



NDA 21-845/S-005

Pfizer, Inc.
Attention: Mr. Robert Clark
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental New Drug Application dated January 18, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Revatio (sildenafil citrate) 20 mg Tablets.

We also refer to our July 17, 2008 action letter and your complete response dated August 6, 2008.

This supplemental New Drug Application provides for the following changes to the package insert:

1) To change the first sentence in the first paragraph of the **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism/Absorption and Distribution** section of the package insert:

FROM

REVATIO is rapidly absorbed after oral administration, with absolute bioavailability of about 40%.

TO

REVATIO is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25-63%).

2) To change the first sentence in the first paragraph of the **CLINICAL PHARMACOLOGY/Pharmacokinetics in Special Populations/Geriatrics** section of the package insert:

FROM

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

TO

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 84% and 107% higher plasma concentrations of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively.

3) To add a final sentence in the first paragraph of the **CLINICAL PHARMACOLOGY/Renal Insufficiency** section of the package insert:

In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased 200% and 79%, respectively, in subjects with severe renal impairment compared to subjects with normal renal function.

4) To change the first sentence in the first paragraph of the **CLINICAL PHARMACOLOGY/Pharmacodynamics/Effects of REVATIO on Blood Pressure** section of the package insert:

FROM

Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.4/5.5 mmHg).

TO

Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8/5 mmHg).

5) To change the first sentence in the first paragraph of the **OVERDOSAGE** section of the package insert:

FROM

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates were increased.

TO

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the labeling submitted August 6, 2008.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved sNDA 21-845/S-005.**”

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 Dan Brum, PharmD, MBA, RAC, Regulatory Project Manager, at (301)796-0578.

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

cc: approved labeling text

**This is a representation of an electronic record that was signed electronically and
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/s/

Norman Stockbridge
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