NDA 020931/S-017

SUPPLEMENT APPROVAL

Pfizer, Inc.
Attention: Tricia Douglas
Director, GPD-GRA
235 East 42nd Street
New York, NY 10017

Dear Ms. Douglas:

Please refer to your supplemental new drug application (sNDA) dated and received May 3, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tikosyn (dofetilide) 125 mcg, 250 mcg, and 500 mcg Capsules.

This Prior Approval supplemental new drug application provides for updates to the approved labeling as follows:

1. Under **DOSAGE AND ADMINISTRATION, Instructions for Individualized Dose Initiation**, the following was added/deleted to/from the section:

   Initiation of TIKOSYN Therapy

   Step 1. Electrocardiographic assessment: Prior to administration of the first dose, the QTc or QT must be checked~~determined~~ using an average of 5–10 beats. If the QTc or QT is greater than 440 msec (500 msec in patients with ventricular conduction abnormalities), TIKOSYN is contraindicated. If heart rate is less than 60 beats per minute, QT interval should be used. Proceed to Step 2 if the QTc or QT is 440 msec. Patients with heart rates <50 beats per minute have not been studied.

   Step 2. Calculation of creatinine clearance: Prior to the administration of the first dose, the patient's creatinine clearance must be calculated using the following formula:

   $$\text{creatinine clearance (male)} = \frac{(140-\text{age}) \times \text{actual body weight in kg}}{72 \times \text{serum creatinine (mg/dL)}}$$

   $$\text{creatinine clearance (female)} = \frac{(140-\text{age}) \times \text{actual body weight in kg} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

When serum creatinine is given in μmol/L, divide the value by 88.4 (1 mg/dL = 88.4 μmol/L).

Step 3. Starting Dose: The starting dose of TIKOSYN is determined as follows:

Calculated Creatinine Clearance	TIKOSYN Dose
>60 mL/min	500 mcg twice daily
40 to 60 mL/min	250 mcg twice daily
20 to <40 mL/min	125 mcg twice daily
<20 mL/min ~~Dofetilide~~Tikosyn is contraindicated	in these patients

Step 4. Administer the adjusted TIKOSYN dose and begin continuous ECG monitoring.

Step 5. At 2–3 hours after administering the first dose of ~~dofetilide~~Tikosyn, determine the QTc or QT (if heart rate is less than 60 beats per minute). If the QTc or QT has increased by greater than 15% compared to the baseline established in Step 1 OR if the QTc or QT is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), subsequent dosing should be adjusted as follows:

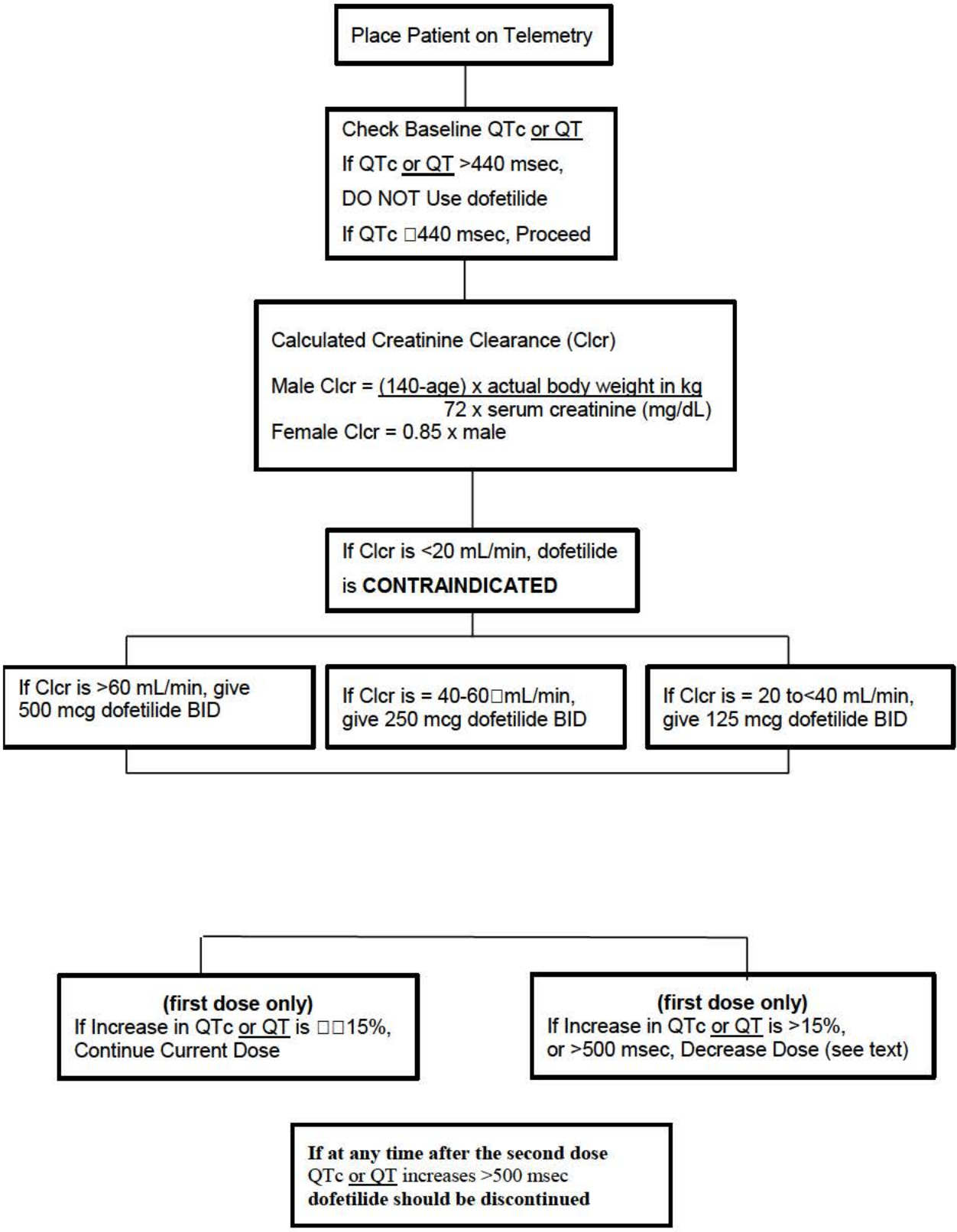
If the Starting Dose Based on Creatinine Clearance is:	Then the Adjusted Dose (for QTc or QT Prolongation) is:
500 mcg twice daily	250 mcg twice daily
250 mcg twice daily	125 mcg twice daily
125 mcg twice daily	125 mcg once a day

Step 6. At 2–3 hours after each subsequent dose of ~~dofetilide~~ Tikosyn, determine the QTc or QT (if heart rate is less than 60 beats per minute) (for in-hospital doses 2–5). No further down titration of ~~dofetilide~~Tikosyn based on QTc or QT is recommended.

NOTE: If at any time after the second dose of ~~dofetilide~~Tikosyn is given the QTc or QT is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), Tikosyn should be discontinued.

Step 7. Patients are to be continuously monitored by ECG for a minimum of three days, or for a minimum of 12 hours after electrical or pharmacological conversion to normal sinus rhythm, whichever is greater.

The steps described above are summarized in the following diagram:



Maintenance of Tikosyn Therapy
Renal function and QTc or QT (if heart rate is less than 60 beats per minute) should be re-evaluated every three months or as medically warranted. If QTc or QT exceeds 500 milliseconds (550 msec in patients with ventricular conduction abnormalities), TIKOSYN therapy should be discontinued and patients should be carefully monitored until QTc or QT returns to baseline levels. If renal function deteriorates, adjust dose as described in Initiation of TIKOSYN Therapy, Step 3.

1. Under **CLINICAL PHARMACOLOGY**, the word "TIKOSYN" is replaced with the word "dofetilide".

2. The revision date and version number were updated.

There were no changes to the Medication Guide.

There are no other changes from the last approved package.

APPROVAL & LABELING

We have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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 Microsoft Word

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
301 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
08/08/2019 09:36:46 AM