DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020664/S-011

SUPPLEMENT APPROVAL

Pharmacia & Upjohn Company
c/o Pfizer Inc.
Attention: Clara I. Arrocain, MD
Associate Director, WW Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Dr. Arrocain:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DOSTINEX® (cabergoline) Tablets, 0.5 mg.

We acknowledge receipt of your amendment dated June 27, 2011.

This Changes Being Effective supplemental new drug application proposes modifications to the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections of labeling for DOSTINEX as well as editorial types of changes. These modifications concern the risk of fibrotic complications (i.e., cardiac valvulopathy and extracardiac fibrotic reactions) that are associated with the use of DOSTINEX. These modifications also provide guidance to healthcare providers regarding pretreatment screening prior to initiating treatment and monitoring procedures during treatment with DOSTINEX. The agreed upon changes to the CONTRAINDICATIONS and WARNINGS sections are as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

1. The revised **CONTRAINDICATIONS** section reads as follows::

   DOSTINEX Tablets are contraindicated in patients with:

   - Uncontrolled hypertension or known hypersensitivity to ergot derivatives.
   - History of cardiac valvular disorders, as suggested by anatomical evidence of valvulopathy of any valve, determined by pre-treatment evaluation including echocardiographic demonstration of valve leaflet thickening, valve restriction, or mixed valve restriction-stenosis. (See **WARNINGS**)
   - History of pulmonary, pericardial, ~~cardiac valvular~~ or retroperitoneal fibrotic disorders. (See ~~**PRECAUTIONS**, Fibrosis~~ **WARNINGS**)

2. The revised **WARNINGS** section, **Fibrotic Complications** subsection, **Cardiac Valvulopathy** sub-subsection reads as follows::

a. Cardiac Valvulopathy:

All patients should undergo a cardiovascular evaluation, including echocardiogram to assess the potential presence of valvular disease. If valvular disease is detected, the patient should not be treated with DOSTINEX. Post marketing cases of cardiac valvulopathy have been reported in patients receiving DOSTINEX. These cases have generally occurred during ~~long-term~~ administration of high doses of DOSTINEX (>2mg/day) used for the treatment of Parkinson's disease. ~~Rare~~ Cases of cardiac valvulopathy have also been reported ~~associated with short-term treatment (<6 months) or~~ in patients receiving lower doses for the treatment of ~~hyperprolactinemia~~ hyperprolactinemic disorders.

Physicians should use the lowest effective dose of DOSTINEX for the treatment of hyperprolactinemic ~~hyperprolactinemia~~ disorders and should periodically reassess the need for continuing therapy with DOSTINEX. Following treatment initiation, clinical and diagnostic monitoring (for example, chest x-ray, CT scan and cardiac echocardiogram) should be conducted to assess the risk of cardiac valvulopathy. ~~In addition, patients receiving long term treatment with DOSTINEX should undergo periodic reassessment of their cardiac status, and echocardiography should be considered. Any patient who develops signs or symptoms of cardiac disease, including~~ The recommended frequency of routine echocardiographic monitoring is every 6 to 12 months or as clinically indicated with the presence of signs and symptoms such as ~~dyspnea~~, edema, new cardiac murmur, dyspnea or congestive heart failure. ~~or a new cardiac murmur, while being treated with DOSTINEX should be evaluated for possible valvulopathy~~

DOSTINEX should be discontinued if an echocardiogram reveals new valvular regurgitation, valvular restriction or valve leaflet thickening.

DOSTINEX should be used with caution in patients ~~who have hemodynamically significant valvular disease or have been~~ exposed to other medications associated with valvulopathy.

3. In the **WARNINGS** section, **Fibrotic Complications** subsection, **Extracardiac Fibrotic Reactions** sub-subsection, the following text was moved from the **PRECAUTIONS** section and revised to read as follows:

b. Extracardiac Fibrotic Reactions:

Postmarketing cases of pleural, pericardial, and retroperitoneal fibrosis have been reported following administration of DOSTINEX. Some reports were in patients previously treated with other ergotinic dopamine agonists. DOSTINEX should not be used in patients with a history of cardiac or extracardiac fibrotic disorders.

Fibrotic disorders can have an insidious onset and patients should be monitored for manifestations of progressive fibrosis. Therefore, during treatment, attention should be paid to the signs and symptoms of:

- Pleuro-pulmonary disease such as dyspnea, shortness of breath, persistent cough or chest pain.
- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb edema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure: Cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical and diagnostic monitoring such as erythrocyte sedimentation rate, chest x-ray, serum creatinine measurements, and other investigations should be considered at baseline and as necessary while patients are treated with DOSTINEX.

Following diagnosis of pleural effusion or pulmonary fibrosis, the discontinuance of DOSTINEX was reported to result in improvement of signs and symptoms.

4. In the **PRECAUTIONS** section, the **Fibrosis** subsection was deleted and information concerning **extracardiac fibrotic reactions** was moved to the **WARNINGS** section (see Item 3 above).

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 (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(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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

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.

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, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
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/

AUDREY L GASSMAN
07/18/2011