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 (clonidine hydrochloride) 0.1 mg, 0.2 mg and 0.3 mg Tablets.

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 appearance of the name has been changed to either “Catapres (clonidine hydrochloride, USP)” or “CATAPRES.”

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

   The pharmacokinetics of clonidine is dose-proportional in the range of 100 to 600 µg. The absolute bioavailability of clonidine on oral administration is 70% to 80%. Peak plasma clonidine levels are attained in approximately 1 to 3 hours.

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 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 in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Neither food nor the race of the patient influences the pharmacokinetics of clonidine.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2.0 ng/mL in patients with normal excretory function. A further rise in the plasma levels will not enhance the antihypertensive effect.

3. Under PRECAUTIONS/General, the third paragraph has been changed from:
CATAPRES tablets 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 tablets can be expected.

4. 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.

5. 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.

6. Under PRECAUTIONS/Drug Interactions, the following sentence has been added as the last paragraph:

Based on observations in patients in a state of alcoholic delirium it has been suggested that high intravenous doses of clonidine may increase the arrhythmogenic potential (QT-prolongation, ventricular fibrillation) of high intravenous doses of haloperidol. Causal relationship and relevance for clonidine oral tablets have not been established.

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](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.


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](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