DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 18891/S-028

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Collette:

Please refer to your supplemental new drug application dated December 3, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Catapres-TTS (clonidine) Transdermal Therapeutic System.

We acknowledge receipt of your amendment dated October 18, 2011.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. Throughout, the presentation of CATAPRES-TTS (clonidine) transdermal therapeutic system has been standardized.

2. The CLINICAL PHARMACOLOGY/Pharmacokinetics section has been revised and now reads as follows:

   Catapres-TTS® (clonidine) transdermal therapeutic system delivers clonidine at an approximately constant rate for 7 days. The absolute bioavailability of clonidine from the Catapres-TTS transdermal therapeutic system dosage form is approximately 60%. Steady-state clonidine plasma levels are obtained within 3 days after transdermal application to the upper outer arm and increase linearly with increasing size of the transdermal patch. Mean steady-state plasma concentrations with the 3.5 cm^2, 7.0 cm^2 and 10.5 cm^2 systems are approximately 0.4 ng/mL, 0.8 ng/mL, and 1.1 ng/mL, respectively. Similar clonidine steady-state concentrations are reached after application to the chest. Steady-state clonidine plasma levels remain constant after removal of one system and application of a new system of the same size.

   Following intravenous administration clonidine displays biphasic disposition with a distribution half-life of about 20 minutes and an elimination half-life ranging from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Clonidine has a total clearance of 177 mL/min and a renal clearance of 102 mL/min. The apparent volume of distribution (V_z) of clonidine is 197 L (2.9 L/kg). Clonidine crosses the placental barrier. It has been shown to cross the blood brain barrier in rats.

   Following oral administration, about 40% to 60% of the absorbed dose is recovered in the urine as unchanged drug within 24 hours. About 50% of the absorbed dose is metabolized in the liver.

After removal of the Catapres-TTS transdermal therapeutic system, clonidine plasma concentrations decline slowly with a half-life of approximately 20 hours.

3. Under WARNINGS/Withdrawal, “tremor” has been added to the second sentence.

4. Under PRECAUTIONS/General, the third paragraph has been changed from:

   CATAPRES-TTS transdermal therapeutic system should be used with caution in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

   To:

   The sympatholytic action of clonidine may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. There are post-marketing reports of patients with conduction abnormalities and/or taking other sympatholytic drugs who developed severe bradycardia requiring IV atropine, IV isoproterenol and temporary cardiac pacing while taking clonidine.

   In hypertension caused by pheochromocytoma, no therapeutic effect of CATAPRES-TTS transdermal therapeutic system can be expected.

5. Under PRECAUTIONS/Information for Patients, the second paragraph has been changed from:

   Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. They should also be informed that this sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

   To:

   Since patients may experience a possible sedative effect, dizziness, or accommodation disorder with use of clonidine, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery. Also, inform patients that this sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

6. Under PRECAUTIONS/Drug Interactions, the following sentence has been added to the end of the first paragraph:

   If a patient receiving clonidine is also taking neuroleptics, orthostatic regulation disturbances (e.g., orthostatic hypotension, dizziness, fatigue) may be induced or exacerbated.

7. Under PRECAUTIONS/Pregnancy, the following sentence has been added to the third paragraph:

   Clonidine crosses the placental barrier (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

8. The DOSAGE AND ADMINISTRATION/Renal Impairment section has been changed from:

   Dosage must be adjusted according to the degree of impairment, and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

To:

Patients with renal impairment may benefit from a lower initial dose. Patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

9. The item number, Copyright date, and Revision date have been updated.

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 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, 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(l)(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).

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.

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 Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

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: 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/

NORMAN L STOCKBRIDGE
05/31/2012