DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21134/S-007

SUPPLEMENT APPROVAL

Pfizer Inc
Attention: Lisa Malandro, MBA
Regulatory Cluster Lead, Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Malandro:

Please refer to your Supplemental New Drug Application (sNDA) dated September 30, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nitrostat ®, (nitroglycerin USP) 0.3, 0.4, 0.6 mg Sublingual Tablets .

We also refer to our approval letter dated March 7, 2014 which contained the following error: The labeling that was attached to the action letter did not incorporate all of the changes mentioned in the action letter. Specifically, the second sentence under Drug Interactions should have been deleted but was not.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain March 7, 2014, the date of the original approval letter.

This Prior Approval supplemental new drug application provides for revisions to Drug Interactions, Carcinogenesis, Mutagenesis, and Impairment of Fertility sections, and Pregnancy Category.

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

Under **Drug Interactions:** ~~Patients receiving antihypertensive drugs, beta-adrenergic blockers, or phenothiazines and nitrates should be observed for possible additive hypotensive effects. Marked orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used concomitantly.~~

Under the second and third paragraph of **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity potential of nitroglycerin was evaluated in r~~R~~ats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years. Rats developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes.

Nitroglycerin was ~~weakly~~ mutagenic in Ames tests performed in 2 different laboratories. Nevertheless, there was no evidence of mutagenicity in an *in vivo* dominant lethal assay with

male rats treated with doses up to about 363 mg/kg/day, PO, or in *ex vivo* cytogenetic tests in rat and dog ~~tissues~~cells.

Under the first paragraph of **Pregnancy Category ~~C~~B:** Animal reproduction and teratogenicity studies have not been conducted with nitroglycerin sublingual tablets. However, t~~T~~eratology studies conducted in rats and rabbits~~, however, were conducted~~ with topically applied nitroglycerin ointment at dosages up to 80 mg/kg/day and 240 mg/kg/day, respectively revealed ~~.~~ n~~N~~o toxic effects on dams or fetuses~~. were seen at any dose tested.~~

APPROVAL & LABELING

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 that includes labeling changes 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
Office of Prescription Drug Promotion (OPDP)
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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), 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 Alexis Childers, Regulatory Project Manager at (301) 796-0442.

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(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/

NORMAN L STOCKBRIDGE
03/07/2014