DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 018482/S-051

SUPPLEMENT APPROVAL

Pfizer, Inc
Attention: Sheetal Alur
Sr. Manager Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Alur:

Please refer to your Supplemental New Drug Application (sNDA) dated November 30, 2012 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Procardia (nifedipine) 10 mg capsules.

This Prior Approval supplemental new drug application provides for the labeling revisions incorporating recommended changes from the FDA which had not been consistently applied to both the Procardia and Procardia XL prescribing information.

The following has been added or ~~deleted~~;

Under **CLINICAL PHARMACOLOGY/ Pharmacokinetics and Metabolism:**

> PROCARDIA is rapidly and fully absorbed after oral administration. The drug is detectable in serum 10 minutes after oral administration, and peak blood levels occur in approximately 30 minutes. Bioavailability is proportional to dose from 10 to 30 mg; half-life does not change significantly with dose. There is little difference in relative bioavailability when PROCARDIA capsules are given orally and either swallowed whole, bitten and swallowed, or bitten and held sublingually. However, biting through the capsule prior to swallowing does result in slightly earlier plasma concentrations (27 ng/mL 10 minutes after 10 mg) than if capsules are swallowed intact. PROCARDIA is highly bound by serum proteins. PROCARDIA is extensively converted to inactive metabolites and approximately 80 percent of PROCARDIA and metabolites are eliminated via the kidneys. The ~~half-life~~elimination half-life of nifedipine ~~in plasma~~ is approximately two hours. Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92–98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

~~In healthy subjects, the elimination half-life of a BID sustained release nifedipine formulation [that was neither Procardia capsules nor Procardia XL (nifedipine) extended release tablets] was longer in elderly subjects (6.7 h) compared to young subjects (3.8 h) following oral administration. A decreased clearance was also observed in the elderly (348 mL/min) following intravenous administration.~~
Following intravenous administration, clearance of nifedipine was decreased by 33% in elderly healthy subjects relative to young healthy subjects.

~~Co-administration of nifedipine with grapefruit juice resulted in approximately a 2-fold increase in nifedipine AUC and Cmax with no change in half-life. The increased plasma concentrations are most likely due to inhibition of CYP 3A4 related first-pass metabolism.~~

Under **PRECAUTIONS / Drug Interactions:**

Nifedipine is metabolized by CYP3A4. Co-administration of nifedipine with phenytoin, an inducer of CYP3A4, lowers the systemic exposure to nifedipine by approximately 70%. Avoid co-administration of nifedipine with phenytoin or any known CYP3A4 inducer or consider an alternative antihypertensive therapy.

Under **PRECAUTIONS / Other Interactions:**

Grapefruit Juice: Co-administration of nifedipine with grapefruit juice resulted in approximately a ~~2-fold increase~~doubling in nifedipine AUC and Cmax with no change in half-life. The increased plasma concentrations ~~are~~ most likely ~~due to~~result from inhibition of CYP 3A4-related first-pass metabolism. Avoid ~~Co-administration of nifedipine with grapefruit juice is to be avoided.~~ingestion of grapefruit and grapefruit juice while taking nifedipine.

Under **PRECAUTIONS / Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 5~~30~~ times the maximum recommended human dose. There is a literature report of reversible reduction in the ability of human sperm obtained from a limited number of infertile men taking recommended doses of nifedipine to bind to and fertilize an ovum *in vitro*. *In vivo* mutagenicity studies were negative.

Under **PRECAUTIONS / Pregnancy:**

Pregnancy Category C: Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies similar to those reported for phenytoin. Digital anomalies have been reported to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic, and fetotoxic

effects, including stunted fetuses (rats, mice, rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits), and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). On a mg/kg basis, all of the doses associated with the teratogenic embryotoxic or fetotoxic effects in animals were higher (~~3.~~5 to 50~~42~~ times) than the maximum recommended human dose of 120 mg/day. On a mg/m^2 basis, some doses were higher and some were lower than the maximum recommended human dose but all were within an order of magnitude of it. The doses associated with placentotoxic effects in monkeys were equivalent to or lower than the maximum recommended human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk ~~to the fetus~~.

Under **PRECAUTIONS / Lactation:**

Lactation: Nifedipine is transferred through breast milk. PROCARDIA should be used during breastfeeding only if the potential benefit justifies the potential risk.

Under **PRECAUTIONS / Geriatric Use:**

Geriatric Use: ~~Although small pharmacokinetic studies have identified an increased half-life and increased Cmax and AUC (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism), clinical studies of nifedipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.~~ Age appears to have a significant effect on the pharmacokinetics of nifedipine. The clearance is decreased resulting in a higher AUC in the elderly. These changes are not due to changes in renal function (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Under **DOSAGE AND ADMINISTRATION**:

Avoid c~~C~~o-administration of nifedipine with grapefruit juice ~~is to be avoided~~ (see CLINICAL PHARMACOLOGY and PRECAUTIONS: Other Interactions).

We have completed our review of this supplemental application. 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).

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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}
Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
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
07/25/2013