DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 018972/S-051

SUPPLEMENT APPROVAL

Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer
Attention: Marcio De Godoy, PhD.
Senior Manager, Worldwide Safety and Regulatory
500 Arcola Road
G4347
Collegeville, PA 10426

Dear Dr. De Godoy:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 4, 2016, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cordarone (amiodarone hydrochloride) 200 mg Tablets.

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. Under **WARNINGS**, the following section was added:

> **Serious Symptomatic Bradycardia When Co-administered with Ledipasvir/Sofosbuvir or with Sofosbuvir with Simeprevir**
> Postmarketing cases of symptomatic bradycardia, some requiring pacemaker insertion and at least one fatal, have been reported when ledipasvir/sofosbuvir or sofosbuvir with simeprevir were initiated in patients on amiodarone. Bradycardia generally occurred within hours to days, but in some cases up to 2 weeks after initiating antiviral treatment. Bradycardia generally resolved after discontinuation of antiviral treatment. The mechanism for this effect is unknown. Monitor heart rate in patients taking or recently discontinuing amiodarone when starting antiviral treatment.

2. Under **WARNINGS**, the following section was revised:

> **Neonatal ~~Hypo- or Hyperthyroidism~~Injury**
> ~~Cordarone can cause fetal harm when administered to a pregnant woman. Although Cordarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If Cordarone is used during pregnancy, or if the patient becomes pregnant while taking Cordarone, the patient should be apprised of the potential hazard to the fetus.~~ Amiodarone can cause fetal harm when administered to a pregnant woman. Fetal exposure may increase the potential for adverse experiences including cardiac, thyroid, neurodevelopmental, neurological and growth effects in neonate. Inform the patient of the potential hazard to the fetus if Cordarone is administered during pregnancy or if the patient becomes pregnant while taking Cordarone .

~~In general, Cordarone Tablets should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus.~~

3. Under **PRECAUTIONS**, the following text was added/deleted:

Pregnancy: ~~**Pregnancy Category D**~~
See "WARNINGS, Neonatal ~~**Hypo- or Hyperthyroidism**~~**Injury".**

Teratogenic Effects

Amiodarone and desethylamiodarone cross the placenta.

Reported risks include:

- neonatal bradycardia, QT prolongation, and periodic ventricular extrasystoles
- neonatal hypothyroidism (with or without goiter) detected antenatally or in the newborn and reported even after a few days of exposure
- neonatal hyperthyroxinemia
- neurodevelopmental abnormalities independent of thyroid function, including speech delay and difficulties with written language and arithmetic, delayed motor development, and ataxia.
- jerk nystagmus with synchronous head titubation
- fetal growth retardation
- premature birth

Nursing Mothers
~~Cordarone~~ Amiodarone and one of its major metabolites, DEA, are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered ~~Cordarone~~ amiodarone have been shown to be less viable and have reduced body-weight gains. The risk of exposing the infant to amiodarone and DEA must be weighed against the potential benefit of arrhythmia suppression in the mother. Advise the mother to discontinue nursing~~Therefore, when Cordarone therapy is indicated, the mother should be advised to discontinue nursing.~~

4. Under **ADVERSE REACTIONS**, the following section was revised:

Postmarketing Reports
In postmarketing surveillance, serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with ledipasvir/sofosbuvir or with sofosbuvir with simeprevir, hypotension (sometimes fatal), sinus arrest, anaphylactic/anaphylactoid reaction (including shock), angioedema, urticaria, eosinophilic pneumonia, hepatitis, cholestatic hepatitis, cirrhosis, pancreatitis, acute pancreatitis, renal impairment, renal insufficiency, acute renal failure, acute respiratory distress syndrome in the post-operative setting, bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest, and ARDS), bronchiolitis obliterans organizing pneumonia (possibly fatal), fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates and/or mass, pulmonary alveolar hemorrhage, pleural effusion, pleuritis, pseudotumor cerebri, parkinsonian symptoms such as akinesia and

bradykinesia (sometimes reversible with discontinuation of therapy), syndrome of inappropriate antidiuretic hormone secretion (SIADH), thyroid nodules/thyroid cancer, toxic epidermal necrolysis (sometimes fatal), erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, bullous dermatitis, drug rash with eosinophilia and systemic symptoms (DRESS), eczema, skin cancer, vasculitis, pruritus, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, thrombocytopenia, agranulocytosis, granuloma, myopathy, muscle weakness, rhabdomyolysis, demyelinating polyneuropathy, hallucination, confusional state, disorientation, delirium, epididymitis, impotence and dry mouth, also have been reported with amiodarone therapy.

5. The revision date was updated.

There are no other changes from the last approved package insert. There were no changes to the Medication Guide.

We have completed our review of this supplemental application, and 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 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

Division of Drug Marketing, Advertising, and Communications
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/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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
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 1
Center for Drug Evaluation and Research

ENCLOSURE:
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
04/22/2016