DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020931/S-012; S-013

SUPPLEMENT APPROVAL
RELEASE REMS REQUIREMENT

Pfizer, Inc.
Attention: Tricia Racanelli, PharmD
Director, Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017

Dear Dr. Racanelli:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received February 17, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tikosyn (dofetilide) 0.125 mg, 0.25 mg, and 0.5 mg Capsules.

We also refer to our REMS Modification Notification letter dated January 26, 2016, and we acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated June 29, 2015.

These "Prior Approval" supplemental new drug applications provide for proposed modification to the approved REMS, to eliminate the requirement for the approved REMS for Tikosyn (dofetilide) (S-013) and propose the following corresponding labeling revisions (S-012).

1. In the Boxed Warning, the following text was deleted (shown as ~~strikethrough~~ text):

> To minimize the risk of induced arrhythmia, patients initiated or re-initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see **DOSAGE AND ADMINISTRATION**. ~~TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education; see **DOSAGE AND ADMINISTRATION**.~~

2. Under **DOSAGE AND ADMINISTRATION**, the following text was deleted from the 5th and 6th bullets (additions shown as <u>underline</u> text and deletions shown as ~~strikethrough~~ text):

- Patients to be discharged on TIKOSYN therapy from an inpatient setting as described above must have an adequate supply of TIKOSYN, at the patient's individualized dose, to allow uninterrupted dosing until the patient <u>can fill a TIKOSYN prescription</u>~~receives the first outpatient supply.~~
- ~~TIKOSYN is distributed only to those hospitals and other appropriate institutions confirmed to have received applicable dosing and treatment initiation education programs. Inpatient and subsequent outpatient discharge and refill prescriptions are filled only upon confirmation that the prescribing physician has received applicable dosing and~~

~~treatment initiation education programs. For this purpose, a list for use by pharmacists is maintained containing hospitals and physicians who have received one of the education programs.~~

3. The revision date and version number were updated.

APPROVAL & LABELING

We have completed our review of these supplemental applications, and they are 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, text for the patient package insert, 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 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).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tikosyn (dofetilide) was originally approved on July 11, 2011, and the most recent modification was approved on November 25, 2015. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the following REMS modifications:

- Removal of the Medication Guide as an element of the REMS
- Removal of the elements to assure safe use from the REMS

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Tikosyn (dofetilide) outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Furthermore, we have determined that elements to assure safe use are no longer necessary because the REMS assessments have indicated that health care providers, including non-certified prescribers, demonstrate acceptable knowledge of the product's risks and Tikosyn's specific drug initiation and monitoring instructions, which can be conveyed appropriately via the current product labeling. In addition, the need for inpatient initiation and monitoring of Tikosyn is well-accepted in clinical practice (see, e.g., the 2014 AHA/ACC/HRS Guideline for the Management of Patients for Atrial Fibrillation).

Therefore, because the elements to assure safe use and the inclusion of the Medication Guide as part of the REMS are no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for Tikosyn (dofetilide).

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
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
03/08/2016