellulose, lactose, corn starch, crospovidone, microcrystalline cellulose, silicon dioxide, and magnesium stearate. The inert ingredients in the film coating for Adalat CC 30 and 60 are: hypromellose, polyethylene glycol, ferric oxide, and titanium dioxide. The inert ingredients in Adalat CC 90 are: hypromellose, polyethylene glycol and ferric oxide.

2. Under **CONTRAINDICATIONS**, the sentence “known hypersensitivity to nifedipine” was replaced with “Adalat is contraindicated in patients with a known hypersensitivity to any component of the tablet”.
3. Under **PRECAUTIONS/Drug Interactions/CYP3A inducers**, the first paragraph was changed from:

CYP3A inhibitors such as ketoconazole, fluconazole, itraconazole, clarithromycin, erythromycin, grapefruit, nefazodone, saquinavir, indinavir, nelfinavir, and ritonavir may result in increased exposure to nifedipine when co-administered. Careful monitoring and dose adjustment may be necessary; consider initiating nifedipine at the lowest dose available if given concomitantly with these medications.

To:

CYP3A inhibitors such as ketoconazole, fluconazole, itraconazole, clarithromycin, erythromycin (Azithromycin, although structurally related to the class of macrolide antibiotic is void of CYP3A4 inhibition)¹, grapefruit, nefazodone, fluoxetine, saquinavir, indinavir, nelfinavir, and ritonavir may result in increased exposure to nifedipine when co-administered. Careful monitoring and dose adjustment may be necessary; consider initiating nifedipine at the lowest dose available if given concomitantly with these medications.

4. Under **PRECAUTIONS/Drug Interactions**, a new section was added. The section reads as follows:

Cisapride: Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

5. Under **PRECAUTIONS**, a new section was added. The section reads as follows:

Patients with Galactose Intolerance

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

6. Under **ADVERSE EXPERIENCES/Urogenital/Reproductive**, erectile dysfunction (ED) was added to the list.

7. Under **OVERDOSAGE**, the following information was added as the sixth paragraph:

Bradycardiac heart rhythm disturbances may be treated symptomatically with β -sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.

8. There are several editorial changes noted throughout the document (the removal of colons from several of the headings, the removal of the zero following a two, the addition of bold lettering in the Carcinogenesis, Mutagenesis, Impairment of Fertility section)
9. The revision date and version number have been updated.

We have completed our review of this supplemental application, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below and indicated in the enclosed labeling.

Please revise your labeling as follows:

1. Under **DESCRIPTION**, revise the third paragraph to read:

Inert ingredients in the formulation are: hydroxypropylcellulose, lactose, corn starch, crospovidone, microcrystalline cellulose, silicon dioxide, and magnesium stearate. The inert ingredients in the film coating for Adalat CC 30 and 60 are: hypromellose, polyethylene glycol, ferric oxide, and titanium dioxide. The inert ingredients in the film coating for Adalat CC 90 are: hypromellose, polyethylene glycol and ferric oxide.

2. Under **PRECAUTIONS/Drug Interactions/CYP3A inducers**, revise the first paragraph to read:

CYP3A inhibitors such as ketoconazole, fluconazole, itraconazole, clarithromycin, erythromycin (Azithromycin, although structurally related to the class of macrolide antibiotic is void of clinically relevant CYP3A4 inhibition), grapefruit, nefazodone, fluoxetine, saquinavir, indinavir, nelfinavir, and ritonavir may result in increased exposure to nifedipine when co-administered. Careful monitoring and dose adjustment may be necessary; consider initiating nifedipine at the lowest dose available if given concomitantly with these medications.

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(l)] 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 via 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 with the revisions listed above 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).

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
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/

MARY R SOUTHWORTH
02/28/2011