DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-931/S-001

Pfizer Inc.
Attn: Robert Clark
235 E. 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug application dated March 19, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tikosyn (dofetilide) 0.125, 0.25 and 0.5 mg Capsules.

We acknowledge receipt of your submissions dated March 24 and July 30, 2004.

This "Changes Being Effected in 30 days" supplemental new drug application provides for draft labeling revised as follows:

1. Throughout, "TIKOSYN™" has been changed to "Tikosyn®."

2. Under **CONTRAINDICATIONS**, the following paragraph has been added after the second paragraph:

   The concomitant use of hydrochlorothiazide (alone or in combinations such as with triamterene) with TIKOSYN is contraindicated (see **PRECAUTIONS, Drug-Drug Interactions**) because this has been shown to significantly increase dofetilide plasma concentrations and QT interval prolongation.

3. The following sub-section has been moved from the **PRECAUTIONS** section to the **WARNINGS** section:

   Hypokalemia and Potassium-Depleting Diuretics
   Hypokalemia or hypomagnesemia may occur with administration of potassium-depleting diuretics, increasing the potential for torsade de pointes. Potassium levels should be within the normal range prior to administration of TIKOSYN and maintained in the normal range during administration of TIKOSYN. (see **DOSAGE AND ADMINISTRATION**)

4. Under **WARNINGS/Use with Drugs that Prolong QT Interval and Antiarrhythmic Agents**, the second sentence has been changed from:

   Such drugs include phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides.

   To:

   Such drugs include phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain oral macrolides, and certain fluoroquinolones.

5. Under **PRECAUTIONS/Information for Patients/**Medications and Supplements, the first sentence has been changed from:

Assessment of patients' medication history should include all over-the-counter, prescription and herbal/natural preparations with emphasis on preparations that may affect the pharmacokinetics of TIKOSYN such as cimetidine (see **CONTRAINDICATIONS**), trimethoprim alone or in combination with sulfamethoxazole (see **CONTRAINDICATIONS**), prochlorperazine (see **CONTRAINDICATIONS**), megestrol (see **CONTRAINDICATIONS**), ketoconazole (see **CONTRAINDICATIONS**), other cardiovascular drugs (especially verapamil - see **CONTRAINDICATIONS**), phenothiazines, and tricyclic antidepressants (see **WARNINGS**).

To:

Assessment of patients' medication history should include all over-the-counter, prescription and herbal/natural preparations with emphasis on preparations that may affect the pharmacokinetics of TIKOSYN such as cimetidine (see **CONTRAINDICATIONS**), trimethoprim alone or in combination with sulfamethoxazole (see **WARNINGS, CONTRAINDICATIONS**), prochlorperazine (see **WARNINGS, CONTRAINDICATIONS**), megestrol (see **WARNINGS, CONTRAINDICATIONS**), ketoconazole (see **WARNINGS, CONTRAINDICATIONS**), hydrochlorothiazide (alone or in combinations such as with triamterene) (see **CONTRAINDICATIONS**), other cardiovascular drugs (especially verapamil - see **CONTRAINDICATIONS**), phenothiazines, and tricyclic antidepressants (see **WARNINGS**).

6. Under **PRECAUTIONS/Drug-Drug Interactions**, **"WARNINGS"** has been added to the first parenthetical of the first sentence in the Cimetidine, Ketoconazole and Trimethoprim Alone or in Combination with Sulfamethoxazole sub-sections.

7. The following has been added to the **PRECAUTIONS/Drug-Drug Interactions** section:

   Hydrochlorothiazide (HCTZ) Alone or in Combination with Triamterene*:* (see **CONTRAINDICATIONS**) Concomitant use of HCTZ alone or in combination with triamterene is contraindicated. HCTZ 50 mg QD or HCTZ/triamterene 50/100 mg QD was co-administered with TIKOSYN (500 mcg BID) for 5 days (following 2 days of diuretic use at half dose). In patients receiving HCTZ alone, dofetilide AUC increased by 27% and C_{max} by 21%. However, the pharmacodynamic effect increased by 197% (QTc increase over time) and by 95% (maximum QTc increase). In patients receiving HCTZ in combination with triamterene, dofetilide AUC increased by 30% and C_{max} by 16%. However, the pharmacodynamic effect increased by 190% (QTc increase over time) and by 84% (Maximum QTc increase). The pharmacodynamic effects can be explained by a combination of the increase in dofetilide exposure and the reductions in serum potassium. In the DIAMOND trials, 1252 patients were treated with TIKOSYN and diuretics concomitantly of whom 493 died compared to 508 deaths among the 1248 patients receiving placebo and diuretics. Of the 229 patients who had potassium depleting diuretics added to their concomitant medications in the DIAMOND trials, the patients on TIKOSYN had a non-significantly reduced relative risk for death of 0.68 (95% CI 0.376, 1.230).

8. Under **DOSAGE AND ADMINISTRATION**, the following has been added as the third bullet point:

   Serum potassium should be maintained within the normal range before TIKOSYN treatment is initiated and should be maintained within the normal range while the patient remains on TIKOSYN therapy. (See **WARNINGS, Hypokalemia and Potassium Depleting Diuretics**) In clinical trials potassium levels were generally maintained above 3.6-4.0 mEq/L.

9. Under **DOSAGE AND ADMINISTRATION/Initiation of TIKOSYN Therapy**/**Step 2**, the term "body weight" has been changed to "actual body weight" in both creatinine clearance formulas (male and female).

10. The list number and issue date of the package insert have been updated.

11. In the Patient Information leaflet, under **Who should not take Tikosyn**/Do not take Tikosyn if you/are taking certain other medicines, including, the following has been added:

    Hydrochlorothiazide alone or in combination with other medicines (such as ESIDRIX, EZIDE, HYDRODIURIL, HYDRO-PAR, MICROZIDE, or ORETIC)*

12. In the Patient Information leaflet, under **Important points about Tikosyn**, the following has been added to the end of the sixth bullet point:

    …, or hydrochlorothiazide alone or in combination with other medicines (such as ESIDRIX, EZIDE, HYDRODIURIL, HYDRO-PAR, MICROZIDE, or ORETIC)*

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

The final printed labeling (FPL) must be identical to the labeling submitted on March 19, 2004.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-931/S-001." Approval of this submission by FDA is not required before the labeling is used.

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

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 contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director

Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge

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